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Immunological Subtypes of Acute Lymphoblastic Leukemia: Beyond Morphology

Farah Jijina

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.

ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults.

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children. Data from the SEER database have shown a 5-year overall survival (OS) of 86% - 89% for children.

The diagnosis of acute leukemia AL is based on clinical and laboratory data. The laboratory evaluation of patients suspected of having acute leukemia (AL) is complex.

Over the years it has evolved significantly with the incorporation of advanced laboratory techniques.

The French-American-British (FAB) cooperative group, first broadly classified acute leukemias based on morphology of blast cells as seen on Wright- or Wright-Giemsa-stained bone marrow smears and a variety of cytochemical stains.

However, morphological diagnosis of acute leukemia may be incorrect up to 9%.

This led to the introduction of flow cytometry immunophenotyping (FCI), and the FAB classification was modified to incorporate these, mainly to distinguish acute myeloid leukemia from acute lymphoblastic leukemia.

In 2001, the 3rd edition of the WHO classification of AL formally introduced the requirement for immunophenotyping and cytogenetic studies for the diagnosis.

The 2008, 4th edition of the WHO classification, added additional cytogenetic disease groups for AML and ALL, introduced the category of mixed-phenotype acute leukemia (MPAL), and included provisional entities of AML that were based on gene mutation studies.

The 2016 WHO classification continued to define some disease entities by a combination of morphologic, immunophenotypic, and molecular genetic changes, but some gene mutations and cytogenetic abnormalities, although not disease defining, offer significant prognostic information.

Laboratory data include a CBC with morphologic assessment of blood and bone marrow, karyotype, appropriate molecular genetic and/or fluorescent in situ hybridization (FISH) testing, and immunophenotyping.

The flow cytometry panel should be sufficient to distinguish AML, T-cell acute lymphoblastic leukemia (T-ALL), B-cell precursor ALL (B-ALL), and acute leukemia of ambiguous lineage on all patients with AL.

ALL can be broadly classified into 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL, and T-cell ALL. Among children, B-cell ALL constitutes approximately 88% of cases; in adult patients, B-ALL represent approximately 75% of cases (including mature B-cell ALL that constitutes 5% of adult ALL), whereas the remaining 25% comprise T-ALL.

Within the B-cell lineage, the profile of cell surface markers differs according to the stage of B-cell maturation, which include early precursor B-cell (early pre-B-cell), pre-B-cell, and mature B-cell ALL.

Early pre-B-cell ALL is characterized by presence of terminal deoxynucleotidyl transferase (TdT), expression of CD19/CD22/CD79a, and the absence of CD10 or surface immunoglobulins.

Pre-B-cell ALL is characterized by presence of cytoplasmic immunoglobulins and CD10/CD19/CD22/CD79a expression and was previously termed common B-cell ALL due to the expression of CD10.

Mature B-cell ALL shows positivity for surface immunoglobulins and clonal lambda or kappa light chains, and is negative for TdT. CD20 may be expressed in approximately 50% of B-cell ALL in adults, with a

Hon Professor, Department of Haematology, KEM Hospital, Consultant Haematologist, Hinduja Hospital, Mumbai, Maharashtra
higher frequency (>80%) observed in mature B-ALL.

T-cell ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to variable expression of CD1a/CD2/CD5/CD7 and expression of TdT. CD52 may be expressed in 30% - 50% of T-ALL in adults.

Hematologic malignancies related to ALL include AL with ambiguous lineage, such as mixed phenotype acute leukemia (MPAL).

MPAL include bilineage leukemias, in which 2 distinct populations of lymphoblasts are identified, with 1 meeting the criteria for acute myeloid leukemia. Another type of MPAL is the biphenotypic type, in which a single population of lymphoblasts expresses markers consistent with B-cell or T-cell ALL, in addition to expressing myeloid or monocytic markers.

Myeloid-associated markers such as CD13 and CD33 may be expressed in ALL, and their presence does not exclude this diagnosis.

In developing countries, leukemia is most common among childhood cancers and it constitutes 3–10%. Leukemias account for 0.15–0.6% of the total medical admissions in many general hospitals in India.

Acute myeloid leukemia (AML) accounts for approximately 20% of AL in children and 80% AL in adults.

In India childhood cancer constitutes less than 5% of the total burden of cancer. Approximately 45,000 children are diagnosed with different types of cancer every year.

ALL is the most commonly reported childhood malignancy and accounts for 30% of all cancers diagnosed in children under 15 years, with B-cell ALL representing about 88% of cases. A Hospital Based Cancer Registry Report of ICMR (2004–2006) reported that acute leukemia is the most common childhood cancer with an estimated prevalence of up to 60 to 85% of all leukaemia’s.

The present article by Rajkumar and Vijay from the Kidwai Institute in Bangalore has studied the immunological subtypes of ALL at their center. All cases of Acute Leukemia where flow cytometric analysis was done during a period of 4-year from January 2012 to August 2015 were included in this retrospective study.

1425 cases were acute Leukemias (70.02%), 918 (64.42%) were Acute lymphoblastic Leukemia, (Adult ALL were 317 (34.5%) and paediatric ALL were 601 (65.46%); 688 were B-ALL (74.94%) AND 230 T ALL (25.05). In 601 children with ALL, B-ALL were 480 (79.86%) and T-ALL were 121 (20.13%). In 317 adults, with ALL, B-ALL were 208 (65.6%) cases and T-ALL were 109 (34.38%). In both adults and children ALL, B-ALL was the most common subtype. AML comprised of 487 (34.17%), MPAL (mixed phenotypic acute leukemia) comprised of 21 (1.47%).

Their findings are consistent with most reported studies including from India.

A number of Indian studies have been carried out, which have taken into account clinical, morphological features, immunophenotyping, cytogenetic and FISH, though the numbers in each study have not been large.

The advantage of the present study is the large number they have been able to analyse. However being a retrospective study no other information regarding the other parameters are mentioned.

The Department of Pathology, Gujarat Cancer and Research Institute, Ahmedabad, conducted a study from January 2015 to December 2015. 455 AL patients were enrolled, of which 184 (40.4%) diagnosed as AML, 214 (47%) as B-ALL, 55 (12.1%) as T-ALL, and 2 (0.4%) as MPAL by morphology, cytochemistry, and immunophenotyping.

Another study from Lok Nayak Hospital, Delhi, studied 100 newly diagnosed consecutive cases of AL from 2011 - 2013. Flow cytometry was performed on peripheral blood/bone marrow aspirate on Beckman Coulter flow cytometer (FC500) using a panel of markers comprising CD10, CD19, CD20, CyCD22, CyCD3, CD2, CD5, CD7, CD13, CD33, CD117, CD11c, CD34, HLA-DR and CD45.

Based on morphology, cytochemistry and immunophenotyping 57 cases of ALL and 43 cases of AML were diagnosed. Amongst ALL cases, 46 were B-ALL and 11 were T-ALL.

A prospective study was conducted in Department of Hematology, PGIMER, Chandigarh. All consecutively diagnosed cases of ALL for a period of 2 years (July 2010 to June 2012) were included. They had 303 Pediatric cases (<15 years) and 207 adult cases (>15 years).

Of the 303 pediatric case 85% (257/303) were classified as B-ALL and 15% (46/303) patients were identified as T-ALL.

Similar results have been published from the Institute of Child Health and Hospital for Children, Chennai.

Today most centers and treating physicians follow international guidelines for the diagnosis and treatment of various disorders. With advances in diagnostic tests and emerging new treatment strategies it is mandatory for us to keep up with these advances even in resource poor settings.

A number of Indian studies have carried out immunophenotyping with cost effective panels especially designed for resource constraints. With the advent of large laboratory chains, it is now possible to carry out these tests even in small centres that do not have in house facilities.
Thus, with the wider availability of the tests, it has become the standard of care today to carry them out prior to starting treatment. The tests themselves though expensive are a fraction of the cost of the overall treatment of a leukaemia. They in fact help to prognosticate and risk stratify the patients thus ensuring optimum utilization of resources.

Most treating oncologists and haematologists do a full diagnostic workup routinely; unfortunately with the wealth of material we have, publications are still meagre, a situation which we should try to overcome.

**Conclusion**

In conclusion, the authors should be commended for the effort of publishing the study with a large number of patients. However, there are a number of Indian studies who have provided more comprehensive data, albeit with smaller numbers.

An ideal way to project our Indian data would be for large institutions to come together and pool their data. This would help us to identify the unique problems we face in diagnosis, management and outcomes and help to give insight into future course of action.

**References**

1. Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology.

**Referees for JAPI**

API Members with minimum ten years experience of clinical practice and who are interested to contribute for JAPI as Referee may please send your details as listed below.

Name, Years of experience, Current designation and Affiliations, Area of interest, List of publications, e-mail id and Mobile number.

kindly send above information at the earliest to: onlinejapi@gmail.com

Prof. Milind Y. Nadkar
Editor-in-Chief, JAPI
Immunological Subtypes of Acute Lymphoblastic Leukemia—Beyond Morphology: Experience from Kidwai State Cancer Institute, Bengaluru, India

Namrata N Rajkumar, Raghavendra H Vijay

Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is disease of lymphoid precursors and is the most common cancer. Diagnosis of ALL is made by evaluating morphology and flowcytometric Immunophenotyping (FCI) and is an important adjunct in diagnosis and determining treatment in ALL, with availability of extensive monoclonal antibodies in the recent years there is tremendous progress in the field of FCI, and is a requirement by World Health Organisation for the classification of acute lymphoblastic Leukemia. Flow cytometric immunophenotyping of the leukemic blasts helps in categorization of acute lymphoblastic leukemia as B-ALL or T-ALL. Though ALL is the most common cancer, there is paucity of study in Indian scenario, and very few reports of immunologically subtyping of ALL is reported.

Aim: To confirm the clinical/morphological diagnosis and to determine immunological subtype of acute lymphoblastic leukemia as per requirement by World Health Organization for the classification of acute lymphoblastic leukemia

Material and Methods: At Kidwai State Cancer institute, Bangalore, we have performed of Immunophenotyping in 1425 untreated cases of acute leukemias during January 2012 - August 2015.

Results: Flow cytometry analysis of 1425 cases of acute Leukemias were performed, 918 (64.42%) were acute lymphoblastic Leukemia, 688 were B-ALL (74.94%), majority(480) of B-ALL were in children (69.76%), 230 were T-ALL (25.05 %), B-ALL was the most common subtype of acute leukemias.

Conclusion: Acute lymphoblastic leukemia is the most common leukemia in adults and children. Immunophenotyping helps in confirming the clinical/morphological diagnosis and in determining the immunological subtype of acute lymphoblastic leukemia, thus has an important role in deciding on the treatment regime. ALL is the disease of lymphoid precursors and is more common cancer in children than adults. B-ALL was the most common subtype of acute leukemias both in adults and in children. T-ALL is less common in pediatric population. Flowcytometric techniques are used to measure (submicroscopic) minimal residual disease (MRD), and is currently incorporated in many ALL treatment protocols as a tool for risk stratification.

Editorial Viewpoint

• Flow cytometric immunophenotyping of the leukemic blasts helps in categorization of ALL.
• This study finds 80% cases as B-ALL with 70% in children.

Introduction

For more than a century, identification of the various cytologic types of acute and chronic leukemias has been achieved largely by microscopic examination of blood and bone marrow preparations stained with Panoptic stain such as Wright’s or Giemsa. Diagnostic hematopathology depends on the applications of flow cytometric immunophenotyping (FCI) and immunohistochemical immunophenotyping combined with the cytomorphology and histologic features. FCI is an important adjunct in diagnosing and determining treatment in Acute Lymphoblastic Leukemia (ALL). Diagnosis of ALL and immunological subtyping as B-ALL and T-ALL, (Table 1) is made by evaluating clinical, morphological and immunophenotypical findings. With availability of extensive

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Immunological sub typing, is a requirement for the classification of Leukemias as per World Health Organisation (WHO) (Table 2). ALL is the disease of lymphoid precursors and is more common cancer in children than adults. 75% of the cases occur in children under 6 years of age. 80–85% of ALL being precursors B cell phenotype. T-ALL comprise about 15% of childhood ALL.

**Materials and Methods**

All cases of acute Leukemias where flow cytometric analysis was done for diagnosis during a period of 4-year from January 2012 to August 2015 were included in this retrospective study.

All specimens were obtained and prepared for morphologic examination using standard monoclonal antibodies in the recent years, there is tremendous progress in the field of FCI. 3

Types of sample suitable for FCI include peripheral blood, bone marrow aspirates(BMA), and core biopsies, fine-needle aspirates, and all types of body fluids. 2

Immunological sub typing, is a requirement for the classification of Leukemias as per World Health Organisation (WHO) (Table 2). ALL is the disease of lymphoid precursors and is more common cancer in children than adults. 75% of the cases occur in children under 6 years of age. 80–85% of ALL being precursors B cell phenotype. T-ALL comprise about 15% of childhood ALL. 4

**Materials and Methods**

All cases of acute Leukemias where flow cytometric analysis was done for diagnosis during a period of 4-year from January 2012 to August 2015 were included in this retrospective study.

All specimens were obtained and prepared for morphologic examination using standard

### Table 1: Immunophenotyping

<table>
<thead>
<tr>
<th>Commonly positive</th>
<th>Variable expression</th>
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<tr>
<td>B-ALL</td>
<td>CD19</td>
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<td>CD20</td>
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### Table 2: WHO classification of ALL

<table>
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<th>Precursor lymphoid neoplasms</th>
<th>B lymphoblastic leukaemia/lymphoma, NOS</th>
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<tr>
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techniques. Peripheral blood smears and bone marrow aspirates were air dried and stained with Giemsa stain. Myeloperoxidase was done routinely in all peripheral smears and bone marrow aspirate smears. Other cytochemical stains, periodic acid-Schiff, nonspecific esterase and specific esterase were done according to the morphological details of the cells.

Four colour flow cytometry analysis was performed using FACS caliber (Becton Dickinson, San Jose, CA, USA). Standard lyse-wash procedure was used. The cells were stained with various combinations of fluorescein isothiocyanate (FITC), phycoerythrin (PE), Allophycocyanin (APC) and Peridinin chlorophyll protein (PerCP) labeled monoclonal antibodies against the following antigens and the specific clones used were obtained from Becton Dickinson, San Jose, CA, 75-75. CD45 PerCP, CD34 APC (8G12), CD10 FITC, CD19 PE (4G7), CD117 PE (104D2), CD13 APC, CD33 FITC (P67 6), CD3 APC, CD7 FITC, CD79a PE, Tdt APC (E17 1519), HLA DR PE, CD4 FITC (SK3), CD34 PE (8G12), MPO FITC, CD64 PE, CD14 PE, CD3 PE (SK7), CD13 PE, CD3 APC, CD8 PE (SK1), CD25 APC, CD56

**Results**

At Kidwai State Cancer Institute, Bangalore, flowcytometric analysis were performed during January 2012- August 2015.

Total of 1925 cases of FCI were performed, 1425 cases were acute leukemias (70.02%), total 918 (64.42%) were acute lymphoblastic leukemia, (adult ALL were 317 (34.5%) and paediatric ALL were 601 (65.46 %) 688 were B-ALL (74.94%) and 230 T-ALL (25.05) (Table 3).

In both adults and children ALL, B-ALL was the most common subtype of acute leukemias. AML comprised of 487 (34.17%), MPAL (mixed phenotypic acute leukemia) comprised of 21(1.47%). In 601 children with ALL, B-ALL were 480(79.86%) and T-ALL were 121 (20.13%). In 317 adults, with ALL, B-ALL were 208(65.6%) cases and T-ALL...
were 109 (34.38%) of Acute leukemias in our study and overall this immunophenotype is associated with worse prognosis than Pre B-ALL. Patients with T-ALL are treated similarly to high risk Pre-B ALL patients, with more intensive chemotherapy, regardless of age and WBC count at presentation. Further newer technologies like Micro array technologies has made it possible to accurately classify leukemias as subsets of B-ALL and T-ALL based on their Gene Expression Profiling. Though ALL is one of the most common cancers in India, immunological subtyping is available in very few centers, our results/incidences of ALL were comparable with reported western literature. Raising T-ALL was noted in an earlier study from India. Raising familiarity of FCI in Indian clinicians, and frequent use of FCI in all cases of ALL, will help us to know many differences in our Indian population and helps in treatment, risk stratification and in prognosis. Hope for future progress lies in the improved understanding of the biology of ALL, that is likely to come from the application of new molecular and genomic technologies to the study of this disease. A major challenge for the future is to ensure that effective treatment of ALL may be made more available to the affected worldwide.

References

Prof. Dir. Dr. K.C. Mohanty era is over.

All time hero, real stalwart, lion-hearted teacher, walking encyclopedia, great thinker and guiding force behind hundreds of chest physicians, physicians, policy makers & all those involved in the fight against tuberculosis, who left a legacy of four generations of chest physicians behind him, left us for heavenly abode on 1st June 2017.

“We always lead… we show the path …” were his words & he lived his life true to that.

Born on 18th June 1940, he hailed from Odisha, after graduation in Medicine, he left for Mumbai to pursue his post-graduate studies in tuberculosis, & took up the first assignment as Honorary TB specialist at the Group of TB hospitals, Sewri and Professor at the department of TB & Chest diseases at Grant Medical College and Sir J. J. Group of Hospitals in 1972. In last 45 years that he served as teacher & dynamic physician and continued to head the department till 1999. He was examiner and inspector of TB and Chest diseases at several universities and institutions across the country, including the University of Bombay and Delhi and the National Board of Examinations. He joined the Department of TB & Chest diseases at the K. J. Somaiya Medical College, Mumbai as Director Professor & Head in 1999 and continued to serve till 2014. During the five decades of services, he treated and cured more than 25 lakhs patients of Tuberculosis. His most pioneering contributions were the introduction of Ciprofloxacin (1989) and Meropenem with clavulanic acid (2010) as anti-TB drugs, the efficacy of immunomodulators, especially levamisole and immunoglobulins in TB, the efficacy of partially supervised TB treatment and the integration of TB-HIV health services. He also scripted and produced a 35 minute film on “TB- The number one killer”.

He received innumerable State & National awards & as a mark of respect various organizations instituted awards, shields & orations in his name. He authored number of chapters & edited more than 20 books.

He was a hardcore environmentalist and tirelessly he worked for upliftment of adivasis & rural areas. He adopted village Pathraj near Karjat & looked after complete needs of the villagers-social, financial, & emotional issues. He constructed Saibaba temple without any professional laborers & architects, and made a community center. Temple offers free meals to all on Sundays & special festival days. He got more than 300 adivasi couples married at village. He had special love for North east region of India & made herculean efforts to integrate north east region to mainland. He was very close to His Excellency Shri PB Acharya – Governor of Nagaland. Prof Mohanty did multiple camps at Nagaland. He visited more than 25 times the North East region & did many multiple state level conferences. He holds record of doing conference at Tavang- at the height of 13,500 feet – one of its type of regional conference done by civilians for privileged parts of India.

He started life at very ground level, struggled very hard to make both ends meet but always kept his spirits up. He always lived life his way, making no compromises.

He was Sai Bhakt, & through his life, he came in touch with various saints & spiritual leaders. Infected one spiritual leader exchanged his life for him & that’s the reason he got life after complete straight line on monitor for full 3 minutes. He lived for 2 decades after that episode. He never opted for any five star hospital attachments. He never accepted any invitation from out of India as speaker. He rejected very lucrative offers from foreign countries to migrate & head departments. He continued to serve the poor & needy. “I am the doctor of mass & not the class” as he would always say. Poorest of poor would get the best of treatment from him.

He always promoted juniors & I am the live example. His Midas touch changed my life completely. I want to become like you, is what I told him in my first meeting with him. “It would need a lot of compromises “ he said. But he saw to it that I rise in my career. I owe everything I have to him.

“If I have to die I want to die in Agam’s hospital” were his last words for me. I was not with him when he spoke this. “He will feel bad if I die anywhere else...” He developed acute viral infection that lead to myocarditis, then ARDS & then gradually multi-system failure. When I last interacted with him (he was intubated & communicated with eyes & notes on paper ) he told me show must go on. Do not cancel conference, I read in his eyes. Very firm message he gave me. 23 NESCON 2017 – a National annual conference on Environmental & respiratory diseases, is dedicated to him. Can there be any other way to offer our tribute to the teacher’s teacher & the best chest physician & TB specialist India ever produced?

Sir, I promise to do it the way you would have done it, the way you would have wanted me to do it.

Dr Mohanty achieved so much in the subject that he chose for himself & generations of physicians would be grateful to him for his contribution to the subject.

May his soul rest in peace.

Dr. Agam Vora

Asst. Hon. & In Charge - Dept. of Chest & TB, Dr. R.N. Cooper Muni. Gen. Hospital, Mumbai
Auramine-o (Synthetic Yellow Cow Dung Powder) Poisoning: Rare but Fatal

Shubhangi Dhadke¹, Vitthal Dhadke², Abhijit Giram³

Abstract

Introduction: Cow dung known since long ago for its germicidal properties, used by Indian villagers to clean the house premises. As cow dung is not available easily, nowadays people have started using synthetic yellow coloured powder (Auramine-o) available easily in grocery shops locally known as “Morechap powder” in districts of Maharashtra. As the poisoning is rare, very few literatures are available mentioning the detailed mechanism of action, clinical presentation and complications.

Aims and Objectives: To study the clinical features, treatment and outcomes of synthetic yellow cow dung powder poisoning.

Material and Methods: 25 patients presenting with confirmed H/O consumption of (Auramine-o) synthetic yellow cow dung powder poisoning were studied. Patient’s routine investigations BSL, RFT, LFT were done. CT brain was done whenever indicated.

Results and Conclusion: Synthetic yellow cow dung powder poisoning was common in young age group and females. Vomiting, respiratory depression were common symptoms. Synthetic yellow cow dung powder poisoning was needed only symptomatic treatment. It was very rare and mortality is low when treated promptly.

Introduction

Cow dung known since long ago for its germicidal properties, used by Indian villagers to clean the house premises. As cow dung is not available easily, nowadays people have started using synthetic yellow coloured powder (Auramine-o) available easily in grocery shops locally known as “Morechap powder” in districts of Maharashtra.

As the poisoning is rare, very few literatures are available mentioning the detailed mechanism of action, clinical presentation and complications.

Aims and Objectives

1. To study the clinical features.

2. To study the response to treatment.

3. To study outcome of (Auramine-o) synthetic yellow cow dung powder poisoning.

Material and Methods

Study design: Prospective study

Source of data: The study was carried out in Dr. V.M. Government Medical College, Solapur.

Duration of study: January 2016 to July 2016.

Inclusion Criteria:

1. Age > 13 yrs.

2. Patients with confirmed H/O consumption of (Auramine-o) synthetic yellow cow dung powder

Sample size - 25 Patients.

25 patients presenting with confirmed H/O consumption of synthetic yellow cow dung powder poisoning were studied. Patient’s routine investigations BSL, RFT, LFT were done. CT brain was done whenever indicated.

Results

Of the 25 cases studied 10 were males and 15 females. Three patients were <20 years of age, 13 were 20-40 and 9 were >40.

From Table 1 shows the clinical features in patients.

All patients were treated with supportive line of treatment.
Four out of 25 patients died, three due to aspiration with seizures and one because of cardiotoxicity. Rest were treated symptomatically and discharged.

Cow dung known since long ago for its germicidal properties, used by Indian villagers to clean the house premises. As cow dung is not available easily, nowadays people started using synthetic yellow coloured powder available easily in grocery shops locally known as “Morechap powder” in districts of Maharashtra state. This issue came into light when people started consuming this yellow synthetic cow dung powder due to closure of “Beedi Industry” as it was banned by Government. This study was conducted to know the socioeconomic causes behind this poisoning, its clinical features and treatments. Study was conducted at Dr. V.M. Government Medical College and Shri Chhatrapati Shivaji Maharaj Sarvopchar Rughnalaya, Solapur, Maharashtra. 25 patients admitted with H/o yellow synthetic cow dung powder consumption from January to July 2016.

All patients had their clothes and body stained with yellow colour which persisted even at the time of discharge. Among 25 patients studied, 10 had GI symptoms as vomiting and epigastric discomfort, 6 had respiratory depression while 4 had convulsions. One had both respiratory depression as well as cardiotoxicity. Two patients died immediately after arrival in Emergency department and two after admission.

**Some Interesting Case Details**

**Case 1**

A 17 year girl presented with H/o consumption of yellow synthetic cow dung powder. She had multiple episodes of vomiting during transportation. On examination, her body and clothes were stained with yellow colour. Even the urine was lemon yellow coloured. She was drowsy and responding to painful stimuli. Vitals were normal. Other systemic examination was normal. Stomach wash, body decontamination was done. IV fluids, PPI and supportive care was given. After 2 hours she had 3 episodes of generalised tonic clonic convulsions which were controlled with antiepileptics. Lab investigations such as CBC, RFT, LFTs were normal. CT Brain was normal. Subsequently she was fully conscious and oriented and discharged on antiepileptic drugs after 4 days.

**Case 2**

A 60 year male admitted with H/o consumption of yellow synthetic cow dung powder. He had multiple episodes of vomiting. On examination he was stuporose, minimally responding to the painful stimuli. GCS was E1V1M1. He was known case of DM and HTN with non-compliance to drugs. P -160 bpm regular, Bp-220/120 mmHg. Cardiovascular and respiratory systems was normal. ECG showed LBBB pattern. He was intubated due to low GCS and mechanical ventilation started. Stomach wash, body decontamination was done. Suddenly he developed ventricular tachycardia which was reverted pharmacologically with amiodarone. The GCS improved to E1V1M1. But after 2 days he died of sudden cardiac arrest.

**Case 3**

One female who consumed the yellow synthetic cow dung powder, had bilateral aspiration due to multiple episodes of vomiting. She died immediately after admission to hospital.

**Case 4**

Other female who arrived in Emergency department with status epilepticus had her body and clothes stained with yellow colour. She had bilateral aspirations and was intubated immediately due to falling saturation and low GCS. But she succumbed in the Emergency department only even after resuscitative efforts.

Rest of the patients who presented with vomiting, epigastric discomfort and respiratory depression were treated symptomatically. Stomach wash and body decontamination was done in all. Skin as well as body secretions were yellow even after 2 days of treatment. All of them were discharged after clinical improvement.

**Discussion**

Total 25 cases were studied. 25 patients presenting with confirmed H/O consumption of synthetic yellow cow dung powder poisoning were studied. Patient’s routine investigations BSL, RFT, LFT were done. CT brain was done whenever indicated.

Because of cheaper cost and easy availability, this poisoning has become popular in last 4 months in Solapur (Vidi Gharkul area). The reason was loss of job due to closure of beedi industry by Government. Surprisingly, there are no cautionary labels on the packet. Even though it is legally banned, the poison is widely available in market and no step is taken to prevent it.

Cow dung powder is available in 2 types – Auramine-O (Yellow) and malachite green (Green).1 Auramine is a neurotoxic poison which causes CNS depression. Centrilobular necrosis due to toxic metabolites leading to severe hepatic damage manifested as
jaundice, upper abdominal pain, and vomiting. Auramine being a cationic dye causes severe ocular injury on eye contact and damages the gastrointestinal mucosa on ingestion. Chronic effects of Auramine dye include carcinogenicity, mutagenicity and its long-term inhalation leads to pneumoconiosis.

Malachite Green is multi-organ toxin which shows delayed toxicity. Rarely do these cases get referred to tertiary or teaching hospitals which add to the reason why synthetic cow dung poisoning is not reported in literatures. Animal and observational research confirms that Malachite Green is multi-organ toxin with delayed toxicity. Very few cases have been reported with Auramine poisoning while there are no references so far about Malachite Green poisoning.

The yellow powder causes GI irritation and damage to the mucosal membrane hence causing epigastric pain, vomiting and discomfort.

Acute exposure initially shows neurological features like seizures, non-specific muscle cramps, spasms, focal deficits and coma. Except for any primary focal neurological deficit, seizures are one of the deadly events caused by many poisons. The sudden onset of seizure episode in poisoning signifies the involvement of both the cerebral hemispheres. Direct CNS effect of the poison is clearly evident from the low GCS score of the patients. In our study we found neurotoxicity in the form of respiratory depression and seizures which is also observed in studies done by Hisham et al.

One male died due to cardiac arrhythmias which needs further evaluation for the correlation with toxicity profile of compound as it is not found in any studies done till date. Cardiotoxicity may be due to poison.

In all patients serum bilirubin and liver enzymes were normal till discharge as opposed to hepatotoxicity mentioned in the studies done by Hisham et al.

Our all patients had yellowish body discoloration but bilirubin and SGOT/SGPT were normal. Hence, the discoloration of skin could be due to deposition of powder in different parts of the body as observed by Krishnamoorthy et al.

Conclusion

Synthetic yellow cow dung powder poisoning was common in young age group and females. Vomiting, respiratory depression were common symptoms. Synthetic yellow cow dung powder poisoning was needed only symptomatic treatment. It was very rare and mortality is low when treated promptly. Strict actions needs to be taken on banning such toxic products which are sold in the market.

References

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Survey of Assessment and Management of Coronary Heart Disease Patients (SMART) in India

Amit Singh¹, Vikram Singh¹, Rupesh Ranjan²

Abstract

Objectives: Survey of Assessment and Management of Coronary Heart Disease Patients was undertaken to describe profile and management pattern of adult Acute Coronary Syndrome (ACS) patients from presentation till discharge, in private tertiary care Indian hospitals.

Materials and Methods: This was an observational, prospective study. Based on standard criteria, patients were diagnosed to have ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). For patients surviving till hospital discharge, demographic characteristics, medical history, time to hospital presentation, investigations, vascular interventions and medical management during the hospital stay were recorded.

Results: In total, 1340 patients with definitive ACS diagnosis and surviving their hospital stay were enrolled. Mean patient age was 58.7 years, 75% were males and 36.9% were diagnosed with STEMI, 8.9% with NSTEMI and 54.2% with UA. 41.9%, 35% and 18.4% patients reached hospital within 6 hours for STEMI, NSTEMI and UA respectively. Pre-existing hypertension and diabetes were observed less frequently in patients with STEMI (54.8%, 31.9%) than in NSTEMI (70.8%, 45.8%) or UA (64.2%, 41.5%). Aspirin, clopidogrel, nitrates, β-Blockers, angiotensin converting enzyme inhibitors and statins were used more frequently in NSTEMI than in STEMI or UA patients. Percutaneous trans-coronary angioplasty was performed more commonly in STEMI (64.2%) than in NSTEMI (41.7%) or UA (41.2%).

Conclusions: UA is the commonest and NSTEMI is the least common type of ACS observed in our study. We observed important differences in patient profile, time to hospital presentation, in-hospital acute pharmacological management and vascular interventions performed between the three different types of ACS.

Editorial Viewpoint

- This is a large study conducted in tertiary care centers in urban metropolitan cities in private set up.
- Major differences compared to previous studies are higher proportion of patients with hypertension as risk factor and lower proportion of STEMI amongst ACS.
- Trend of fewer patients reaching hospital within 6 hours is worrisome.

Acute Coronary Syndromes (ACS) represents the most common causes of mortality in patients with cardiovascular disease.

The central pathogenesis of ACS consists of fissuring or erosion of atheromatous plaque with superimposed platelet aggregation and thrombosis. This is complicated by micro-fragmentation and distal embolization with alterations in vascular tone and ultimately partial or complete occlusion of perfusion to affected myocardium. Clinical manifestations of ACS are dependent upon the severity of obstruction in the affected coronary artery, the presence or absence of collateral perfusion,
and the volume and myocardial oxygen demand within the affected territory. Complete coronary occlusion in absence of collateral perfusion results in ST-Elevation Myocardial Infarction (STEMI), involving myocardial necrosis and accompanying increase in blood levels of sensitive enzyme markers. Transient or partial coronary occlusion results in Non-ST-Elevation Myocardial Infarction (NSTEMI), involving myocyte necrosis of a lesser extent and minor increase in blood levels of enzyme markers. Untreated or partial coronary occlusion without rise in blood levels of myocardial enzyme markers.

The distinction between acute myocardial infarction and minimal myocardial injury is of immediate practical importance as emergency reperfusion treatment is indicated for acute infarction but not for the remainder of the ACS.

The Survey of Assessment and Management of Coronary Heart Disease Patients (SMART) study was undertaken to describe any differences in patient profile and in-hospital management practices between different types of ACS, in private tertiary care centres in India.

Materials and Methods

Patients

The study was conducted from January 2005 to December 2007 in eight private, tertiary care centres located in urban metropolitan cities and having advanced coronary care facilities. Approval from the local ethics committee was taken prior to study commencement and informed consent was obtained from each patient participating in the study. Patients were included in this study if they were ≥18 years old, were admitted for ACS as a presumptive diagnosis, survived till discharge from hospital and had ≥1 of the following at hospital presentation in addition to symptoms of ACS: electrocardiographic (ECG) changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of cardiovascular disease. Patients with serious co-morbidities like advanced malignancy, end-stage renal disease; life-threatening infections etc. were excluded from this study. The qualifying ACS was not to be precipitated or accompanied by trauma or surgery.

The demographic and baseline patient characteristics along with their medical history and duration of symptoms prior to hospital presentation were recorded in a case report form.

Diagnosis

Pre-established criteria of electrocardiogram changes (ST-segment deviation, T-wave inversion, Q-wave anomaly, new onset of left bundle branch block) and serial increases in serum biochemical markers of cardiac necrosis (creatine kinase muscle brain [CK-MB], troponin) were employed at all study sites for classification of ACS into STEMI, NSTEMI or UA. STEMI was identified when new ST-segment elevation was ≥1 mm or new left bundle branch block (LBBB) in the ECG had one or more positive cardiac biochemical marker of necrosis. Presence of one or more positive cardiac biochemical marker of necrosis without new ST-segment elevation on the ECG suggested NSTEMI, while UA was identified by the absence of both ST-segment elevation on the ECG and serum biochemical markers indicative of myocardial necrosis.

Statistical Analysis

Data realization was performed to compute observed frequency of parameters like gender, type of ACS, risk factors, usage of standard medications at different time points (before admission, at admission and at discharge) and type of re-vascularization procedure. Age of patients (<40, 40-70 and >70 years) and duration of symptoms prior to presentation at hospital (<6, 6-12, 12-24 and >24 hours) were presented as categorical variable. The comparisons for all these parameters were made between the three patient types of STEMI, NSTEMI and UA. All tests were two-sided and considered significant at 0.05. The statistical analysis was performed using SPSS 17.0.

Results

In total, 1340 patients with a definite diagnosis of ACS and surviving till discharge from hospital were enrolled. This included 494 (36.9%) patients with STEMI, 120 (8.9%) with NSTEMI and 726 (54.2%) with UA.

Baseline Characteristics

About 75% of the study patients were male. While mean age of the total study patients was 58.7 ± 14.8 years, 7.2% were aged <40, 76% aged between 40 and 70 and 16.7% were aged 70 years. STEMI was the most common diagnosis in the age group of <40 years and UA was the most common diagnosis in other age groups. Significantly fewer patients with STEMI had diabetes (p<0.001) or hypertension (p<0.001) as known co-morbidities as compared to those with NSTEMI or UA.

Time to Hospital Presentation

Overall, 28.6% of ACS patients reached hospital within 6 hours, 9.2% in 6-12 hours, 14.8% in 12-24 hours and 41% after 24 hours of symptom onset. Significantly (p<0.001) higher proportion of STEMI patients reached hospital within 12 hours as compared with those having NSTEMI or unstable angina.

Medication Usage Prior to Hospitalization

Chronic usages of cardiovascular medications prior to hospital presentation have been summarized in Table 1. Overall frequency of these medications was consistent with known co-morbidities. β-blocker usage was significantly
Table 1: Medication usage prior to hospitalization

<table>
<thead>
<tr>
<th>Drugs</th>
<th>STEMI (n=494), n (%)</th>
<th>NSTEMI (n=120), n (%)</th>
<th>UA (n=726), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>191 (38.7)</td>
<td>51 (42.5)</td>
<td>281 (38.7)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 (15.2)</td>
<td>25 (20.8)</td>
<td>129 (17.8)</td>
</tr>
<tr>
<td>β-Blocker*</td>
<td>140 (28.3)</td>
<td>55 (45.8)</td>
<td>240 (33.1)</td>
</tr>
<tr>
<td>ACEI</td>
<td>104 (21.1)</td>
<td>23 (19.7)</td>
<td>148 (20.4)</td>
</tr>
<tr>
<td>Statin</td>
<td>140 (28.3)</td>
<td>34 (28.3)</td>
<td>208 (28.6)</td>
</tr>
</tbody>
</table>

* p<0.05 for difference between STEMI & NSTEMI; † p<0.05 for difference between NSTEMI and UA; ACEI: Angiotensin converting enzyme inhibitors; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina

Table 2: Pharmacological management at hospital presentation

<table>
<thead>
<tr>
<th>Drugs</th>
<th>STEMI (n=494), n (%)</th>
<th>NSTEMI (n=120), n (%)</th>
<th>UA (n=726), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin*</td>
<td>393 (79.6)</td>
<td>108 (90.0)</td>
<td>493 (67.9)</td>
</tr>
<tr>
<td>Clopidogrel*</td>
<td>380 (76.9)</td>
<td>111 (92.5)</td>
<td>468 (64.5)</td>
</tr>
<tr>
<td>β-Blocker*</td>
<td>296 (59.9)</td>
<td>92 (76.7)</td>
<td>361 (49.7)</td>
</tr>
<tr>
<td>ACEI†</td>
<td>217 (43.9)</td>
<td>53 (44.2)</td>
<td>228 (31.4)</td>
</tr>
<tr>
<td>Statin†</td>
<td>377 (76.3)</td>
<td>103 (85.8)</td>
<td>445 (61.2)</td>
</tr>
<tr>
<td>Nitrates*</td>
<td>246 (49.8)</td>
<td>73 (60.8)</td>
<td>325 (44.8)</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors*</td>
<td>111 (22.5)</td>
<td>33 (27.5)</td>
<td>189 (26.0)</td>
</tr>
</tbody>
</table>

* p<0.05 for difference between STEMI and NSTEMI; † p<0.05 for difference between STEMI & UA; ACEI: Angiotensin converting enzyme inhibitors; GP: Glycoprotein; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina

Table 3: Therapeutic or diagnostic vascular interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>STEMI (n=494), n (%)</th>
<th>NSTEMI (n=120), n (%)</th>
<th>UA (n=726), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytics</td>
<td>28 (5.6)</td>
<td>2 (1.6)</td>
<td>30 (4.1)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>429 (86.8)</td>
<td>107 (89.1)</td>
<td>641 (88.2)</td>
</tr>
<tr>
<td>PTCA</td>
<td>317 (64.1)</td>
<td>50 (41.6)</td>
<td>299 (41.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>21 (4.2)</td>
<td>14 (11.6)</td>
<td>49 (6.7)</td>
</tr>
</tbody>
</table>

CABG: Coronary artery bypass grafting; NSTEMI: Non-ST-segment elevation myocardial infarction; PTCA: Percutaneous transluminal coronary angioplasty; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina

Table 4: Medications prescribed at discharge

<table>
<thead>
<tr>
<th>Drugs</th>
<th>STEMI (n=494), n (%)</th>
<th>NSTEMI (n=120), n (%)</th>
<th>UA (n=726), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>461 (93.3)</td>
<td>108 (90.0)</td>
<td>657 (90.5)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>306 (61.9)</td>
<td>74 (61.6)</td>
<td>437 (60.2)</td>
</tr>
<tr>
<td>β-Blocker*</td>
<td>353 (71.5)</td>
<td>94 (78.3)</td>
<td>438 (60.3)</td>
</tr>
<tr>
<td>ACEI†</td>
<td>261 (52.8)</td>
<td>57 (47.5)</td>
<td>301 (41.5)</td>
</tr>
<tr>
<td>Statin†</td>
<td>435 (88.1)</td>
<td>105 (87.5)</td>
<td>575 (72.2)</td>
</tr>
</tbody>
</table>

* p<0.05 for difference between STEMI and UA; † p<0.05 for difference between NSTEMI and UA; ACEI: Angiotensin converting enzyme inhibitors; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina

Discussion

Patient profile and management patterns of ACS patients in India have been described in past as well.\(^4\)\(^-\)\(^6\) SMART study differs from the previous such studies in being the only one involving private tertiary care hospitals exclusively. Key features and observations of these studies have been summarized in Appendix 1.

When compared to the results of previous three studies, characteristics of our study patients are similar in many aspects like mean age of ACS patients, proportion of male patients and prevalence of diabetes as a co-morbid condition. However, some important differences noted in our study include higher prevalence of hypertension as comorbid condition, lower proportion of STEMI patients and fewer patients reaching hospital within 6 hours of symptom onset. Important differences in in-hospital management of ACS patients noted in SMART study as compared to previous studies include less frequent usage of β-blockers and preference for PTCA over fibrinolytics as the reperfusion tool.

We noted some important differences amongst the STEMI patient group as compared to the NSTEMI and/or UA patient groups, trans-coronary angioplasty (PTCA) was performed significantly more commonly in patients with STEMI as compared to patients with NSTEMI or UA (p<0.001).

Medications Prescribed at Discharge

Summary of medications prescribed at discharge from hospital has been presented in Table 4. In comparison to patient with STEMI, post-discharge pharmacological management appeared to be less intense in patients with UA as evidenced by significantly lower frequency of β-blocker, angiotensin converting enzyme inhibitors (ACEI) and statin prescription.
Appendix 1: Comparison Indian ACS registries

<table>
<thead>
<tr>
<th>Setting</th>
<th>Misiriya KJR et al.4</th>
<th>Mohanan PP et al.3</th>
<th>Xavier Denis et al.6</th>
<th>SMART</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1865</td>
<td>25748</td>
<td>20468</td>
<td>1340</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>58.3</td>
<td>60.4</td>
<td>57.5</td>
<td>58.7</td>
</tr>
<tr>
<td>Males</td>
<td>72.9%</td>
<td>77.4%</td>
<td>76.4%</td>
<td>75%</td>
</tr>
<tr>
<td>Co-existing diabetes</td>
<td>35.2%</td>
<td>37.6%</td>
<td>30.4%</td>
<td>38.3%</td>
</tr>
<tr>
<td>Co-existing hypertension STEMI</td>
<td>31.5%</td>
<td>48.4%</td>
<td>37.7%</td>
<td>61.3%</td>
</tr>
<tr>
<td>Symptom duration before hospital presentation STEMI: &lt;6 hours for 61.5% NSTEMI/UA: &lt;6 hours for 62.3%</td>
<td>55.9%</td>
<td>37%</td>
<td>60.6%</td>
<td>36.8%</td>
</tr>
<tr>
<td>β-blocker usage</td>
<td>77.6%</td>
<td>65.8%</td>
<td>59.3%</td>
<td>55.8%</td>
</tr>
<tr>
<td>Statin/lipid lowering drug (LLD) usage</td>
<td>71.3%</td>
<td>70%</td>
<td>52%</td>
<td>69%</td>
</tr>
<tr>
<td>Re-perfusion modality</td>
<td>Coronary intervention: 4.0% Fibrinolytics: 68.9%</td>
<td>PTCA: 6.7%</td>
<td>CABG: 1.4%</td>
<td>Fibrinolytics: 24.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Appendix 2: List of investigators and corresponding sites

- JPS Sawhney - Sir Gangaram Hospital, New Delhi
- Rajiv Rajput - Indraprastha Apollo Hospital, New Delhi
- Jairam Aithal - Hiranandani Hospital, Mumbai
- Deepak Tomar - Metro Heart Institute, New Delhi and Noida
- D B Pahlajani - Breach Candy Hospital, Mumbai
- Sanjay Tyagi - GB Pant Hospital, New Delhi
- R R Kasliwal - Escorts Heart Institute, New Delhi
- Pradeep Shetty - Narayana Hrudayala, Bangalore

Some of which are consistent with observations made in previous studies. The STEMI patients were younger in our study as well as in the study by Xavier et al.6 No age difference was observed between the STEMI and other ACS patient groups in other two studies.4,5 Proportion of males was significantly higher amongst STEMI patients as compared to NSTEMI patients in SMART (80.1% vs. 74.1%) as well as the previous three studies (79.0% vs. 65.0%; 77.3% vs. 75.5%; 81.5% vs. 68.6%).4,5 In our study, presence of hypertension and diabetes as comorbid conditions was observed less frequently amongst STEMI patients (54.8%, 31.9%) as compared to NSTEMI (70.8%, 45.8%) and UA (64.2%, 41.5%) patients. This is consistent with observations reported by Misiriya et al.4 where, the observed frequency of hypertension and diabetes in STEMI patients (29.0%, 24.0%) was significantly lower than that in NSTEMI/UA patients (43.0%, 41.1%). Similarly, the prevalence of hypertension and diabetes observed by Xavier et al.6 amongst STEMI patients (31.4%, 26.9%) was significantly lower than in NSTEMI patients (47.5%, 35.8%). However, while prevalence of diabetes was significantly lower; prevalence of hypertension was significantly higher in STEMI patients as compared to NSTEMI and UA patients.5

In our study as well as in the study reported by Xavier et al.6 STEMI patients had a shorter duration of symptoms before presenting to hospital.

With respect to differences in in-hospital medical management, β-blockers and statins/LLD were used significantly less frequently for STEMI patients (59.9%, 76.3%) as compared to NSTEMI patients (76.7%, 85.8%) in our study. This is consistent with the observations reported by Mohanan PP et al.3 (61.9%, 67.6% for STEMI; 67.6%, 69.7% for NSTEMI) and by Xavier Denis et al.6 (57.5%, 50.8% for STEMI; 61.9%, 53.9% for NSTEMI). However, Misiriya et al.4 reported more frequent use of β-blockers and statins/LLD in STEMI patients (80.5%, 72.4%) than in NSTEMI patients (77.6%, 71.2%).

Re-perfusion (fibrinolytics or Percutaneous transluminal coronary angioplasty [PTCA] or Coronary artery bypass grafting [CABG]) was attempted more frequently in STEMI patients as compared to NSTEMI and/or UA patients in SMART study as well as in the studies.5,6

Possible reasons that may explain differences observed between SMART and previously reported studies include the facts that our study involved only private, tertiary care hospitals located in urban metropolitan cities and having advanced coronary care facilities. This may have bearing on the background health profile and risk factors of study patients, their socio-economic status, time taken to reach hospital and the in-hospital care provided. This fact may also be considered a limitation of our study since the data does not represent medical care practice at large. Another limitation of our study is the fact we included only those ACS patients who survived.
till discharge.

**Conclusion**

UA is the commonest and NSTEMI the least common type of ACS observed in our study. We observed important differences in patient profile, time to hospital presentation, in-hospital acute pharmacological management and vascular interventions performed between the three different types of ACS.

**References**

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Acute Stylet Peritoneal Dialysis in Acute Kidney Injury: The Soul Never Dies

Amith Vijay Leon D’Souza¹, Nishad Raveendran¹, Rajendra Singh Tanwar¹, Piyush Kimmatkar¹, Pankaj Beniwal², Dhananjai Agarwal³, Vinay Malhotra⁴

Abstract

Background: Acute Kidney Injury (AKI) has a significant mortality rate. In developing countries, mortality due to AKI is high due to lack of access to dialysis facilities and related cost. The main goal of International Society of Nephrology (ISN) 0 by 25 initiative is to eliminate deaths due to AKI. Peritoneal dialysis is an underutilized modality in such a scenario. The aim of this study was to look into effectiveness of starting Acute stylet Peritoneal Dialysis (PD) in a resource constraint settings.

Methods: In this prospective study conducted over a year, patients with AKI due to various aetiologies were subjected to Acute stylet PD. The clinical Outcome, demographic, biochemical and treatment data was assessed. Descriptive statistics was used to analyze the data.

Results: A total of 79 (41 anuric, 33 oliguric and 5 nonoliguric) patients were included in the study. Sepsis was the predominant cause of AKI. Recovery was seen in 34% of patients. Patients with relatively preserved urine output recovered with PD in comparison to the anuric patients (p value <0.01). 58% of patients, majority of whom were anuric needed Hemodialysis (HD) in due course (7 ± 3 days) of time. The mortality in our study was 7.5%.

Conclusion: Acute stylet PD can be considered as a modality of Renal Replacement Therapy (RRT) to treat a selected (oliguric, nonoliguric) group of AKI patients and as a bridge therapy for HD in those AKI patients in anuria.

Editorial Viewpoint

• Dialysis facilities are limited to major cities in our country and further restrictions are there due to cost factor.
• This study reaffirms the role of acute stylet PD as a modality of treatment in AKI patients.

Introduction

The prevalence of Acute Kidney Injury (AKI) is increasing worldwide accounting for about 13.3 million cases per year of which 11.3 million are in low and middle income countries. Only limited data is available regarding the epidemiology of AKI from developing countries with half of the studies regarding AKI is from North America while only two studies are from Africa. AKI causes around 1.2 million deaths in developing countries and many of these deaths occur because patient progresses to a stage where Renal Replacement Therapy (RRT) is required and they don’t have access to the same. Dialysis facility is limited to major cities in many of low and middle income countries and its accessibility is further restricted by the cost factor. The International Society of Nephrology has started the “0 by 25” initiative with an aim to bring down the AKI related mortality to Zero by 2025. In India fewer than 10% patients with renal failure have access to RRT.

In our study we assessed whether acute stylet Peritoneal Dialysis (PD) can be used as emergency treatment option in patients with AKI needing RRT. Acute stylet PD which can be done at a low cost in resource limited set ups if found to be effective can be used as a bridge therapy to HD/CRRT and can prevent many deaths due to AKI.

Material and Methods

A prospective study was conducted at SMS Medical College, Jaipur, India between March 2015 and February 2016. In this study we enrolled 79 patients with AKI due to multiple etiologies. These patients needed dialysis, but Hemodialysis was not possible at that moment due to various reasons. Hence, all the patients were started on Acute Peritoneal Dialysis using rigid PD catheter (Acute Stylet...
PD). Skin of the patient was cleaned from Xiphisternum up to groins with chlorhexidine and all aseptic precautions were taken. Artificial ascitis (Priming) was created with two litres of peritoneal dialysis fluid. The rigid catheter was inserted over a trochar into the peritoneum in the midline 2cms below umbilicus. Standard 1.7% dextrose PD solution with bicarbonate (as acetate) buffer was used. Each cycle of PD lasted for 1 hour, with an inflow time of 10 minutes, dwell time of 30 minutes and an outflow time of 20 minutes. Dwell volume was 2 liters and 1 liter for patients with respiratory embarrassment. One session of PD lasted for 35±3 cycles. PD catheters were removed within a period of 48 hours. For a second session of PD (if needed) a new catheter was inserted. Peritoneal fluid sample was taken at the end of each session of PD and was sent for culture and sensitivity.

After each session of PD, the patients were reassessed clinically and by biochemical parameters and non-recovering patients were shifted to intermittent HD. The demographic, clinical, biochemical and treatment data of the cases were analyzed by standard analytical methods.

**Results**

A total of 79 patients were studied. The most common cause of AKI was sepsis (31.64%), followed by post partum AKI (13.92%) and Acute Gastroenteritis (11.3%). The other cause are listed in Table 1. A total of 41 patients were anuric (<100 ml/day) at presentation and 33 were oliguric (<400 ml/day) while 5 patients were having preserved urine output at presentation. Of the total 79 patients initiated on PD, 27 patients recovered with PD (defined as decreasing trend of serum creatinine, improvement in urine output) and 46 patients were converted to HD in an average of 7±2 days period. Six patients expired within 2 days of initiation of PD due to their original disease or its complications but not due to any complications related to PD (Figure 1). Age distribution of the patients recovered with PD is shown in Table 2. 67% of the patients who recovered with PD were oliguric at presentation and 22% were nonoliguric and 11% were anuric (Figure 2). 21 of 38 (55.26%) of patients with relatively preserved urine output recovered with PD while only 6 of 41 (14.63%) anuric patients recovered with PD (p value<0.01). The maximum response to PD was seen in patients with Cardio Renal Syndrome in which 4 out of 5 patients recovered with PD. This was followed by patients with acute gastroenteritis, in which 6 out of 9 patients and in post partum AKI in which 6 out of 11 patients recovered with PD. The etiology wise distribution of patients recovered with PD is given in Table 1. Total number of patients who developed peritonitis (defined by peritoneal fluid culture positivity) was 4(5.06%), while 3 patients developed bleeding from PD catheter site but none had a significant hemorrhage leading to termination of PD or blood transfusion. Three patients had outflow problem for which PD was terminated and they were shifted to HD. No other complications were noted during the procedure. Among 27 patients who recovered with PD, 16 patients required session of PD at a later date.

**Discussion**

The epidemiology of AKI in underdeveloped countries is different from that of developed
world in that AKI is usually community acquired and it affects young previously healthy individuals. The most common etiologies are dehydration secondary to diarrheal disease, malaria, obstetrical causes, sepsis, nephrotoxic drugs and envenomation.\textsuperscript{3,6,23} In our study the most common etiology was sepsis followed by obstetrical causes and acute gastroenteritis. Deaths from AKI can be minimized by timely initiation of RRT. But in developing world, where access to dialysis is limited to major cities many patients succumb to death due to lack of timely dialysis.

In our study all the 79 patients were requiring dialysis due to various indications. But due to various practical problems we were not able to start the patient on HD and all of them were started on Acute PD.

Maximum response rate with Acute PD was seen in patients with Cardio renal syndrome (CRS) i.e. 4 out of 5 patients improved with PD. Various studies have already reported good results of PD in patients with CRS.\textsuperscript{9,10} Patients with acute gastroenteritis and patients with post partum AKI also showed >50\% response rate. Similar results were seen in a study by Hayat et al\textsuperscript{11} which showed a 90\% survival in AKI patients treated with acute stylet PD in which the predominant cause was acute gastroenteritis. None of the patients with burns and acute pancreatitis improved with PD and only 4 of 25 patients with sepsis improved with PD. The efficiency of PD in hypercatabolic states is questioned in various studies.\textsuperscript{7} But a study by Chitalia et al\textsuperscript{8} from India showed that PD can be effective in mild to moderate hypercatabolic AKI. In our study PD was found to be less effective in patients with hypercatabolic states.

Our study showed greater recovery rates among elderly patients with AKI than younger patients with AKI (12/25 patients >50 years and 15/54 years <50 years) with PD. PD is essentially a form of CRRT that correct the volume and metabolic status in a gentle way without producing hemodynamic instability. In patients who are more vulnerable to hemodynamic instability like elderly patients, Peritoneal Dialysis may give better results as compared to hemodialysis.\textsuperscript{10,12}

Probably the most important finding in our study is the relatively better recovery rates among patients with preserved urine output. In other words 21 of 38(55.26\%) of patients with urine output >100 ml recovered with PD while only 6 of 41(14.63\%) anuric patients recovered with PD (p value<0.01). The outcome of AKI patients with anuria is found to be inferior to patients with preserved urine output.\textsuperscript{13,14} In spite of extensive searches we were not able to find any study comparing efficacy of PD in anuric and non anuric AKI. So we couldn’t conclude whether the increased responsiveness shown by non anuric AKI patient in our study is significant or is it just an extension of the better outcome of AKI patients with preserved urine output.

Flexible peritoneal dialysis catheter is preferred over rigid catheters for peritoneal access in acute PD, also as they are associated with lower rates of peritonitis and allows higher dialysate flow rates, but is expensive and needs expertise for insertion.\textsuperscript{15-18} Rigid catheters carries a higher risk of peritonitis, poor dialysate flow rate, catheter dysfunction and bowel perforation.\textsuperscript{19,20} In our study none of the patient had major complications in the form of bowel or bladder perforation, or hemorrhage requiring transfusion. Five patients had catheter dysfunction and three of them had outflow failure requiring termination of PD and in the remaining two patients we were able to continue PD after catheter repositioning. Even though older studies showed a higher rate of peritonitis, recent studies using even rigid catheters showed rate of peritonitis between 2.8\% to 4\%,\textsuperscript{8,16,21,22} In our study the rate of peritonitis was 5.06\%.

Numerous studies have assessed the role of acute PD in AKI\textsuperscript{23} including few studies using rigid catheter for peritoneal access\textsuperscript{8,16,21,22} and there has been a resurgence in the interest in the use of PD in AKI.\textsuperscript{24,25} Three prospective Randomized Controlled Trials (RCTs) compared PD with extracorporeal blood purification therapies of which two were using rigid catheters. Study by Phu et al from Vietnam concluded that Continuous Renal Replacement Therapy (CRRT) is clearly superior to PD in terms of mortality, while one study from India\textsuperscript{22} and one study from Brazil\textsuperscript{26} showed similar mortality rates. Aim of our study was not to compare between PD and other extracorporeal blood purification therapies. Rather our study is an attempt to confirm the efficacy of acute stylet PD as a rescue therapy in AKI in resource constraint settings. In our study 34\% patients recovered with PD and the total mortality rate was 13.9\% which could have been much higher if there was a delay in the initiation of dialysis.

Acute stylet PD can be done in the remotest locations, is less expensive, technically less demanding and requires minimum infrastructure than hemodialysis. Of note, acute stylet PD in Hyderabad, India can save a life with less than 150 US dollars (Nayak KS), the cost for a 72 hours PD session.\textsuperscript{29} In our centre we were able to provide at a cost less than half of this amount. We postulate that acute Stylet PD may be The Aspirin of RRT in AKI.

Limitations of the Study

The delivered dose of PD was not calculated in our study. Till now there are no consensus regarding dosage of dialysis in AKI.\textsuperscript{30} Although evidence to support this target is limited, one of the most widely accepted
recommendation is to target a weekly Kt/V urea of 2.1. A Kt/V in this range can be easily achieved with standard volume PD. And most importantly the dose not necessarily means the efficacy of PD in AKI and other clinical and biochemical parameters should also be considered in patient with AKI.

**Conclusion**

Acute PD can be considered a viable modality option in the treatment of AKI especially in resource constraint/emergent settings. The feasibility and success of PD for AKI depends on appropriate patient selection, proper PD technique, and center experience. We suggest that PD can be considered as a modality of RRT to treat a selected (oliguric, nonoliguric) group of AKI patients. Further it may act as a bridge therapy in AKI patients with anuria in probably reducing the mortality in AKI. It is a simple, inexpensive and efficient modality of RRT that may help in achieving one of the goals of The ISN “0 by 25” initiative.

**References**

Evaluation of Effect of Ascorbic Acid on Ferritin and Erythropoietin Resistance in Patients of Chronic Kidney Disease

N Nand\textsuperscript{1}, S Venu\textsuperscript{2}, AR Deshmukh\textsuperscript{2}, R Mittal\textsuperscript{2}

\textbf{Abstract}

This study was planned to evaluate the effect of short term intravenous ascorbic acid on reducing ferritin and erythropoietin resistance in patients of chronic kidney disease (CKD) on maintenance haemodialysis (MHD).

\textbf{Methods:} Forty adult patients [20 patients in group A with increased serum ferritin level (>500 ng/ml), transferrin saturation (TSAT) \&leq;20\% and 20 patients in group B with normal serum ferritin level (<200 ng/ml), TSAT \&leq;20\%] of end stage renal disease (ESRD) with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. Group A was given intravenous (i.v.) ascorbic acid in a dose of 500 mg once a week after each 4 hours session of dialysis for 3 weeks in a month (total 1500 mg/month), for a period of 3 months along with erythropoietin 6000 IU subcutaneous (S/C) twice weekly without iron therapy. Group B was given erythropoietin (6000 IU S/C twice weekly after each hemodialysis) and intravenous (IV) iron 100 mg/week for 3 months. Hematological and renal investigations, erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (HsCRP), serum ferritin and TSAT were done at baseline and then one monthly intervals for three months whereas intact parathyroid hormone (iPTH) was measured at the start and end of the study.

\textbf{Results:} At the end of 3 months of study, in group A, Hemoglobin (Hb) and TSAT significantly increased while ferritin, HsCRP and erythropoietin resistance index (ERI) decreased significantly. In group B, the increase in Hb and TSAT were not significant statistically while ferritin increased significantly and fall in HsCRP and ERI were not significant statistically. The mean rise in Hb between subsequent months was higher in group A as compared to group B.

\textbf{Conclusion:} Short term i.v ascorbic acid could be a new successful adjuvant in reducing ferritin and erythropoietin resistance and enhancing Hb and TSAT in CKD patients on MHD.

\textbf{Introduction}

The prevalence of CKD as per a recent Indian population based study\textsuperscript{1} was reported to be 17.2\% and anemia is a major co-morbidity of CKD patients. Replacement therapy with recombinant human erythropoietin (EPO) is a key treatment of anemia. The potential role of adjuvant therapies in enhancing the efficacy of EPO in patients receiving maintenance hemodialysis has received increasing attention in recent years.\textsuperscript{2-3} The important reason for adjuvant therapies is that they may help to reduce epoetin requirements or allow dialysis patients to achieve increased hemoglobin concentrations, and derive more cost-effectiveness and greater clinical benefits from epoetin treatment. Recent research highlights how the use of such epoetin adjuvant like ascorbic acid has the potential to improve the efficiency of anemia therapy in patients with kidney diseases.\textsuperscript{4} Ascorbic acid improves
sensitivity to erythropoietin, either by increasing iron mobilization from tissue storage or by way of antioxidant effects. A few published studies during the past decade have addressed this issue. The commonest causes of ESA resistance are non-compliance, absolute or functional iron deficiency and inflammation. Administration of intravenous ascorbic acid to hemodialysis (HD) patients with functional iron deficiency may promote better anemia control and iron utilization. But all these previous studies were small and some were uncontrolled. The results are also varied and till now no study has been done in India. Therefore the present study was designed to know whether short term intravenous ascorbic acid could be a new successful adjuvant in reducing ferritin and erythropoietin resistance in CKD patients on maintenance hemodialysis.

Material and Methods

Forty adult patients [20 patients in group A with increased serum ferritin level (>500 ng/ml), transferrin saturation (TSAT) ≤20% and 20 patients in group B with normal serum ferritin level (<200 ng/ml), transferrin saturation ≤20%] of ESRD with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. All the patients were subjected to detailed history, clinical examination and investigations with special reference to renal, hematological and special investigations included in the study protocol. A pre-informed written consent was obtained in every case. Group A was given intravenous ascorbic acid in a dose of 500 mg once a week after each dialysis for 3 weeks in a month (total 1500 mg/month), for a period of 3 months along with erythropoietin 6000 IU S/C twice weekly after each hemodialysis and iron therapy was not given to this group due to hyperferritinemia. Group B was given erythropoietin (6000 IU S/C twice weekly after each hemodialysis) and IV iron 100 mg/week for 3 months. Hematological and renal investigations, ESR, HsCRP, serum ferritin and transferrin saturation were done at baseline and then one monthly intervals for three months whereas iPTH was measured at the start and end of the study. Serum ferritin was measured using a two-site sandwich immunoassay based on direct chemiluminometric technology, which uses constant amounts of two anti-ferritin antibodies. Serum transferrin was measured using calorimetric method with precipitation. Hs-CRP was measured using latex – enhanced immunonephelometric assay. Intact Parathyroid hormone (iPTH) was measured on the Elecsys 1010 using a sandwich principle. Statistical analysis was performed using SPSS software version – 17.0. For comparison of means of same parameter in two groups unpaired students t test was used and p-values obtained to determine the statistical significance. For comparison of means of same parameter in a single group at two point of time during follow up paired students t test was used and p-values obtained to determine the statistical significance. For comparison of means of different parameters at 0, 1, 2, and 3 months repeated measures analysis of variance (ANOVA) test was used and p-values obtained to determine the statistical significance. The p values were two tailed and probability level of significant difference was set at <0.05 for both paired and unpaired students t test and ANOVA test.

Results

113 Patients of ESRD undergoing regular maintenance hemodialysis were screened. 62 patients were found to be erythropoietin resistant. The serum ferritin and transferrin saturation levels of these 62 patients were repeated and 52 patients with transferrin saturation of 20% or less were selected for the study. Depending on the serum ferritin levels, these 52 patients were divided into two groups A and B. Group A included 25 patients with increased serum ferritin level (>500 ng/ml) and Group B included 27 patients with normal serum ferritin level (<200 ng/ml). Out of these 52 patients, 12 patients couldn’t complete the study. 5 patients (2 in group A and 3 in group B) left the study in between due to some unknown causes and 7 patients (3 in group A and 4 in group B) expired during the study. So finally 40 patients (20 in each group) completed the study. Study included 12 males and 8 females patients in group A and 15 male and 5 female patients in group B. Mean age of the study participants was 45.5±14.54 years in group A and 49.8±12.79 years in group B. Hypertension was the most common cause of CKD (7 patients in each group) followed by diabetic nephropathy (6 in group A and 5 in group B), chronic glomerulonephritis (3 in each group) and obstructive uropathy (3 in each group). 1 patient in each group had chronic pyelonephritis and autosomal dominant polycystic kidney disease was present in 1 patient of group B. The various hematological and renal parameters in group A and group B were alike at baseline. The parameters at 1, 2 and 3 months are shown in Tables 1 and 2.

At the end of 3 months of study, in group A, Hb significantly increased from 6.78±0.75 to 10.01±0.54 g/dl (P <0.001) and TSAT increased from 18.55±1.41 to 34.21±3.25% (P <0.001), while ferritin, ESR, HsCRP and ERI decreased significantly from 1286±217.31 to 814.10±104.46 ng/ml (P <0.001), 53.05±8.09 to 30.08±7.03 mm 1st hr (P <0.001), 3.40±1.73 to 1.87±1.27 mg/dl (P <0.05) and 32.17±9.12 to 22.18±5.24 IU/kg Hb in 100 ml (P <0.001). In group B, the increase in Hb and TSAT were not significant statistically (P=0.359,
Table 1: Basic parameters in two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (Baseline ±S.D.)</th>
<th>Group B (Baseline ±S.D.)</th>
<th>P value (paired)</th>
<th>Group A (At 3 Months ±S.D.)</th>
<th>Group B (At 3 Months ±S.D.)</th>
<th>P value (paired)</th>
<th>Group A vs B (at 3 months)</th>
<th>P Value (unpaired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>6.78±0.75</td>
<td>10.01±0.54</td>
<td>&lt;0.001</td>
<td>7.25±0.88</td>
<td>7.41±0.69</td>
<td>0.359</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>20.35±2.25</td>
<td>30.04±1.62</td>
<td>&lt;0.001</td>
<td>21.13±2.08</td>
<td>22.33±2.07</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.Urea (mg%)</td>
<td>114.10±13.21</td>
<td>100.15±13.09</td>
<td>&lt;0.001</td>
<td>118.4±13.12</td>
<td>107.5±11.44</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>18.55±1.41</td>
<td>34.21±3.25</td>
<td>&lt;0.001</td>
<td>18.69±1.40</td>
<td>19.86±1.61</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Uric Acid (mg%)</td>
<td>7.27±0.88</td>
<td>6.55±0.69</td>
<td>&lt;0.001</td>
<td>6.49±1.08</td>
<td>5.45±1.78</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Phosphate (mg%)</td>
<td>6.45±1.02</td>
<td>5.65±0.69</td>
<td>&lt;0.001</td>
<td>8.1±1.77</td>
<td>7.07±0.99</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.Creatinine (mg%)</td>
<td>5.90±1.28</td>
<td>5.11±0.98</td>
<td>&lt;0.001</td>
<td>6.90±1.08</td>
<td>5.79±1.25</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. albumin (mg/dl)</td>
<td>3.8±0.80</td>
<td>3.89±0.69</td>
<td>0.886</td>
<td>3.59±0.44</td>
<td>3.73±0.44</td>
<td>0.404</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| B. ERI in group A was correlated with baseline hemoglobin and other inflammatory parameters by using Spearman coefficient of correlation and it was observed that ERI was negatively correlated to hemoglobin, hematocrit, serum ferritin and serum albumin (p >0.05) and positively correlated to ESR and HsCRP (p >0.05) but this correlation was statistically not significant. The changes in serum sodium, serum potassium, serum calcium, serum proteins, iPTH, proteinuria and GFR, blood pressure in both the groups were not found to be statistically significant (p>0.05).

**Discussion**

Management of anemia in patients with ESRD with EPO has been a major advance. The use of EPO has decreased the amount of blood transfusions and enhanced the quality of life in the ESRD patients. EPO hyporesponsiveness is reported in HD patients. To resolve EPO hyporesponsiveness, it has been recommended that the dosage of EPO be gradually increased. However, the probable undesirable side effects related to the use of high erythropoietin doses in theory has led physicians to reduce the dosage of erythropoietin.

"Trapped" iron storage or decreased availability of iron is the most common factor for the resistance to the effect of ESAs. Hemodialysis patients may suffer from anemia, despite an iron overload which we call as "functional iron deficiency anemia". This is because in patients with kidney diseases, especially on dialysis, iron tends to be shifted out of circulation into storage tissues, making it less available for erythropoiesis. This syndrome of decreased accessibility of storage iron is referred to as functional iron deficiency anemia. This condition is characterized by low TSAT, despite normal or increased total body iron storage (TSAT ≤20% and ferritin ≥500 ng/ml). Inflammation has also been considered as one of the most important cause of erythropoietin hyporesponsiveness and in turn anemia. Inflammation also causes increased ferritin production and impaired transferrin saturation and this prevents iron delivery to erythrocytes precursors by shunting iron to reticuloendothelial storage pool leading to a state of functional iron deficiency.

In this study, we found that the use of low amount of intravenous ascorbic acid for short duration in patients who had hyperferritinemia and EPO hyporesponsiveness (Group A) improved anemia, transferrin saturation significantly and also reduced the high level of ferritin, inflammatory parameters (HsCRP, ESR) and erythropoietin resistance significantly in these patients. In group B patients with normal ferritin level and EPO hyporesponsiveness, where only erythropoietin and intravenous iron was given (no adjuvant therapy), the rise in hemoglobin, transferrin saturation was not significant and there was also a significant rise in serum ferritin levels, with no significant fall in erythropoietin resistance index, suggestive of persistent EPO hyporesponsiveness.

The results of this study in group A is consistent with the hypothesis that ascorbic acid (a reducing
Excessive vitamin C treatment may worsen uremic-related oxalosis. Hence, supplementation not exceeding 150 mg/day (1050 mg weekly) is still considered a safe dose. Therefore in this study, the dose 500 mg of IV ascorbic acid once a week for 3 weeks in a month (total 1500 mg/month), was less than the recommended regimen. The bioavailability is variable in HD patients receiving oral ascorbic acid. Furthermore, gastrointestinal upset (especially at a large dose) and noncompliance may reduce the efficacy of oral treatment. Therefore we administered ascorbic acid intravenously in this study. We did not measure the plasma oxalate level, which is another limitation of this study. The significant decrease in inflammatory parameters levels in this study in group A could be attributed to amelioration of oxidative stress and inflammation by ascorbic acid.

In this study, ERI was used as an index to evaluate the dose-response effect of EPO therapy. In group A, it was found that there was a fall in ERI at the end of 3 months, which was statistically significant, whereas in group B, the fall in ERI was not significant statistically. This suggests that ascorbic acid given to group A cases has decreased EPO resistance probably by overcoming EPO hyporesponsiveness secondary to functional iron deficiency state through improved iron utilization and anti-inflammatory property. Other workers also showed a decrease in erythropoietin resistance and dose of EPO decreased by 24% in 50% of the patients, 30% in 65% of the patients respectively, following intravenous ascorbic acid therapy.

The main differences of this study from the others are as follows: (1) fixed dose of erythropoietin was used so that the adjuvant effect of ascorbic acid could be evaluated (2) at the time of hyperferritinemia, IV iron was not given to the patients (3) we used low dosage of intravenous ascorbic acid (total 1500 mg/month). The decision to use the lower dosage was based on limiting the probable collection of oxalate in patients, because we were not measuring oxalate levels.

We tried to exclude all other factors responsible for erythropoietin resistance. In this study rain canal water was used which did not contain aluminum. Every bout of infection was treated aggressively as early as possible. Therefore, probable factor which was operative for the less rise in hemoglobin and the marked rise in ferritin level in group B was most probably due to chronic inflammatory state which is essentially a basic feature of CKD.

Therefore short term intravenous ascorbic acid could be a new successful adjuvant in reducing ferritin and erythropoietin resistance in CKD patients on maintenance hemodialysis. However, further studies are needed to determine at what ferritin levels maximum response from intravenous ascorbic acid treatment could be attained, and to ascertain the best dosage interval for optimal effect and minimal possible toxicity.

References


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Study of Carotid Artery Intimomedial Thickness in Patients with Rheumatoid Arthritis and its Co-relation with Severity of the Disease

LA Gauri¹, Q Fatima², S Diggi³, A Khan⁴, A Liyakat⁵, K Nagar⁶

Abstract

Introduction: RA is a chronic inflammatory state, predisposing for atherosclerosis as it is an immunoinflammatory process. This study focuses on use of Carotid artery intimomedial thickness (CIMT) as a marker for subclinical atherosclerosis.

Objective: To study the assessment of atherosclerosis by Carotid Intimo-Medial Thickness (CIMT) in patients with rheumatoid arthritis and Correlation of ultrasonographic findings with severity of disease (using DAS-28 score).

Material and Methods: A prospective, case-control study involving 50 cases of diagnosed RA cases, and 50 healthy control. Sonological examination of the carotid and the vertebral arteries was done using a L&T SEQUINA color Doppler scanner with a linear band probe of frequency 6.6 to 14 MHz's.

Results: This case control study was carried out in 100 subjects (50 cases and 50 controls). Cases comprised of 41 rheumatic women (Mean age 42.08±12.13 yrs) and 9 (mean age 48.4±12.8 years) rheumatic men. Mean CIMT of the study group (0.5996±0.109mm) was significantly greater (p<0.001) than that of control group (0.5290±0.006mm). We observed carotid plaques in 18% subjects of study group compared to 2% in controls (p<0.001). Mean age in the study group was 46.56±12.82 years and that of controls was 46.38±11.69 years (p>0.05). In the study group mean CIMT was significantly increased in RA factor positive patients than in RA factor negative patients. We also calculated the DAS-28 score of the study group subjects and found that 8, 27 and 15 were having Mild, Moderate & severe disease activity respectively.

Conclusion: CIMT has significant correlation with the age, and CIMT increases with age. Mean CIMT was found to be more with RF+(ve) patients indicating acute inflammation also has a role. When compared, the mean CIMT in each DAS sub group the result was found to be statistically insignificant.

Editorial Viewpoint

• Rheumatoid arthritis predisposes to atherosclerosis.
• This study finds carotid intimo-medial thickness increased in rheumatoid factor positive patients.

Important complication of RA, with coronary artery disease (CAD) being the major cause of mortality in these patients¹. Both men and women with rheumatoid arthritis are twice as likely to suffer from myocardial infarction as compared to gender population. Carotid artery intimomedial thickness (CIMT) is a reliable, simple and noninvasive marker of subclinical atherosclerosis.²

Noninvasive techniques such as B-mode ultrasound can directly assess the intima-media thickness (IMT), which corresponds to the thickness of the histologic intima and media.³,⁴

Intimomedial thickness of the common carotid artery was recommended as a useful parameter to assess the presence of coronary artery disease in a publication of the American Heart Association.⁵

Lesions found on coronary arteriography correlate with the

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Introduction

Rheumatoid arthritis (RA) offers a prime example of a chronic inflammatory state. Atherosclerosis is emerging as an
presence of lesions in the carotid arteries. The increasing incidence of cardiovascular disease in the Indian society and the possible utility of the simple technique of IMT measurement were the motivation to undertake this study.

**Aims and Objectives**

1. To study the assessment of atherosclerosis by Carotid Intimo-Medial Thickness (CIMT) in patients with rheumatoid arthritis.
2. Correlation of ultrasonographic findings with severity of disease (using DAS-28 score).

**Material and Methods**

This study was conducted in Rheumatology Division, Department of Medicine, S.P. Medical College attached to P.B.M. associated group of hospitals during June 2009 to October 2010.

This was a prospective, case-control study involving 50 patients of RA attending indoor as well as outdoor clinic in the department of medicine and 50 healthy, age (within one year) and sex matched controls. Adult patients more than 16 years of age and satisfying the American College of Rheumatology (formerly the American Rheumatism Association) criteria for RA were included in the study only if they had disease duration greater than 5 years. Patients with disease onset below 16 years, disease duration less than 5 years, and RA overlap with other rheumatic diseases were excluded from the study.

**Diagnostic Criteria**

The study was conducted after approval by the departmental ethics committee. All the patients were subjected to clinical evaluation in the form of detailed history and physical examination. The laboratory investigations carried out in RA patients included hemoglobin, total and differential white cell counts, platelets, ESR, blood glucose, liver and kidney function tests, serum lipids, ECG, chest X-ray, urine analysis, C-reactive protein and rheumatoid factor. Thyroid profile was done if thyroid dysfunction is clinically suspected. Plain radiographs of the hands and wrists were taken.

Patients and control subjects exhibiting traditional risk factors like hypertension (blood pressure >140/90 mm Hg), smoking, diabetes mellitus, and clinically manifest atherosclerosis by way of CAD, peripheral vascular disease (PVD), cerebrovascular disease etc. were excluded from the study. Similarly, patients and controls known to have dyslipidemia and on treatment for the same were excluded. All the controls were subjected to a thorough clinical evaluation and estimation of blood sugar and lipids. Control subjects and RA patients found to have dyslipidemia after enrolment in the study were included in the analysis.

**Instrumentation**

Sonological examination of the carotid and the vertebral arteries was done using a L&T SEQUINA color Doppler scanner with a linear band probe of frequency 6.6 to 14 MHz's.

Ultrasound examination of the carotids was carried out both in cases and controls. The various factors that were studied include continuous variables like age, BMI, disease duration, systolic and diastolic blood pressure, lipids and categorical variables like gender, seropositivity status (presence or absence of rheumatoid factor), and erosions on radiographs.

DAS-28 score was calculated by the following formula:

\[ \text{DAS28} = 0.56 \sqrt{(\text{tender joints})} + 0.28 \sqrt{(\text{swollen joints})} + 0.70 \text{Ln(ESR)} + 0.014 \text{VAS} \]

**Results**

Table 1 shows patient profile. In the group having CIMT <0.55mm Mean CIMT of control group was 0.4975+0.004mm and that of study group was 0.5010+0.003mm. When we compare these means the results was statistically found insignificant (p>0.05) while in the group having CIMT >0.55mm mean CIMT of the control group was 0.6100+0.005mm and that of study group was 0.6710+0.008mm and the difference was found statistically significant (p<0.001).

We arbitrarily divided patients in two age groups i.e. < 50 and >50 years. In the age group < 50 years there were total 29 subjects in control and study groups each. When we compared mean CIMT of control and study group, the difference was found to be statistically highly significant (p=0.005) similarly in the age group >50 years the difference was also statistically highly significant (p=0.001) between control and study (n=21 each) groups.

In the control group when subjects were grouped according to age <50 and >50 years the mean CIMT was found to be increased and the results when compared were statistically highly significant (p=0.004), similar results were found in the study group where the difference was statistically highly significant (p<0.001) (Table 2).

In our study, out of 50 subjects of study group, rheumatoid factor was positive in 34(68%). Mean CIMT of patients having rheumatoid factor positive and negative was 0.6353+0.109mm and 0.5238+0.006mm respectively and the result was statistically found to be highly significant (p<0.001) on comparison (Table 3).

The subjects of study group were classified according to DAS-28 score to mild (DAS-28 <3.2); moderate (DAS-28 >3.2 -<5.1) and Severe (DAS-28 >5.1) rheumatoid arthritis group (Table 4). When we compared the mean CIMT of subjects belonging to mild (n=8) with mean CIMT 0.5713+0.009mm and moderate
Mean CIMT of the study group subjects (0.5996±0.109mm) was significantly greater (p<0.001) than that of control group subjects (0.5290±0.006mm). Similar results were obtained by Mahajan et al. 7

We observed carotid plaques in 18% of subjects of study group compared to 2% in control group (p<0.001). Similar results were found by Mahajan et al. 7

The mean age of the study group subjects was 46.56 ±12.82 years and that of control group was 46.38±11.69 years (p>0.05).

When we compared the mean CIMT according to the age group ≤50 years the mean CIMT of study group subjects was increased significantly (p=0.005) in compared to control group, in age group >50 years the mean CIMT of study group subjects was increased highly significantly (p=0.001) compared to control group subjects.

Within the control group mean CIMT of subjects having age >50 years compared to ≤50 years was statistically significant (p=0.004) similarly within the study group mean CIMT of subjects having age >50 years was increased significantly (p<0.001) in comparison to subjects having age ≤50 years i.e. age has a significant correlation with the increase in CIMT both in study and control subjects. Similar results were obtained by Mahajan et al. 7

When we compared other parameters like sex, blood pressure, pulse rate, respiratory rate, blood urea, serum creatinine, blood sugar, BMI and hemoglobin the results were found to be insignificant (p>0.05) within the study and control groups subjects and the effect of these on CIMT was also found to be insignificant similar to other previous studies.

When we divided study group subjects according to positivity of rheumatoid factor and compared mean CIMT, we found mean CIMT to be significantly increased in rheumatoid factor positive patients. Similar result was found by Ristic

### Table 1: Patient profile

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study group</th>
<th>Control group</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.56 ±12.82</td>
<td>46.38 ±11.69</td>
<td>0.073</td>
<td>0.942</td>
</tr>
<tr>
<td>BP systolic</td>
<td>121.96 ±7.93</td>
<td>118.92 ±8.56</td>
<td>1.841</td>
<td>0.069</td>
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<tr>
<td>BP diastolic</td>
<td>79.80 ±5.00</td>
<td>77.84 ±3.15</td>
<td>2.344</td>
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<td>Pulse rate</td>
<td>78.52 ±6.35</td>
<td>76.64 ±5.78</td>
<td>1.549</td>
<td>0.125</td>
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<tr>
<td>Respiratory rate</td>
<td>16.44 ±1.36</td>
<td>15.74 ±2.49</td>
<td>1.741</td>
<td>0.085</td>
</tr>
<tr>
<td>BMI</td>
<td>22.21 ±1.66</td>
<td>22.85 ±1.01</td>
<td>2.325</td>
<td>0.022</td>
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<tr>
<td>Hemoglobin (Hb)</td>
<td>9.69 ±1.39</td>
<td>9.75 ±0.81</td>
<td>0.283</td>
<td>0.778</td>
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<tr>
<td>Blood urea (BU)</td>
<td>25.99 ±8.12</td>
<td>26.14 ±4.08</td>
<td>0.113</td>
<td>0.913</td>
</tr>
<tr>
<td>Serum creatinine (SC)</td>
<td>0.79 ±0.24</td>
<td>0.73 ±0.12</td>
<td>1.429</td>
<td>0.156</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>89.36 ±25.92</td>
<td>88.20 ±6.36</td>
<td>0.307</td>
<td>0.760</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>187.48 ±35.68</td>
<td>154.74 ±22.64</td>
<td>5.478</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>119.14 ±40.67</td>
<td>94.96 ±15.57</td>
<td>3.926</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>49.22 ±29.33</td>
<td>45.92 ±6.96</td>
<td>0.774</td>
<td>0.441</td>
</tr>
<tr>
<td>LDL</td>
<td>100.48 ±32.71</td>
<td>74.88 ±10.03</td>
<td>5.291</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL</td>
<td>18.48 ±7.99</td>
<td>17.04 ±3.50</td>
<td>1.166</td>
<td>0.246</td>
</tr>
</tbody>
</table>

### Table 2: Distribution of cases according to CIMT in both groups

<table>
<thead>
<tr>
<th>CIMT group (mm)</th>
<th>Study group</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.55</td>
<td>31</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>&gt;0.55</td>
<td>19</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of CIMT in study groups according to disease duration

<table>
<thead>
<tr>
<th>Disease Duration (yrs)</th>
<th>Total CIMT (mm)</th>
<th>Mean ± SD</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7</td>
<td>0.5045 ±0.003</td>
<td>6.188</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&gt; 7-10</td>
<td>0.4817 ±0.003</td>
<td>5.364</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>0.5200 ±0.004</td>
<td>5.089</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Comparison of Mean values of CIMT according to DAS-28 score group

<table>
<thead>
<tr>
<th>DAS-28 score group</th>
<th>Mean ± SD</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3.2</td>
<td>0.5712 ±0.010</td>
<td>0.251</td>
<td>0.803</td>
</tr>
<tr>
<td>&gt;3.2-&lt;5.1</td>
<td>0.5815 ±0.117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3.2-&lt;5.1</td>
<td>0.5815 ±0.117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5.1</td>
<td>0.5996 ±0.109</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(n=27) disease activity with mean CIMT 0.5815±0.117mm the result was found statistically insignificant and similar results were found when the subjects of moderate and severe (n=15) disease activity with mean CIMT of 0.5996±0.109mm were compared (p>0.05).

In our study, out of 50 subjects of study group, rheumatoid factor was positive in 34(68%). Mean DAS-28 score of patients having rheumatoid factor positive and negative was 4.2535±1.189 and 4.7825±1.296 respectively and the result was statistically found to be insignificant (p>0.05) on comparison.

### Discussion

This case control study was carried out in 100 subjects (50 cases and 50 controls). Cases comprised of 41 rheumatic women (Mean age 42.08±12.13 yrs) and 9 (mean age 48.4±12.8 years) rheumatic men. The control group comprised of 50 unrelated sex and age matched (within one year) healthy controls. Mean CIMT of the study group subjects (0.5996±0.109mm) was significantly greater (p<0.001) than that of control group subjects (0.5290±0.006mm). Similar results were obtained by Mahajan et al. 7

We observed carotid plaques in 18% of subjects of study group compared to 2% in control group (p<0.001). Similar results were found by Mahajan et al. 7

The mean age of the study group subjects was 46.56±12.82 years and that of control group was 46.38±11.69 years (p>0.05). When we compared the mean CIMT according to the age group ≤50 years the mean CIMT of study group subjects was increased significantly (p=0.005) in compared to control group, in age group >50 years the mean CIMT of study group subjects was increased highly significantly (p=0.001) compared to control group subjects.

Within the control group mean CIMT of subjects having age >50 years compared to ≤50 years was statistically significant (p=0.004) similarly within the study group mean CIMT of subjects having age >50 years was increased significantly (p<0.001) in comparison to subjects having age ≤50 years i.e. age has a significant correlation with the increase in CIMT both in study and control subjects. Similar results were obtained by Mahajan et al. 7

When we compared other parameters like sex, blood pressure, pulse rate, respiratory rate, blood urea, serum creatinine, blood sugar, BMI and hemoglobin the results were found to be insignificant (p>0.05) within the study and control groups subjects and the effect of these on CIMT was also found to be insignificant similar to other previous studies.

When we divided study group subjects according to positivity of rheumatoid factor and compared mean CIMT, we found mean CIMT to be significantly increased in rheumatoid factor positive patients. Similar result was found by Ristic.
et al, Cuomo et al and Churakov et al while Mahajan et al did not find any significant correlation.

When we studied the mean CIMT of study group subjects according to the disease duration we found that with increased disease duration, there was an increase in mean CIMT and the result was statistically highly significant (p<0.001) and similar result was found by Mahajan et al. Similar result was found by Carroti et al, Cuomo et al and Churakov et al.

We also calculated the DAS-28 score of the study group subjects and found that 8 were having mild, 27 were having moderate and 15 were having severe disease activity. Out of 8 mild, 5 subjects were having DAS-28 score <2.6 i.e. they were in remission. When we compared the mean CIMT in each DAS sub group the result was found to be statistically insignificant. Similar result was found by Carroti et al, Cuomo et al and Singh et al.

When we compared the mean CIMT of male and females in each DAS sub group i.e. mild, moderate and severe the result was statistically insignificant i.e. gender does not have influence on the mean CIMT. Similarly Radovits et al in his study concluded that Gender does not have influence on DAS-28 score >3.2.

When we compared DAS-28 score according to rheumatoid factor presence or absence, no statistically significant result was found (p>0.05). Same was the observation by Leeb et al.

When we compared DAS-28 score according to disease duration ≤7 and >7 years the results were statistically insignificant (p>0.05). Same was the observation by Leeb et al.

**Conclusion**

Of the various parameters assessed in this study, the following results were obtained. CIMT has significant co-relation with the age, and CIMT increases with age. Mean CIMT was found to be more with RF+(ve) patients indicating acute inflammation also has a role. There is no co-relation of CIMT with Sex, blood pressure, respiratory rate, blood urea serum creatinine, blood sugar, BMI and hemoglobin. When compared, the mean CIMT in each DAS sub group the result was found to be statistically insignificant.

**References**

Indian Adolescent Living with HIV-AIDS: Current Clinical Scenario

Kavita S Joshi¹, Bhushan D Bhaware², Amar R Pazare³

Abstract

Introduction: Statistics suggest that, HIV has now largely become the disease of young patients. Hence, the adolescent HIV/AIDS needs to be handled and managed separately from adult HIV. Relatively fewer Indian data exist to characterize the associations in adolescents and young adults infected with HIV disease. The present study explores the current challenges in the management of HIV infected adolescents.

Objectives: The study was aimed at evaluating, relationship between CD4 count and duration of antiretroviral therapy (ART), effects of ART on body mass index and the adverse effects of antiretroviral drugs in adolescent HIV positive patients.

Methods: This was a cross-sectional study involving 60 HIV positive adolescent patients attending tertiary care Institute KEM Hospital, Parel over duration of one year conducted at Mumbai. Patients on ART between age group 12 to 19 years. ART naïve patients were excluded from the study.

Results: 60 adolescent HIV positive patients attended our OPD including 37 males (61.67%) and 23 females (38.33%). The most common mode of transmission was vertical (80%). Education level was: school dropouts – 15%, primary education – 30%, Completed SSC – 31.7%, higher secondary – 23%. Among ADRs were 12 (63.15%) cases of anaemia due to Zidovudine, 4 (21.05%) hepatitis due to Nevirapine, 2 (10.52%) Tenofovir induced AKI and 1 (5.26%) Nevirapine rash. Wilcoxon matched pairs test showed a highly significant increase in the BMI (p <0.0001) post therapy. The mean CD4 of the patients at baseline and current presentation was 295.57 ± 109.81 and 630.93 ± 188.70 cells/mm³ respectively. The CD4 count was seen to be increasing with the increase in the duration of HAART treatment.

Conclusion: High efficacy of HAART and availability of free ART under government programme has increased the duration of survival of the adolescent population with HIV. Treatment with HAART showed a favourable response with a statistical significant increase in CD4 count. Longer the duration of HAART, higher was the gain in CD4 count. Indian adolescent receiving long term ART, Lipodystrophy is not a troubling issue. Indian adolescent seems to be more tolerance of ART than the other parts of world.

Introduction

Recent times have witnessed a transition in the prognosis of Human Immunodeficiency Virus (HIV) infection, from a fatal disease to a chronic manageable disease. Into the third decade of the HIV and Acquired Immunodeficiency Syndrome (AIDS) epidemic, there are 34 million people worldwide living with HIV, five million of whom are aged between 15 and 24 years.¹ Adolescents have been described as the ‘fulcrum’ and the ‘centre of the epidemic’, with 42% of new HIV infections occurring in this age group in 2010.² In India, although adolescent and youth ages (ages 15-29 years) account for almost 25 per cent of the country’s population, a substantial 31 per cent of these are affected with AIDS.³ This suggests that young people are at a high risk of contracting HIV infection. These statistics suggest that HIV, has now largely become, the disease of young patients. Hence, the adolescent HIV/AIDS, a separate epidemic, needs to be

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handled and managed separately from adult HIV.

**Adolescents have been** categorized as a vulnerable group for HIV infection due to many reasons. Adolescents undergo a range of psychosocial developments while growing physically. Young people are more vulnerable to Sexual transmitted diseases (STIs) than adults. Physiologically, girls are more vulnerable to STIs than boys. Also, sex education, unsafe sexual practices, social norms, lack of information, exposure of young children to drug injections etc. contribute to this risk.3

It may be important to review the appropriateness of antiretroviral therapy (ART) dosing in younger adolescents as children transition from paediatric doses into adult doses.4 Adequate options for paediatric appropriate antiretroviral drugs may also play a role in the outcomes in adolescents. Often choices are limited and formulations are inappropriate. Adequate adherence to medication may on the other hand, be an important factor in older adolescents and youth where all of the psychosocial factors may play a role in an individual’s ability or willingness to be adherent.5

Highly active anti-retroviral therapy (HAART) has changed the face of HIV/AIDS by causing a dramatic decrease in HIV-related morbidity and mortality.6 However, adverse events such as vomiting, anaemia; hepatitis, pancreatitis, peripheral neuropathy, lipoatrophy, lipodystrophy, and Steven Johnson Syndrome have been reported with the use of HAART.7,8 The prevalence of adverse events related to these drugs may rise with increased use of antiretroviral therapy.

Anti-retroviral treatment has also been associated with metabolic complications, alterations in body fat distribution and chronic kidney disease.9 Less data exist to study the associations in adolescents and young adults infected with HIV in early childhood. The study was aimed at evaluating, relationship between CD4 count and duration of antiretroviral therapy (ART), effects of ART on body mass index and the adverse effects of antiretroviral drugs in adolescent HIV positive patients.

**Methods**

**Study design**

This was a cross-sectional study involving 60 HIV positive adolescent patients on HAART attending OPD over duration of one year.

**Setting / Source of data**

KEM Hospital, Parel, Mumbai.

**Methodology**

Patients on HAART between age group 12 to 19 years were included in this study. 74 patients fulfilling inclusion criteria were screened for the study. 14 patients denied consent, hence sixty consecutive HIV positive adolescent patients attending tertiary care institute of metropolitan City of Mumbai who fulfilled the inclusion criteria were recruited over a period of one year. Institutional Ethics Committee (II) Seth G S Medical College and KEM Hospital granted permission for this study. Written informed consent of the patients or their legal guardians was obtained. Assent was taken as and when required. The detailed history of the patients, including the details of opportunistic infections, treatment history and adverse drug events, was recorded. Demographic details such as height and weight at the time of diagnosis, as obtained from patient’s case records, and the time of recruitment in the study were also recorded. Detailed clinical examination was performed by the clinicians who assessed for fat loss in the extremities, buttocks, face and accumulation of fat in the abdomen and dorsocervical spine. All data was recorded at one time and compared to data at the time of diagnosis available from previous records.

**Statistical Analysis**

Sample size was calculated using Raosoft formula. Descriptive statistics were used. Wilcoxon matched pairs test was used to compare parameters from baseline to post therapy.

**Results**

60 adolescent HIV positive patients were studied which included 37 males (61.67%) and 23 females (38.33%). The age range of these patients was between 12 to 19 years with a mean age of 16.73 years. The baseline height was 132.63 cm which showed a significant increase to 145.27 cm at the time of assessment. This increase in height is attributed to the accelerated growth phase during the adolescent period.

The patient characteristics like demographics, mode of transmission, parents survival status, level of education, clinical staging and opportunistic infection are summarised in Table 1. It was also noted that the significantly higher number of school dropouts had both parents deceased (Table 2). The correlation between school drop out with parents survival p=0.0011 using Fishers Exact test. This shows that schooling of HIV positive adolescents is affected if both the parents are deceased. The mean duration of ART in the patients included in the study was 3.7±1.66 years.

Common Opportunistic infections in the study patients infected with HIV is depicted in Table 1 and clinical staging of the study patients is depicted in Figure 1.

The adherence of the patients to the therapy was 93.23±12.8%. Common treatment regimens used were Zidovudine, Lamivudine and Nevirapine (ZLN) in 48%, Stavudine, Lamivudine and Nevirapine (SLN) in 25%, Tenofovir, Lamivudine and Nevirapine (TLN) in 13.33%, Zidovudine, Lamivudine and Efavirenz (ZLE ) in 8.33%
of patients showed a significant increase after starting HAART. The mean age of the patients affects the growth parameters such as height, weight and BMI. There was significant improvement in the haemoglobin levels compared to the baseline as shown in the Table 3 with other baseline investigations.

**CD4 Count**

The mean CD4 of the patients at baseline and current presentation (Figure 4) was 295.57 ± 109.81 and 630.93 ± 188.70 cells/mm3 respectively. On comparing it was found that the mean current CD4 count was significantly higher as compared to that at baseline. *p<0.0001 Wilcoxon matched pairs test. The CD4 count was seen to be increasing with the increase in the duration of HAART treatment (Figure 5).

**Discussion**

Adolescents are a subset of the population between the age group of 12-19 years. However, many published studies carried out on HIV infected adolescent patients, have included patients over 19 years of age as adolescents in their studies.10–12 Hence, the data obtained from these studies may not represent the adolescent population exclusively.

In our study, the proportion of males was more than the females (61.67% and 38.33% respectively). In studies by Murphy DA et al,15 Ding H et al14 related to REACH project and Modi M et al,15 the proportion of adolescent females participating in the study was much more (77%, 73.4% and 67% respectively) as compared to males. However, in a study by Martinez J et al,16 the proportion of males was more i.e. 60%. Thus, the proportion of males and females in the adolescent group vary in different studies. Our study was conducted in a tertiary government health care setup in the metropolitan city of Mumbai, which is commonly accessed by people belonging to the lower socioeconomic status. To add to it, the social taboo associated with HIV negatively impacts the access of such facilities by women. This could possibly be the reason for higher percentage of males in our study.

Vertical transmission was found to be the most common mode of transmission of HIV, which was seen in 80% of the patients in our study, similar to other studies. However, vertical transmission was higher in our study compared to other studies, viz. Modi M et al15 (64%) and Harrison A et al17 (73.4%). Modi M et al study was conducted in 2001, during which period ART was not freely available. Availability of ART freely in recent years have led to prolonged survival of patients contracting HIV perinatally. Also, transmission through sexual route was seen in fewer patients (5%) in our study. This could be attributable to changing trends in the pattern of sexual behaviour in adolescents, which is possibly due to school health and sex education programmes resulting in increased awareness about HIV prevention. Blood transfusion was responsible for HIV infection in 10% patients in our study. Use of 4th generation HIV ELISA tests, which are more sensitive and specific for detection of HIV, may be responsible for better screening of donors and hence, lesser incidence in our study.

At the time of diagnosis, most of the patients were in Stage 1 (41.67%) and Stage 2 (23.33%), while few were in Stage 3 (20%) and Stage 4 (15%). At the last visit,
however, 95% patients were in Stage 1 and 5% were in Stage 4. Thus, early initiation of HAART therapy showed a decreased incidence of opportunistic infections.

53(88.33%) of patients had BMI less than 50 percentile at diagnosis. The BMI of the patients increased significantly at the last visit compared to the baseline. It was also noticed that the rise in BMI to normal was significant after starting HAART. This implies that ART has a positive influence on BMI indicating an improved health status of the patients. There have also been contradicting evidences from other studies suggesting that the increase in BMI is seen only in adults and not adolescents (Tremeschin MH et al)\(^\text{18}\) and also that there is no increase in BMI post-HAART therapy (Verweel G et al)\(^\text{19}\). These varied results highlight the possibility of increase in BMI only if the baseline BMI at the initiation of HAART is very low. In our study, the baseline BMI was less than 5 percentile in 40% boys and 35% girls below 17 years, which would likely confirm this hypothesis. Piloya T et al showed adolescents who had been switched to Zidovudine (AZT) based regimen but were previously exposed to Stavudine (d4T) for at least six months and children on d4T, 55% had abnormal fat redistribution.\(^\text{20}\) In our study there was no loss of fat from any part of the body during the follow up of the patients. Though 33% of the patients received Stavudine-based regimen, lipodystrophy was not found. Serum Cholesterol and Triglyceride levels were found normal on ART. Our study does not concur with study conducted by National Autonomous University of Mexico by María Rocio Muñoz and colleagues.\(^\text{21}\) They found 54% of patients (2-18 years) developed changes in metabolic parameters or redistribution of fat. The absence of lipodystrophy, hyperlipidaemia, redistribution of fat or presence of metabolic syndrome was not seen in Indian adolescents in spite of long durations of ART drugs may be because of poor baseline BMI. Also the patients from our resource poor lower socio economic group have limited access to refined food; our facility is government run tertiary care centre. Vigano A et al proved that replacing Stavudine with Tenofovir and protease inhibitor with Efavirenz for 96 weeks in lipoatrophic paediatrics patients led to a restoration of physiological fat accrual.\(^\text{22}\) We are not facing such challenges as of now.

The mean CD4 counts of patients in our study were 295.57 and 630.93 at the baseline and last visit, respectively. This highly significant rise in CD4 counts in patients on HAART highlights the efficacy of HAART in HIV infected
Table 3: Blood investigations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Current</th>
<th>p value</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.81 ± 1.059</td>
<td>10.95 ± 1.11</td>
<td>0.027</td>
<td>Wilcoxon matched pairs test</td>
</tr>
<tr>
<td>Total leucocyte count</td>
<td>4892.2 ± 1132</td>
<td>4901.7 ± 1239.5</td>
<td>0.903</td>
<td>Wilcoxon matched pairs test</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>83.28 ± 8.79</td>
<td>81.15 ± 6.38</td>
<td>0.027</td>
<td>Wilcoxon matched pairs test</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150: 60 (100%)</td>
<td>&gt;150: 0</td>
<td>0.1187</td>
<td>Fisher’s exact test</td>
</tr>
<tr>
<td></td>
<td>&gt;150: 4 (6.67%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

adolescents. Also, there was a trend towards increase in CD4 count with the increase in duration of HAART. The CD4 count at the end of one year of ART was 491.5, which increased to 994.5 in patients who received HAART for approximately 8 years. The CD4 count typically increases at a rate that correlates with time, baseline CD4 count and viral load suppression. Age at the time of initiation of HAART treatment also plays an important role in the efficacy of therapy. In older patients, the CD4 T cells do not increase as much as that seen in younger people because of age-related degeneration of thymus.

**Limitation of the study**

Given the limitation of a cross-sectional study, a prospective observational study of longer duration with a larger sample size is required for in understanding the trends in the parameters associated with adolescent HIV. Viral load would have been better marker for effect of ART, however it could not be done due to financial constraints.

**Conclusion**

The present study shows significant beneficial effect of HAART in adolescents with HIV infection. High efficacy of HAART and availability of free treatment has increased the duration of survival of the adolescent population with HIV. This was evident from the fact that the presence of higher percentage of patients in the study, infected via vertical transmission as neonates, reached adolescence. Treatment with HAART showed a favourable response with a statistical significant increase in CD4 count. Longer the duration of HAART, higher was the gain in CD4 count seen. Among the Indian adolescent receiving long term ART, Lipodystrophy is not a troubling issue. Indian adolescent seems to be more tolerance of ART than the other parts of world. Increased awareness and decreased social taboo associated with HIV seem to be responsible for increased adherence to HAART.

**Acknowledgements**

The authors wish to acknowledge the contribution of Dr. Rajani Rokade, from Pharma Soulz, for assistance with manuscript preparation.

**References**

sexually transmitted infections among adolescent girls infected with HIV. Sex Transm Infect 2007; 83:468–469.


SOFA Score and Critically Ill Elderly Patients

Vishal Gupta¹, Niteen D Karnik², Dhiraj Agrawal³

Abstract

Objective: To study correlation between SOFA Score and Outcome in Elderly Patients admitted In Intensive Care Unit.

Method: A single centre prospective observational study in Medical Intensive Care Unit (MICU) of large teaching Institute. A total of 84 elderly patients were studied and the outcome was correlated with SOFA Score at admission and 48 hours after admission.

Results: Elderly patients constituted 10.94% (84 out of 764) of total MICU admissions. Critically ill elderly patients had a very high mortality of 73.8% (62 out of 84), as compared to their younger counterparts with mortality rates of 43.53% (296 out of 680) with a highly significant P value of <0.0001. The mean SOFA scores are statistically significantly higher at both time points in the expired group (7.84±3.74 and 8.64±3.72 respectively on admission and at 48 hours).

Conclusion: There is positive correlation between mortality and SOFA score at admission and at 48 hours. SOFA score thus can be effectively used as predictive scoring system for critically ill elderly patients.

Introduction

SOFa (Sequential Organ Failure Assessment Score) has been validated recently by European society of Intensive Care Medicine and Society of Critical Care Medicine as a marker of sepsis.¹

The SOFA score was created in a consensus meeting of the European Society of Intensive Care Medicine in 1994 and further revised in 1996.² This score was developed to quantify the severity of patient’s illness, based on the degree of organ dysfunction data on six organ failures and are scored on a scale of 0-4³ (Table 1).

Sequential assessment of organ dysfunction during the first few days of ICU admission is a good indicator of prognosis. Elaborate scoring systems like Acute Physiology and Chronic Health Evaluation (APACHE) II and III and Logistic Organ Dysfunction System (LODS), used as markers of severity and Intensive Care Unit (ICU) mortality, are cumbersome. Recently predictive value of SOFA score for in-hospital mortality was found equivalent to more complex LODS in 7932 ICU encounters with suspected infection.⁴ Studies have used SOFA scores on admission, at 48 hours and even the mean and highest SOFA score as useful predictors of outcome.⁵,⁶

Demographic transition has led to an expanding geriatric population universally with an increase in elderly (age>60 years) patients requiring ICU care. Geriatric patients may not get a priority for ICU beds in resource restricted developing countries. Severity scores and organ failure scores can be useful in predicting outcomes, justifying ICU admissions and guiding treatment in geriatric patients. Studies on geriatric patients in Indian ICUs are few.⁷ Hence we decided to study the elderly patients in critical care setting and to use the SOFA score for risk stratification and outcome.

Material and Methods

The study was conducted in Medical and Neurological Intensive Care Unit (MNICU) of a tertiary care teaching hospital as a single centred prospective observational study. All critically ill elderly patients (age≥60 years) admitted in the MNICU over 12 months period from 01.05.2013 to 30.04.2014 were enrolled. Sample size was estimated to be 60 based on admission in MNICU in previous year. Death, transfer out or discharge from MNICU were study endpoints.

Study Procedure

The study was conducted in compliance with the protocol and regulatory requirements. Approval of Ethics Committee was taken prior to the initiation of the study. Patients who were 60 years of age or older and admitted in
Results

A total of 764 patient were admitted in MNICU in the one year study period, out of them 84 (10.94%) were elderly (Table 2). 51 (60.71%) were males and 33 (39.29%) patients were females respectively. (M: F =1.54:1).

The maximum number of patients 65 (77.38%) was in the age group of 60-70 years followed by 14 (16.66%) in the group 71-80 years and 5(5.95%) in age group of more than 80 years. Mean age was 67.14+6.8 years.

Table 1: The SOFA score (0-4) based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems

<table>
<thead>
<tr>
<th>SOFA Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration; PaO2/FiO2, mmHg</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200</td>
<td>≤100</td>
</tr>
<tr>
<td>Coagulation; platelets*10^9/mm³</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤100</td>
<td>≤50</td>
<td>≤20</td>
</tr>
<tr>
<td>Liver; bilirubin, mg/dL</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2-5.9</td>
<td>6-11.9</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Cardiovascular; hypotension</td>
<td>No MAP &lt;70 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS; Glasgow coma scale</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>≤3</td>
</tr>
<tr>
<td>Renal; creatinine, mg/dL or urine output, mL/day</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2-3.4</td>
<td>3.5-4.9</td>
<td>≥5</td>
</tr>
</tbody>
</table>

Table 2: Incidence of elderly patients admitted in MNICU (N=764)

<table>
<thead>
<tr>
<th>Total admissions</th>
<th>N=764</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>84</td>
<td>10.94%</td>
</tr>
<tr>
<td>Nonelderly</td>
<td>680</td>
<td>89.06%</td>
</tr>
</tbody>
</table>

MNICU during the 12 months study period were included after obtaining written and informed consent from patients/patients relatives. The relevant history, clinical examination findings, comorbidities and etiological history were entered in case record form. SOFA score of every patient was calculated on admission and at 48 hrs. Death, discharge or transfer to general wards were study endpoints. Patients if readmitted to the ICU were only included in the study on first admission only. All the investigations, ventilator related parameters and treatment given were entered in the case record form. The length of MNICU stay and outcome were determined. The statistical tests used were students T test, Mann Whitney test and Spearman’s Rho analysis.

Table 3: Various premorbidities in elderly patients admitted in MNICU

<table>
<thead>
<tr>
<th>Premorbidities</th>
<th>N=84</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>50</td>
<td>59.52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27</td>
<td>32.14</td>
</tr>
<tr>
<td>Heart diseases*</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>9</td>
<td>10.71</td>
</tr>
<tr>
<td>Old Koch’s’</td>
<td>8</td>
<td>9.52</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7</td>
<td>8.33</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6</td>
<td>7.14</td>
</tr>
<tr>
<td>Renal calculi / benign prostatic hypertrophy</td>
<td>4</td>
<td>4.76</td>
</tr>
<tr>
<td>Liver disease (Chronic hepatitis b, 2-alcoholic liver disease)</td>
<td>3</td>
<td>3.57</td>
</tr>
<tr>
<td>Malignancy (renal cell carcinoma-1, acoustic schwannoma-1, breast cancer-1)</td>
<td>3</td>
<td>3.57</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2</td>
<td>2.38</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>2</td>
<td>2.38</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>2</td>
<td>2.38</td>
</tr>
<tr>
<td>Chronic deep venous thrombosis</td>
<td>1</td>
<td>1.19</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>1</td>
<td>1.19</td>
</tr>
<tr>
<td>Spondylosis</td>
<td>1</td>
<td>1.19</td>
</tr>
<tr>
<td>Past Surgery**</td>
<td>1.5</td>
<td>17.85</td>
</tr>
</tbody>
</table>

*Heart diseases: IHD (18), Rheumatic heart disease (1), Atrial Septal Defect (1), Pulmonary Thromboembolism / Pulmonary Hypertension (1); **Past surgery - Hernia/ hydrocele (4), cholecystectomy (2), below knee amputation (2), THR, TKR, Pneumonectomy, Mastectomy, Appendicectomy, CABG, Cataract surgery

51 patients (60.71%) stayed only for 1-7 days in MNICU followed by 20(23.8%) patients staying for 8-14 days. Average duration of stay (in days) in MNICU was 9.72±15.06 days. 13 patients (14.49%) had MNICU stay more than 14 days. Only 5(5.95%) patients needed more than 4 weeks stay in MNICU.

Table 4: Etiological spectrum in critically ill elderly patients admitted in MNICU

<table>
<thead>
<tr>
<th>Various etiology’s</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>20</td>
<td>23.80</td>
</tr>
<tr>
<td>Monsoon related illness</td>
<td>14</td>
<td>16.67</td>
</tr>
<tr>
<td>Pneumonia (CAP)</td>
<td>10</td>
<td>11.90</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>8.33</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>7</td>
<td>8.33</td>
</tr>
<tr>
<td>GBS</td>
<td>5</td>
<td>5.95</td>
</tr>
<tr>
<td>COPD</td>
<td>5</td>
<td>5.95</td>
</tr>
<tr>
<td>Poisoning</td>
<td>2</td>
<td>2.38</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9</td>
<td>10.71</td>
</tr>
<tr>
<td>Other infections</td>
<td>5</td>
<td>5.95</td>
</tr>
</tbody>
</table>

Table 3 lists their co-morbidities. Hypertension, diabetes mellitus, heart diseases and cerebrovascular accidents were the leading comorbidities.

Table 4 gives the etiological spectrum. Most common aetiology in critically ill elderly patients was Stroke (23.8%) followed by Monsoon related illness (16.67%), Pneumonia (11.9%), Malignancy (8.33%), Congestive cardiac failure (8.33%), Guillain Barre Syndrome and COPD (5.95%) in our setup.

Out of 20 stroke patients 14 had intracranial bleed, 4 had thromboembolic infarct and 2 had cortical venous sinus thrombosis.

In monsoon related illness, there were 5 cases of Malaria (3 Vivax, 1 falciparum and 1 mixed) 4 of dengue, 4 of unidentified Acute Febrile Illness and 1 of Leptospirosis. Other infection were one case each of tuberculosis meningitis, acute pyelonephritis, mucormycosis, tetanus and empyema.

Among miscellaneous group, 3 had diabetic ketoacidosis. There
were one patient each of myasthenia gravis, neuroleptic malignant syndrome, thyrotoxicosis, acute pulmonary thromboembolism, acute pulmonary oedema, disseminated intravascular coagulopathy. There were 7 cases of malignancy (Intra cranial tumors 4; carcinoma breast with metastasis-1 and haematological malignancy-2). One organophosphorus poisoning and one snake envenomation was admitted.

Table 5 gives mortality outcome. The mortality was significantly higher (73.8%) in elderly in comparison with the non-elderly group. (43.53%). (p<0.0001) The overall mortality was 46.85%. Mortality was highest in Middle old (Age 70-80) (87.71%) followed by old old (Age >80) (80%), the young old (Age 60-70) had a mortality of 70.76%.

The mean age of expired patients (67.61 ± 7.12) was comparable to the survived patients (65.30 ± 5.58). p=0.33.

The mean SOFA score at admission and 48 hours were 7.09 ± 3.81 and 7.88 ± 3.71 respectively. Table 6 shows various SOFA grades and no. of expired patients in each grade at admission and 48 hours.

Table 7 shows mean SOFA score in the two groups of expired and survived patients on admission and at 48 hours respectively.

Discussion

The growing demand for Intensive care Unit beds in developing countries along with an expanding ageing population will make predictive scoring system like SOFA necessary for geriatrics patients as they compete with younger patients for ICU beds. Recently the third international consensus definition for sepsis by critical care task force has described sepsis as ‘Life threatening organ dysfunction caused by dysregulated host response to infection.’ Organ dysfunction in present definition uses increase of SOFA score by two or more points which in turn contributes to 10% increased mortality.

In our study we have used SOFA score at admission and after 48 hours of admission for assessing the severity of clinical condition and prediction of mortality in critically ill elderly patients. The mean SOFA score on admission as well as after 48 hours was significantly higher in expired patients as compared to those who survived. The mean score was 7.82 ± 3.74 at admission and 8.64 ± 3.72 at 48 hour for the expired patients as compared to 5.30 ± 3.35(p = 0.01) and 6.50±3.03(p=0.048) for the survived patients respectively. Our study substantiates similar result of higher SOFA score in expired patients in other studies by Sodhi et al, Qiao Q et al (Table 8). Sodhi et al used only SOFA score at admission unlike study by Qiao et al our study which used SOFA score at admission and 48 hours.

Using logistic regression analysis, we found positive correlation between mortality and SOFA score at admission (R = 0.27837 and the two-tailed P value =0.0179) and also at 48 hours (R = 0.28522 and the two-tailed P value= 0.01516) by Spearman’s rho correlation analysis. 12 patients had expired within 48 hours of admission.

The 12 patients who had expired within 48 hours had very high SOFA score. Mean 12 ± 3.3.

Initial SOFA score and outcome (survival or death): Using Univariate logistic regression (SPSS software version 22.0, the odds ratio of the patient expiring by the end of stay in the MICU, increases by a factor of 1.29 or 29% for every 1 point rise in the initial SOFA Score.

Table 5: Comparing mortality outcome in critically ill elderly Vs nonelderly patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Total No.</th>
<th>Expired</th>
<th>Survived</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>84</td>
<td>62</td>
<td>22</td>
<td>73.8%*</td>
</tr>
<tr>
<td>Nonelderly</td>
<td>680</td>
<td>296</td>
<td>384</td>
<td>43.53%*</td>
</tr>
<tr>
<td>Total</td>
<td>764</td>
<td>358</td>
<td>406</td>
<td>46.85%</td>
</tr>
</tbody>
</table>

*P< 0.0001

Table 6: SOFA grades and number of expired patients in each grade at admission (n=84) and at 48 hours (n=72)*

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>Total no. of patients at admission (%)</th>
<th>Number of patients Expired</th>
<th>Percentage of expired</th>
<th>Total number of patients at 48 hours</th>
<th>Number of patients expired</th>
<th>Percentage of expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6</td>
<td>39</td>
<td>23</td>
<td>58.9%</td>
<td>28</td>
<td>15</td>
<td>53.1%</td>
</tr>
<tr>
<td>7 to 12</td>
<td>37</td>
<td>32</td>
<td>86.4%</td>
<td>33</td>
<td>10</td>
<td>100%</td>
</tr>
<tr>
<td>13 to 18</td>
<td>8</td>
<td>7</td>
<td>87.5%</td>
<td>10</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>19 to 24</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>62</td>
<td>73%</td>
<td>72</td>
<td>50</td>
<td>69.4%</td>
</tr>
</tbody>
</table>

*12 patients expired within 48 hours of admission.
including admission and 48 hours. The area under the ROC curve was used to predict mortality which was 0.74 for admission and 0.91 for 48 hours. The highest value of 0.98 was for SOFA max score. Our study design did not have SOFA max score. 

The elderly were 10.94% of 764 admission in MNICU, which is comparable to study conducted by Said et al7 and Belaychi et al in Morocco,8 however it is quite low compared to Sodhi et al (52%), Vosylius et al9 (51%) and various US data which vary from 42%-52%.10

Age has always been believed to be strongly associated with severity of illness, even when adjusted for degree of physiological impairment, age remains a predictor of mortality.9,11 The mean age in our study was 67.14 ± 6.8 years. The elderly had a significant higher mortality 73.8%(n=84) as compared to non elderly 43.53% (n=680) (p< 0.001), a finding consistent with most studies in elderly like Vosylius et al. Sorhi et al using more than 65 years as elderly found a similar mortality of 20.1% in elderly population and 19.2% in non elderly control population. (P >0.05).8 In Sorhi’s study post-operative patients comprised 28.61% while only 24.6% were medical patients. Post-operative patients are expected to have good outcome following planned surgeries. It would be interesting to get a subset analysis of the outcome in medical patient to compare with our data. For the same reason, even in nonelderly group our mortality of 43.58% is much higher than the 19.2% mortality of Sorhi’s study.

In a resource stretched tertiary referral public hospital like ours geriatrics patients would be competing with critically ill young patients with tropical fevers, poisoning, ARDS, sepsis and even obstetrics medical emergencies.

In the present study, we found that elderly population was extremely heterogeneous in terms of presence of various premorbid conditions. The most common premorbidity was Hypertension in 59.52% patients followed by Diabetes mellitus (32.14%), 25% patients had history of IHD, 10.71% patients had previous stroke, 9.52% had old healed Koch’s and 8.33% had COPD.

In our study the most common etiology was (23.8%) followed by monsoon related illness (16.67%) and pneumonia (11.9%). The spectrum of disease varies among various studies depending on the cohort and country. In a study in Egypt, 31.6% of patients were admitted with diabetes mellitus complications, 19.8% with cardiovascular complications, 13.8% with disturbed level of consciousness and 12.8% with pulmonary complications.7 In the study in Morocco, Infectious disease was the leading cause of hospitalisation, irrespective of age.8

Our study was conducted in resource restricted setting of ICU in tertiary centre of a tropical metropolis which has high incidence of acute infectious diseases like malaria, dengue, leptospirosis etc., more commonly seen in young patients. This may limit the numbers and variety of geriatric cases admitted. We also studied the survivors till they were discharged or transferred from ICU, hence subsequent mortality could not be judged. These factors may have limitations in our study.

Organ dysfunction may develop or worsen during stay in ICU. Sequential scoring like SOFA after 48 hours can be helpful in monitoring and predicting the clinical outcome rather one time scoring. A falling SOFA score will indicate improving clinical condition and guide further therapy.

References

Consensus on “Basal insulin in the management of Type 2 Diabetes: Which, When and How?”

Samit Ghosal¹, Binayak Sinha², Anirban Majumder³, Ashok Kumar Das⁴, Awadhesh Kumar Singh⁵, Biswajit Ghoshdastidar⁶, Debasish Maji⁷, Ghanshyam Goyal⁸, Jagat Jyoti Mukherjee⁹, Kalyan Kumar Gangopadhyay¹⁰, Mathew John¹¹, Sanjay Chatterjee¹², Shalini Jaggi¹³, Subir Ray¹⁴, Sujoy Majumdar¹⁵, Surendra Kumar Sharma¹⁶ (IDEA-2016 Expert Group)

Abstract

Introduction: Type 2 diabetes mellitus (T2DM) has attained epidemic proportions and continues to increase despite the availability of a number of oral antidiabetic medications and major advances made in insulin delivery since its discovery nearly a hundred years ago. One, amongst many other reasons responsible for the inability to achieve adequate glycaemic control in a substantial proportion of T2DM patients is the delayed initiation and inappropriate intensification of insulin treatment. Appropriate initiation and intensification of insulin is critical for the successful achievement of tight glycaemic control.

Objective: To provide simple and easily implementable guidelines to primary care physicians on basal insulin initiation and intensification, along with use of basal insulin in special situations (hepatic failure, renal failure and gestational diabetes mellitus).

Methods: Each consensus statement on basal insulin initiation, intensification and use of basal insulin in special situations was evaluated for dosing and titration based on established guidelines, data from approved pack inserts, prescribing information or summary of product characteristics for each insulin type, and published scientific literature. These evaluations were then factored into the national context based not only on the clinical experience of the expert committee representatives’ but also based on the common therapeutic practices followed in India to successfully achieve optimal glucose control.

Results: Recommendations on initiation and intensification of basal insulin, and its use in special situations, have been developed. The key recommendations are to initiate basal insulin when 2 or 3 oral antidiabetic medications fail to achieve target glycaemic control, or in symptomatic patients with glycated haemoglobin value greater than 9%. Depending upon patient characteristics, any of the four available basal insulins [Neutral protamine Hagedorn (NPH), Glargine (IGlar), Detemir (IDet), Degludec (IDeg)] can be used. However, IDeg has a longer duration of action, comparatively lesser hypoglycaemia (both overall and nocturnal) and more flexibility in administration timing compared to IGlar and IDet. Inability to maintain glycaemic control should lead to prompt intensification of basal insulin treatment by adding mealtime insulin, consisting of one to three injections of either rapid-acting insulin analog or regular insulin; depending upon patient characteristics, intensification can also be achieved by transition from basal insulin to twice daily premixed insulin analogs/premixed human insulin/insulin co-formulations. IDeg/IDet can be used in all grades of renal and hepatic impairment; and IDet has been approved for use in gestational diabetes mellitus.
Introduction

Diabetes mellitus is a major health issue of the 21st century. As per the International Diabetes Federation (IDF) Atlas (7th edition), the second largest population of people with diabetes reside in India, and the number of diabetic patients aged between 20 and 79 years in India is estimated to increase from 69.2 million in 2015 to 123.5 million by 2040.1 Diabetes accounts for 14.5% of global all-cause mortality among people of age group 20 and 79 years. The highest number of deaths due to diabetes occur in China, India, USA and the Russian federation. Type 2 diabetes mellitus (T2DM), a subtype of diabetes, is the fourth most common disease worldwide, and is associated with significant morbidity and mortality.2

Insulin is the oldest available treatment option for T2DM. Unlike oral antidiabetic agents (OADs), insulin has the potential to reduce elevated glycaemic values from any value to the recommended glycaemic targets. Basal and premixed insulins are the preferred insulin options in the out-patient setting. Basal insulin provides a constant ‘background’ level of insulin that plays a key role in modulating the endogenous production of glucose from the liver.3,4 It constitutes approximately 40% of the total daily insulin secretion.5 Available basal insulin preparations can be administered by primary care physicians and the specialists alike with minimal risk and fear of inducing hypoglycaemia. Administration of basal insulin is a convenient way to initiate insulin in a subject with T2DM to achieve the desired glycaemic target. Most basal insulins are dosed at bed time and titrated based on the fasting plasma glucose value (FPG). Neutral Protamine Hagedorn (NPH) was the first basal insulin introduced and was in use for a fairly long time; however, an increase in risk of nocturnal hypoglycaemia, a short duration of action (12-18 h) necessitating twice daily administration, and excess variability in its absorption and action/delayed to development of long-acting basal insulin analogs with longer duration of action, less intra-patient variability, less pronounced peak in time-action profiles and less risk of nocturnal hypoglycaemia. Both, insulin Glargine (IGlar) and insulin Detemir (IDet), are long-acting basal insulin analogs and have been preferred over NPH because of longer duration of action, lower nocturnal hypoglycaemic risk and less variability. Despite these advantages, both IGlar and IDet do not last for full 24 h necessitating twice daily dosing to achieve glycaemic control in a number of subjects; moreover, both IGlar and IDet do not mix with other insulins. Therefore, a basal insulin, with a longer duration of action, flat peakless profile, less day-to-day variability, less overall and nocturnal hypoglycaemia, and more flexibility was warranted. IDeg is an ultra-long acting basal insulin analog with a flat peakless profile, least variability, once-daily dosing in all the patients, flexible timing of administration, lower nocturnal hypoglycaemia, mean elimination half-life of ~25 hours and the ability to mix with other insulins. The findings of published scientific literature comparing different basal insulins are summarized in Table 1. Real world data of IDeg in Sweden, United Kingdom, Japan and India is associated with reduced HbA1c level, insulin dosage and hypoglycaemia (Table 2).

In spite of advancements in insulin regimens, there are both patient- and physician-related barriers that hinder the use of insulin in the management of diabetes.27,28 These barriers can be addressed by educating, counselling and supporting the patients, and enhancing the soft and hard skills of the physicians by training them about initiation and intensification of insulin regimens. In a survey of 600 physicians across 6 countries, 50% of the physicians stated that they did not have any experience with available insulins, 40% stated that due to lack of simple guidelines for insulin titration/intensification they were not able to adequately prescribe insulin to the patients.29 Hence, simple, evidence based, and practical guidelines on insulin initiation and intensification are required to overcome insulin-related barriers among physicians. There is a lack of unified, simple and easily implementable recommendations and guidelines on the use of basal insulin in Indian T2DM patients. To address this concern, a group of experts from all across India held a consensus meeting in Kolkata, India on 08 July 2016. The idea of the consensus meeting on the use of basal insulin in current clinical practice was initiated by Integrated
Table 1: Summary of published comparisons of different basal insulins

<table>
<thead>
<tr>
<th>Study Design (Ref)</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Acting Insulin Analogues vs. NPH</td>
<td>Hypoglycaemia outcome from meta-analysis of randomized trials</td>
<td>IGlar in comparison to NPH</td>
</tr>
<tr>
<td>IGlar vs. NPH</td>
<td></td>
<td>• Statistically significant reduction in nocturnal hypoglycaemia</td>
</tr>
<tr>
<td>Meta-analysis of post-FDA approval studies⁴</td>
<td>To investigate the efficacy and safety of glimepiride combined with either morning or bedtime IGlar or bedtime NPH in patients with T2DM in terms of HbA1c, blood glucose levels, body weight</td>
<td>IGlar in comparison to NPH</td>
</tr>
<tr>
<td>Open-label, randomized, controlled trial⁴</td>
<td></td>
<td>• Statistically significant improvement in HbA1C with morning dose than with NPH insulin (0.40% [CI, 0.23% to 0.58%]; p=0.001) or bedtime IGlar (0.28% [CI, 0.11% to 0.46%]; p=0.008)</td>
</tr>
<tr>
<td>An investigator-initiated open, parallel-group clinical trial involving seven centres⁶</td>
<td>To compare changes in HbA1c and diurnal glucose profiles and symptomatic hypoglycaemia with the use of IGlar+Met against NPH+Met at 12 and 36 weeks in patients with T2DM</td>
<td>IGlar in comparison to NPH</td>
</tr>
<tr>
<td>A meta-analysis of controlled trials (24-48 weeks long except one 52-week study)⁷</td>
<td>To assess IGlar versus OD or BID NPH in patients with T2DM in terms of risk for hypoglycaemia</td>
<td>• Statistically significant less frequent nocturnal hypoglycaemia with morning (17%) and bedtime doses (23%) than with bedtime NPH insulin (38%) (p&lt;0.001).</td>
</tr>
<tr>
<td>A one-year, multicentre, open, randomised study¹⁰</td>
<td>To compare the efficacy and safety of IGlar with NPH along with OADs in patients with T2DM.</td>
<td></td>
</tr>
<tr>
<td>Randomised, open label, parallel, 24 week multicentre trial¹¹</td>
<td>To compare associated hypoglycaemia risks of insulin glargine and NPH insulin added to oral therapy of T2DM to achieve 7% HbA1c</td>
<td></td>
</tr>
<tr>
<td>IDet vs. NPH</td>
<td>Hypoglycaemia outcome from meta-analysis of randomized trials</td>
<td>IGlar in comparison to NPH</td>
</tr>
<tr>
<td>Meta-analysis of post-FDA approval studies⁴</td>
<td></td>
<td>• Statistically significant reduction in overall and nocturnal hypoglycaemia (number of episodes per patient year of exposure)</td>
</tr>
<tr>
<td>26-week randomized, controlled trial¹²</td>
<td>To analyse weight gain in OD-IDet or NPH in already overweight T2DM patients requiring intensified insulin therapy</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>20-week, multicentre, randomized, open-label, 3-arm, parallel-group trial¹³</td>
<td>To compare the effectiveness and tolerability of IDet versus NPH administered OD with ≥1 OAD in poorly controlled T2Dm patients</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistically significant lesser weight gain (difference: 1.5 kg, p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistically significant lesser BMI increase (difference: 0.6 kg/m²; p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistically significant lower incidence of hypoglycaemia [relative risks 0.62 (all events) and 0.43 (nocturnal); p&lt;0.0001 for both]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Evening IDet had 24 h and nocturnal hypoglycaemia statistically significant reduced by 53% (p=0.019) and 65% (p=0.031), respectively compared with evening NPH. Nocturnal hypoglycaemia was statistically significant reduced further by 87% with morning IDet compared with evening NPH (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistically significant less weight gain with evening IDet vs. NPH (0.7 kg vs. 1.6 kg, p=0.005 for evening IDet vs NPH)</td>
</tr>
</tbody>
</table>
Table 1: Summary of published comparisons of different basal insulins

<table>
<thead>
<tr>
<th>Study Design (Ref)</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>A parallel-group, multicentre randomised trial. Over 24 weeks</td>
<td>To assess efficacy and tolerability of IDet or NPH insulin added to oral therapy for T2DM in a treat-to-target titration protocol</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>26-week, multinational, open-label, parallel group, randomized trial</td>
<td>To compare efficacy and safety of IDet with NPH in combination with mealtime IAsp in T2DM</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>IDet/IGlar vs. NPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analyses. of 14 randomized controlled with a duration &gt;12 weeks</td>
<td>Comparison of IDet or IGlar with NPH insulin in T2DM patients in terms of HbA1c, BMI, symptomatic, severe and nocturnal hypoglycaemia</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>Inter-comparison of Long Acting Insulin Analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDet vs. IGlar</td>
<td>To compare IDet with IGlar when administered as an add-on to glucose lowering drugs in insulin naïve patients with T2DM</td>
<td>IDet in comparison to IGlar</td>
</tr>
<tr>
<td>IDeg vs. IGlar</td>
<td>To compare the changes in various glycemic parameters in insulin-naïve T2DM patients who were initiated on IGlar or IDeg in real world setting</td>
<td>IDeg in comparison to IGlar</td>
</tr>
<tr>
<td>Retrospective real world comparative Indian data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-year, randomized, treat-to-target trial (BEGIN Once Long)</td>
<td>To compare efficacy and safety in insulin-naïve patients with T2DM inadequately controlled with OADs when treated with IDeg vs IGlar</td>
<td>IDeg in comparison to IGlar</td>
</tr>
<tr>
<td>78 Week, randomized, Treat to target trial (BB – T2)</td>
<td>To compare long term glycaemic control in patients with advanced T2DM patients on basal – bolus therapy</td>
<td>IDeg in comparison to IGlar</td>
</tr>
<tr>
<td>26-week, randomized, open-label, parallel-group, treat-to-target trial (Flex – T2)</td>
<td>To compare the efficacy and safety of insulin degludec given in Variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily</td>
<td>IDeg in comparison to IGlar</td>
</tr>
<tr>
<td>2×32-week randomized, double-blind, crossover, multicentre, treat-to-target phase 3b clinical trial</td>
<td>To confirm superiority of IDeg compared with IGlar in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia during the maintenance period (after 16 weeks of treatment).</td>
<td>IDeg in comparison to IGlar</td>
</tr>
<tr>
<td>Contd...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1: Summary of published comparisons of different basal insulins

<table>
<thead>
<tr>
<th>Study Design (Ref)</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-comparison of Long Acting Insulin Analogues and NPH</td>
<td>IGLar in comparison to NPH and IDet</td>
<td>• IGLar+OAD use was associated with higher probability of reaching target HbA1c level without hypoglycemia as compared to NPH+OAD (RR=1.32 [1.09, 1.59]) and similar effect as IDet+OAD (RR=1.07 [0.87, 1.33])</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 28 randomized clinical trials from major medical databases up to Dec 201220</td>
<td>To compare efficacy and safety outcomes of IGLar with NPH and IDet, added to OADs or/and in combination with bolus insulin.</td>
<td>• IGLar+OAD demonstrated statistically significant lower risk of symptomatic hypoglycemia as compared to NPH+OAD (RR=0.89 [0.83, 0.96]) but not with IDet + OAD (RR=0.99 [0.90, 1.08])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In basal-bolus regimens:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- IGLar demonstrated similar proportion of T2DM patients achieving target HbA1c as compared to NPH (RR=1.14 [0.91, 1.44]) but higher than IDet (RR=1.38 [1.11, 1.72])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of severe hypoglycemia was lower in IGLar than in NPH (RR=0.77 [0.63, 0.94]), with no differences in comparison with IDet (RR=1.10 [0.54, 2.25])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- IGLar + OAD has comparable safety profile to NPH, with less frequent adverse events leading to treatment discontinuation than IDet + OAD (RR=0.40 [0.24, 0.69])</td>
</tr>
</tbody>
</table>

BID=twice daily; CI=confidence interval; FBS=fasting blood sugar; FDA=Food and Drug Administration; IGLar=insulin Glargine; HbA1c=glycated haemoglobin; IAsp=insulin Aspart; IDeg=insulin Degludec; IDet=insulin Detemir; Met=metformin; NPH=Neutral Protamine Hagedorn; OAD=oral anti diabetics; RR=relative risk; SMBG=self-measured plasma glucose; T2DM=type 2 diabetes mellitus.

Table 2: Post approval studies of Insulin Degludec

<table>
<thead>
<tr>
<th>Properties</th>
<th>Sweden24</th>
<th>UK25</th>
<th>Japan26</th>
<th>India27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in HbA1C (%)</td>
<td>0.30</td>
<td>0.70</td>
<td>0.60</td>
<td>0.36</td>
</tr>
<tr>
<td>Reduction in insulin dosage (%)</td>
<td>14</td>
<td>-</td>
<td>10-20</td>
<td>27</td>
</tr>
<tr>
<td>Reduction in overall hypoglycaemia (%)</td>
<td>22</td>
<td>90</td>
<td>-</td>
<td>70</td>
</tr>
</tbody>
</table>

HbA1c=glycated haemoglobin

Diabetes and Endocrine Academy (IDEA), and was supported by Novo Nordisk India. The objectives of the meeting were to:

- **Evaluate the published evidence on use of basal insulins in T2DM patients**
- Examine the existing evidence for dosing and titration from currently available treatment guidelines, such as the American Diabetes Association/European Association for the Study of Diabetes (ADA)/EASD), IDF, American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), National Institute for Health and Care Excellence (NICE) and Canadian Diabetes Association (CDA)
- **Evolve consensus/unified statement of recommendations for initiation of basal insulin, intensification of insulin treatment, and the use of insulin in special situations based on published guidelines, evidence and clinical experience, which are simple and easily implementable**

**Methods**

During the consensus meeting on basal insulin in the management of diabetes, the expert group committee deliberated and finally proposed recommendations by consensus for initiation of insulin with a basal insulin, intensification of insulin treatment with a basal insulin and additional rapid or short acting insulin, and the use of basal insulin in special situations, including hepatic failure, renal failure and gestational diabetes mellitus.

The consensus was proposed based on established guidelines (from globally recognised professional bodies as well as those published within India), prescribing information or summary of product characteristics for each insulin type, and published scientific literature. These evaluations were then factored into the national context based not only on the clinical experience of the expert committee representatives’ but also on the common therapeutic practices followed in India. The evaluations were debated and discussed within the expert group committee. The final proposed consensus-based recommendations were proposed and collectively recorded for each insulin regimen without any bias, and as much as possible in an unambiguous language.

The global and national guidelines, and widely accepted and evaluated consensus statements that were evaluated by the expert group include: ADA Standard of Medical Care 2016 (ADA 2016), consensus statement by AACE/ACE on the comprehensive T2DM management algorithm2016 Executive Summary (AACE/ACE Consensus statement 2016), Global guideline for T2DM IDF (IDF 2012), NICE-UK: Clinical Guidelines on
Type 2 diabetes (NICE UK, 2009) and Canadian Diabetes Association guidelines (CDA, 2013).\textsuperscript{30-34}

**Consensus 1: Insulin Initiation with Basal Insulins (Which, When and How)**

**Current place in guidelines**

Most guidelines (ADA/EASD, IDF, AACE/ACE, NICE and CDA) recommend initiation with basal insulin early in the natural history of diabetes.\textsuperscript{28-32} The ADA and CDA guidelines recommend initiating either intermediate acting (IA) or long acting (LA) basal insulin. IDF recommends using either LA or IA basal insulin for insulin initiation. NICE recommends LA or IA insulin for basal insulin initiation.\textsuperscript{30-34}

ADA 2016 guidelines for management of diabetes mellitus recommends that one could initiate basal insulin if HbA1c target is not achieved after three months of Metformin treatment. Basal insulin should be initiated at a dose of 10 U/day or 0.1-0.2 U/kg/day, and further adjusted by 10-15% or 2-4 U once or twice weekly to reach fasting blood glucose (FBG) target. In case of hypoglycaemia, it recommends determining and addressing the cause of hypoglycaemia, followed by a dose reduction by 4 U or 10-20% of the applied dose.\textsuperscript{30}

The NICE guidelines are a little more conservative in approach, and recommends insulin along with Metformin and Sulfonylurea in patients with T2DM where HBA1c value is ≥7.5%.\textsuperscript{31}

IDF 2012 recommends initiation of basal insulin after failure of 2 OADs to maintain target HbA1c value (Metformin/Sulfonylurea/-glucosidase inhibitor/DPP-4 inhibitor/thiazolidinedione).\textsuperscript{32}

AACE/ACE consensus statement 2016 recommends the use of single daily dose of basal insulin, as a part of dual/triple therapy, when glycated haemoglobin (HbA1c) value is ≥7.5%. In these subjects, basal insulin is given along with Metformin and another OHA (dual therapy). If the target HbA1c goal is not achieved in 3 months, then the patients are given triple therapy where basal insulin is given along with Metformin and two other OHAs. If the target goal is still not achieved in 3 months, then ‘add or intensify insulin’ algorithm is followed where LA basal insulin is given at a total daily dose (TDD) of 0.1-0.2U/kg when HbA1c < 8% or at TDD of 0.20.3 U/kg when HbA1c > 8%. The dose may be titrated every 2-3 days to reach the glycaemic goal. In a fixed regimen, the guideline recommends to increase the TDD by 2 U whereas in an adjustable regimen the insulin doses can be adjusted by adding 20% of TDD, 10% of TDD, and 1 U for corresponding mean FBG > 180 mg/dL, 140 to 180 mg/dL, and 110-139 mg/dL, respectively. In case of hypoglycaemia, TDD can be reduced by 10-20% and 20-40% for FBG values < 70 mg/dL and < 40 mg/dL, respectively. They recommend use of basal insulin analogues over NPH as it provides insulin concentration for a prolonged period of time and to either discontinue or reduce sulfonylurea after the start of basal insulin.\textsuperscript{31}

CDA 2013 suggests the starting dose of 10U OD at bedtime with titration of 1 U/day until target of FPG 72-126 mg/dL is reached.\textsuperscript{34}

**Published scientific literature**

Basal insulin should be initiated when glycaemic targets are not achieved with Metformin alone or together with other OAD(s). The approved pack inserts recommend the starting dose of basal insulin as 10 U or 0.2-0.3 U/kg/day. Most basal insulins should be dosed at bedtime and titrated based on mean FPG levels.\textsuperscript{35}

Various studies have shown a significant higher reduction in FPG, lesser incidence of total and nocturnal hypoglycaemia, lesser dose requirement and higher flexibility with the use of IDeg when compared to other basal insulin analogues and NPH insulin; this is due to its flat and stable glucose-lowering effects with a half-life of > 25 h and duration of action > 42h.\textsuperscript{5,18,19,36}

**IDEACON Expert Group Recommendation**

**Expert Group Recommendation 1: Basal Insulin for Insulin Initiation: Which, When and How?**

Consensus1.1: Basal insulin for insulin Initiation: Which insulin?
- NPH insulin can be given once or twice daily (most patients will require twice daily administration)
- Basal insulin analogues are preferred because of lesser nocturnal hypoglycaemia
- Both IGlar and IDet (sometimes in twice daily doses) are effective
- IDet is weight neutral
- IDeg has a longer duration of action, lesser incidence of overall and nocturnal hypoglycaemia, flexibility in administration timing compared to IGlar/IDet

Consensus1.2: Basal insulin for insulin Initiation: When?
- Basal insulin can be considered when Metformin fails to achieve target glycaemic control
- Basal insulin is recommended when 2 or 3 OAD agents fail to achieve target glycaemic control
- Basal insulin can be recommended at diagnosis in patients with HbA1c > 9% with symptoms

Consensus1.3: Basal insulin for insulin Initiation: How?
- It is recommended to start basal insulin (IDeg/IGlar/IDet) at a dose of 10 U once daily subcutaneously at bedtime OR 0.1-0.2 U/kg/day subcutaneously.
- Consensus 1.4: Basal insulin titration
- The recommended target for titration of basal insulin dose is the FPG value, which should be 80-130 mg/dL.
Consensus 2:
Intensification of Insulin Treatment

Current place in guidelines

ADA 2016 recommends intensification of insulin treatment with one rapid-acting bolus insulin injection before the largest meal together with continued use of basal insulin or switching from basal insulin to twice-daily premixed (or biphasic) insulin analogs (70/30 Aspart mix, 75/25 or 50/50 Lispro mix) to cover post prandial glucose (PPG) excursions when FBG target is reached. The bolus insulin dose can be initiated at 4 U or 0.1 U/kg or 10% of basal dose. If HbA1c is < 8%, basal dose should be decreased by the same amount.

The dosing of twice daily (BID) premix insulin should be as per the previous basal insulin dose where the premix insulin doses needs to be calculated by splitting the total current basal dose either as 2:1 (2/3rd of the dose in the morning [AM] and 1/3rd of the dose in the evening [PM]) or 1:1 (½ of the dose in the morning and ½ of the dose in the evening). Both bolus and premix doses may be titrated by 1-2 U or 10-15% once or twice weekly until self-measured plasma glucose (SMBG) target is reached. In case of hypoglycaemia, the corresponding insulin doses can be decreased by 2-4U or 10-20%.

The AACE consensus statement 2016 treatment algorithm recommends intensifying treatment by combining basal insulin with mealtime bolus insulin when glycaemia is uncontrolled on basal insulin alone. Rapid-acting analogs (Aspart, Lispro or Glulisine) are preferred over regular insulin because they have a more rapid onset and offset of action and are associated with less hypoglycaemia. The simplest approach is to cover the largest meal with a prandial injection of a rapid-acting insulin analog (initiate with 10% of basal dose or 5U) before the largest meal (i.e. Basal Plus 1). If glycaemic goal is not reached, then treatment can be progressively intensified by adding bolus injections before 2 (i.e. Basal Plus 2) or 3 meals (Basal Plus 3). Another way to intensify insulin treatment is to switch to a full basal-bolus program, which provides greater flexibility for patients with variable meal times and carbohydrate content.

In this program, the TDD of insulin (0.3-0.5 U/kg) is distributed as 50% basal insulin and 50% prandial insulin. The 50% prandial insulin dose is further divided into 3 doses, administered before each major meal. Titration of insulin dose can be done every 2-3 days to reach the desired glycaemic goal. Prandial dose can be increased by 10% or 1-2 U, if 2-h postprandial or next pre-meal glucose is consistently > 140 mg/dL. In case of hypoglycaemia, TDD basal and/or prandial insulin can be reduced by 10%-20% or 20%-40%, if blood glucose level is consistently < 70 mg/dL and < 40 mg/dL, respectively.

CDA 2013 recommends intensification of insulin treatment to basal bolus program. Forty percent of the TDD of insulin (0.3-0.5 U/kg) is distributed as basal insulin dose, and the remaining 60% as prandial insulin dose. The prandial insulin dose should be divided based on number of meals per day (generally 3 times per day) using either rapid acting analogue or short-acting insulin.

IDF 2012 also recommends intensification of insulin therapy with basal and meal-time prandial insulins.

NICE 2009 recommends insulin intensification from basal to BID premix or basal-bolus; or from BID premix to basal-bolus.

Published scientific literature

The cumulative progression of T2DM results in the inability of basal insulin alone to correct excessive PPG necessitating intensification of insulin treatment. In a 52-week, phase 3, randomised, open-label, treat-to-target non-inferiority trial, IDeg was compared with IGlar in a basal bolus treatment regimen with IAsp in patients with T2DM of age ≥18 years and HbA1c of 7-10%. Patients were randomised in a 3:1 ratio to receive IDeg or IGlar. The target FPG was 3.9 to < 5 mmol/L. After 52 weeks, IDeg was considered to be non-inferior to IGlar in terms of decrease in HbA1c value. There was a statistically significant reduction in overall and nocturnal hypoglycaemia with the use of IDeg compared to IGlar. The rates of severe hypoglycaemia and adverse events were comparable.
between both insulin therapies. In a one-year randomized study, BID premixed insulin was compared to basal insulin with either basal plus one prandial insulin or basal-bolus up to 3 prandial injections. The results indicated that basal insulin plus a single prandial injection was as effective in improving glycaemic control as premixed insulin while basal-bolus up to 3 prandial injections was only slightly more effective than premixed insulin. In a 26-week, randomized, open-label, treat-to-target trial, T2DM patients who were inadequately controlled with OD or BID pre- or self-mixed insulin with/without OADs were randomized 1:1 to receive BID injections of IDegAsp (combination of IDeg with rapid acting insulin in a single injection) or Biphasic IAsp 30. The FPG target was 4.0–5.0 mmol/L. IDegAsp was found to be superior in lowering HbA1c and FPG levels, overall, nocturnal and severe hypoglycaemia and had lower mean daily insulin dose than BIAsp30. In another 26-week, statistically significant improvement in overall and nocturnal hypoglycaemic episodes in patients treated with IDegAsp than BIAsp30.41 In a post-hoc analyses, the combination of IDeg with Liraglutide (IDegLira) was compared to IDeg and Liraglutide alone in T2DM patients, regardless of the stage of diabetes progression (baseline HbA1c as ≤7.5-9%). HbA1c reductions were significantly greater with IDegLira than IDeg or Liraglutide alone, indicating its high efficacy for patients with early or advanced T2DM.42

**IDEACON Expert Group Recommendation**

<table>
<thead>
<tr>
<th>Insulin Intensification</th>
<th>Recommendations in prescribing information</th>
<th>Results from PK/PD and clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal/Hepatic failure diseases</td>
<td>NPH In patients with renal/hepatic impairment, No PK/PD study reported glucose monitoring should be intensified and the human insulin dose adjusted on an individual basis.</td>
<td>No change in PK or PD</td>
</tr>
<tr>
<td></td>
<td>IGlar In patients with renal/hepatic impairment, No PK/PD study reported insulin requirements may be diminished due to reduced insulin metabolism.</td>
<td>No change in PK or PD</td>
</tr>
<tr>
<td></td>
<td>IDet In patients with renal/hepatic impairment, No change in PK or PD glucose monitoring should be intensified and the Levemir dose adjusted on an individual basis.</td>
<td>No change in PK or PD</td>
</tr>
<tr>
<td></td>
<td>IDeg Insulin degludec can be used in renal/hepatic impaired patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis.</td>
<td>No change in PK or PD</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td>NPH There are no restrictions on treatment of diabetes with NPH insulin during pregnancy, as NPH insulin does not pass the placental barrier.</td>
<td>No randomized control trials reported</td>
</tr>
<tr>
<td></td>
<td>IGlar Use of lantus may be considered during pregnancy if clinically indicated (I think we need to add a rider as for IDet)</td>
<td>No Randomized control trials reported</td>
</tr>
<tr>
<td></td>
<td>IDet Treatment with IDet can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.</td>
<td>IDet was studied in an open-label randomised controlled clinical trial pregnant women with type 1 diabetes</td>
</tr>
<tr>
<td></td>
<td>IDeg There is no clinical experience with use of IDeg in pregnant women.</td>
<td>No clinical experience with use of IDeg in pregnant women.</td>
</tr>
</tbody>
</table>

IAsp=insulin Aspart; IDeg=insulin Degludec; IDet=insulin Detemir; IGlare-insulin Glargin; NPH=Neutral Protamine Hagedorn

**Expert Group Recommendation 2: Insulin intensification**

Consensus 2.1: Insulin intensification. When?
- When basal insulin has been titrated to achieve an acceptable FBG value, but A1C still remains above target

Consensus 2.2: Basal insulin intensification. How?
- Add mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (Aspart, Lispro or Glulisine) or regular insulin
- Transition from basal insulin to twice-daily premixed insulin analogs or premixed human insulin or insulin co-formulation.
- Add glucagon-like peptide-1 (GLP-1) analogue to preexisting basal insulin
Consenus 3: Basal insulins in Special Situations (Renal Failure, Hepatic Failure and Gestational Diabetes Mellitus): Which, when and How?

Recommendations as per pack inserts

Table 3 summarizes the recommendations for use of basal insulin as per pack inserts in patients with renal failure, hepatic failure and gestational diabetes mellitus (GDM).

Current place in guidelines

In patients with gestational diabetes mellitus

All guidelines, including ACOG, IDF, NICE and DIPSI recommend rapid-acting insulins (IAsp) to be safe and effective in achieving targeted PPG values during pregnancy since they do not cross the placenta. IDF guideline recommends initiation of insulin, if FPG is ≥90 mg/dL or PPG ≥140 mg/dL in 1-hour or ≥120 mg/dL in 2-hours after 2 weeks of medical nutrition therapy and exercise. The usual recommendation is to use NPH or IDet as a basal insulin (IDF 2015).39 Rapid acting insulin analogues (IAsp) have been found to be safe and effective in achieving the targeted post prandial glucose value during pregnancy.43

Published scientific evidence

In patients with gestational diabetes mellitus

One open-label, randomised controlled clinical trial has been conducted in pregnant women with type 1 diabetes with no safety issues.44

In patients with hepatic impairment

A clinical trial was conducted to examine the effect of hepatic impairment on pharmacokinetics of IDet. A total of 24 subjects, including 6 healthy subjects and 18 subjects with hepatic impairment (6 subjects in each Child Pugh groups A, B, and C) participated in the study. There was a statistical significant difference in AUC0→∞ between healthy and severe hepatic impaired patients. The clearance increased with increasing degree of hepatic impairment. No statistically significant difference in Cmax, t1/2 or MRT was found between the groups. Hence, hepatic impairment was not associated with clinically important changes in IDet pharmacokinetic parameters and the patients should use typical starting doses of IDet with subsequent dose adjustment according to their individual therapeutic response.45

In patients with renal impairment

There is a high frequency of renal impairment in diabetic patients and hence they have an increased risk of hypoglycaemia.46 Few studies have reported that insulin analogues, IDet, IDeg, IAsp maintain their pharmacokinetic profile in patients with renal failure. A clinical trial was conducted to examine the effect of renal impairment on pharmacokinetics of IDet. A total of 28 subjects, including 6 healthy subjects and 16 subjects with renal impairment (6 subjects each with mild and moderate renal impairment and 4 subjects with severe renal impairment) participated in the study. IDet did not show any significant alterations in any pharmacokinetic parameters (Cmax, t1/2 or MRT) with renal impairment and the patients should use typical starting doses of IDet with subsequent dose adjustment according to their individual therapeutic response.45 In a study, the pharmacokinetic properties of IDeg was assessed in 30 subjects; 6 subjects each with normal renal function, mild, moderate or severe renal impairment or with end stage renal disease undergoing haemodialysis. There were no statistically significant differences in absorption or clearance of IDeg in renal impaired subjects compared with normal renal function; indicating that pharmacokinetic properties of IDeg are preserved in patients with renal impairment and specific dose adjustments may not be required for subjects with renal impairment.47 In a multicentre, prospective, randomized trial, the efficacy of OD IGlar (0.5 U/kg/day) and TID insulin glulisine (IGlu; 0.25 U/kg/day) was compared in a total of 107 T2DM patients with glomerular filtration rate < 45 mL/min. There was no statistical significant difference in the mean blood glucose levels on day 1 to day 6 between the treatment groups; indicating that both treatment groups can achieve equivalent control of hyperglycaemia in T2DM patients.48


Expert Group Recommendation 3:

Basal insulin in special situations

Consensus 3.1: Basal insulin in special situations (Renal failure)
- Insulin requirements may be diminished due to reduced insulin metabolism.
- No PK/PD studies have been reported for NPH and IGlar; PK/PD studies for IDeg and IDet indicate no change in PK/PD
- IDeg/IDet can be used in all grades of renal impairment
- Glucose-monitoring should be intensified and the insulin dose adjusted on an individual basis
Basal insulin is recommended in this paper include the following:

- Insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism
- No PK/PD studies have been reported for NPH and IGLar; PK/PD studies for IDeg and IDet indicate no change in PK/PD
- IDeg/IDet can be used in all grades of hepatic impairment
- Glucose-monitoring should be intensified and the insulin dose adjusted on an individual basis

The consensus based recommendations expert committee has also provided certain special situations; hence the adjusted on an individual basis

The doses of basal insulin need to be for effective T2DM management.

Thus, simple, concise and easily managed in primary care settings.

The recommendations presented in this paper include the following:

Basal insulin is recommended when 2 or 3 OAD agents fail to achieve target glycaemic control and in patients with HbA1c> 9% with symptoms

- Basal insulin analogues are preferred because of lesser nocturnal hypoglycaemia and meal time flexibility
  - I Deg has longer duration of action, lesser hypoglycaemia (both overall and nocturnal) and flexibility in administration timing compared to IGLar/IDet
  - Basal insulins (IDeg/IGlar/IDet) should be initiated at a dose of 10 U OD subcutaneously at bedtime or as 0.1-0.2 U/kg/day subcutaneously
  - IDeg/IDet can be used in all grades of renal and hepatic impairment
  - IDet can be considered useful in GDM

Intensification of insulin treatment should be done by adding mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (Aspart, Lispro or Glulisine) or regular insulin to basal insulin or transition from basal insulin to BID premixed insulin analogs/premixed human insulin/insulin co-formulations or addition of GLP-1 analogues to existing basal insulin

The strength of the current consensus recommendations is that it has been developed with due considerations to national context based on experience and common therapy practices in India while drawing on recommendations from globally acceptable guidelines and relevant clinically published evidence. The final proposed consensus-based recommendations were collectively recorded for each insulin regimen in easily implementable steps.

The weakness of this consensus statement is that it does not provide guidance regarding allowance or discontinuation of OADs and insulin screenagouges along with various insulin regimens.

We hope that these consensus recommendations will be a useful reference tool for physicians and that their impact will be validated through observational research in real-life practice involving large number of physicians and in the setting of routine outpatient care of T2DM in India

Acknowledgement

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Metformin Hydrochloride 850 mg SR + Glimpiride 1 mg

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Glycomet®-GP 2
Metformin Hydrochloride 650 mg SR + Glimpiride 2 mg

Glycomet®-GP 2/850
Metformin Hydrochloride 650 mg SR + Glimpiride 2 mg

Glycomet®-GP FORTE
Metformin Hydrochloride 1000 mg SR + Glimpiride 2 mg

Glycomet®-GP 3
Metformin Hydrochloride 650 mg SR + Glimpiride 3 mg

Glycomet®-GP 3/850
Metformin Hydrochloride 650 mg SR + Glimpiride 3 mg

Glycomet®-GP FORTE
Metformin Hydrochloride 1000 mg SR + Glimpiride 4 mg

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Metformin Hydrochloride 500 mg SR + Glimpiride 0.5 mg

Glycomet®-GP 0.5 FORTE
Metformin Hydrochloride 1000 mg SR + Glimpiride 0.5 mg

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Glycomet® Trio 2mg
Metformin HCl 500 mg SR + Glimperide 2 mg + Voglibose 0.2 mg

↓

Uptitrate to

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Metformin HCl 500 mg SR + Glimperide 1 mg + Voglibose 0.3 mg

Glycomet® Trio 2mg/0.3mg
Metformin HCl 500 mg SR + Glimperide 2 mg + Voglibose 0.3 mg

In Obese Type 2 Diabetes with HbA1c > 9%

Start Early

Glycomet® Trio Forte 1mg
Metformin HCl 1000 mg SR + Glimperide 1 mg + Voglibose 0.2 mg

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Metformin HCl 1000 mg SR + Glimperide 2 mg + Voglibose 0.2 mg

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- Pain worsened by movement
- Moderate or Severe pain

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- Phonophobia

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Glycemic Pentad

Abstract

**Background:** Conventionally, diabetes management involved targeting the triad of FPG, PPG, and HbA1c. However, several studies have suggested the quintessential need for a paradigm shift to incorporate glycemic variability and quality of life in the holistic diabetes control regimen. Aim: To generate a consensus and ratify the position of Glycemic Variability (GV) and Quality of Life (QOL), along with the traditional triad, in diabetes management in India. To evaluate whether the triple fixed dose combination of metformin, glimepiride, and voglibose can accomplish the goals of glycemic pentad.

**Methodology:** Glycemic pentad forum was instituted comprising of 55 experts from different regions of India in the field of diabetology who discussed various evidences related to the topic and shared their experiences and expressed their opinion on the relevance of glycemic pentad in the present diabetes management and whether triple fixed dose combination of metformin, glimepiride, and voglibose is able to achieve glycemic pentad targets.

**Results:** Forum has come to a consensus that the conglomerate of quintuple elements – FPG, PPG, HbA1c, glycemic variability and quality of life to be termed as glycemic pentad and these milestones to be considered for any antidiabetic therapy. Experts opined that combination therapy is required to achieve the Glycemic Pentad, as monotherapy might not address all the five arms of Glycemic Pentad. Group also agreed that the diabetes management in Indians require separate attention due to their distinct dietary habits (high carbohydrate content) and socio-economic status (economically weak and poorly educated). Therefore, minor adjustments to the standard practices in the western countries are suggested. After evaluating various drugs in the current market to identify candidates that could regulate the elements of Glycemic Pentad, the forum assume that a triple fixed dose combination of metformin, glimepiride, and voglibose could be a better choice in Indians as the combination is safe, affordable and effective in attaining optimal glucose levels and reducing the complications.

**Conclusions:** Glycemic pentad deserves a prominent position in the diabetes management in India. The triple fixed dose combination of metformin, glimepiride, and voglibose has essential commodities to achieve glycemic pentad targets.

Introduction

Diabetes is one of the lifestyle oriented, metabolic diseases characterized by decreased insulin sensitivity and hyperglycemia ultimately causing aberrant glucose homeostasis. Diabetes management strategies have been recommended in several guidelines aims at controlling the triumvirate of FPG, PPG, and HbA1c, which are conventionally referred as glycemic triad. The American Diabetes Association recommends targeting HbA1c levels to <7.0% (53mmol/mol), pre-prandial glucose levels to 80 - 130 mg/dl (4.4 – 7.2 mmol/l) and peak postprandial plasma glucose levels to < 180 mg/dl (10.0 mmol/l) in order to achieve better glycemic control. However, “one size fits all” concept is NOT suitable for the management of diabetes and therefore individualized treatment based on the patient’s status is recommended. For instance, higher HbA1c target might be appropriate in people with co-morbidities and who are prone to hypoglycemia or when there is a high risk associated with possible hypoglycemia.

**Importance of PPG Control in Diabetes**

Even though control of fasting hyperglycemia is essential, obtaining optimal glycemic control requires regulation of additional parameters. Growing body of evidence indicates that reducing postprandial glucose excursions is equally or perhaps more important for achieving HbA1c goals. Contribution of PPG relative to fasting glycemia is predominant when the HbA1c levels are approximately below 7.5% in people with non-insulin-treated type 2 diabetes and the contribution decreases progressively with increasing HbA1c levels. Convincing evidence suggest that oxidative stress and...
excessive protein glycation might occur as harmful consequences of sustained chronic hyperglycemia. The IDF guidelines on controlling post-meal glucose recommends that postprandial hyperglycemia is harmful and should be lowered by incorporating a variety of both non-pharmacologic and pharmacologic therapies.4

Diet and Postprandial Hyperglycemia in Indian Context

Asian Indian diabetic patients are different from other ethnicities. Carbohydrate content in Indians diet constitutes about 65%, which is more than that is recommended for diabetic patients.7 Of the whole ingredients in an individual’s diet, carbohydrates has the greatest influence on blood glucose level, and both the amount and type of carbohydrate intake are the important determinants of postprandial glucose.8 Consumption of such imbalanced diet with high carbohydrates could cause increased insulin resistance, metabolic syndrome, and type 2 DM. The amount of carbohydrates consumed affects blood glucose levels and insulin responses and a clear link between carbohydrate intake and post-prandial glucose level exists in diabetic population.9 Since Indians consume diet with high glycemic index and load, postprandial glucose control and overall glycemic control in Indian diabetic population demands a separate attention.

Glycemic Pentad: Emerging Concept

Traditionally, diabetes control strategies mainly targeted to reduce the triad of fasting and postprandial blood sugars and HbA1c. However, optimal glycemic control in UKPDS and ADVANCE trials failed to prevent macrovascular events and death.10,11 Importance of factors other than average blood glucose in causing diabetes complications have been consistently debated and the advances in research has paved the way to include two more variables, i.e. glycemic variability and quality of life, to the existing components. These five elements are collectively referred as “glycemic pentad”. Different components of glycemic pentad are shown in Figure 1.

Glycemic Variability

It was observed in the Diabetes Control and Complications Trial (DCCT) that in spite of similar HbA1c levels, patients treated with conventional methods showed a remarkable progression to retinopathy over a period of time when compared to intensively treated subjects.12 Furthermore, controlling glycemic triad does not prevent the occurrence of diabetic complications and recent studies have shown that mortality rate increased even after maintaining good HbA1c13 and HbA1c derived information is insufficient to explain all of the risk associated with complications of diabetes.14 High frequency glycemic excursions in conventionally treated patients could be an explanation for this observation.9 Subsequent studies established a relation between oscillating glucose levels and oxidative stress and corroborated the hypothesis that HbA1c together with glycemic variability might be a superior indicator of glucose control than mean HbA1c alone.6,9 Oscillating blood glucose levels rather than chronic hyperglycemia has been shown to have harmful effects on parameters of cardiovascular (CV) risk such as endothelial dysfunction.15,16 This led to the emergence of new aspect in glycemic control, i.e., glycemic variability17 and was included in the concept of the ‘glycemic tetrad’.18

Glycemic variability (GV) can be simply defined as the degree of daily blood glucose fluctuations (peaks and nadirs) in an individual.19 It comprises of both postprandial glucose spikes as well as the hypoglycemic episodes. Glycemic variations are of two types: Variations measured within a day are called as intraday glycemic variations and the glucose variations measured at the same time on two consecutive days are called as inter day glucose variations. Defective glycemic regulation and reduced insulin availability are presumptive etiological factors of GV.20 Even though certain degree of glycemic variations is observed in normal individuals, it increases in people with diabetes and impaired blood glucose tolerance.19

Several studies attribute hyperglycemia and dysglycemia (peaks and nadirs) to the occurrence of various microvascular and macrovascular complications
in diabetes. Excessive protein glycation end products and activation of oxidative stress are suggested to be underlying pathophysiological mechanisms causing these vascular complications. Hypoglycemia along with glycemic variations can influence the onset and progression of diabetes complications and can be troublesome in patients treated in intensive care units (ICUs) for clinical conditions other than diabetes.

Several methods to effectively measure postprandial hyperglycemia and GV are available currently. Ambulatory glucose profiling (AGP) is one such technique which retrospectively analyze blood glucose levels from the data collected with flash glucose monitoring (FGM). The FGM and continuous glucose monitoring (CGM) provides information that could not be obtained with periodic capillary blood glucose monitoring, provides all-over the day coverage and alerts and alarms for actual or looming hypo- and hyperglycemia. This information can be used to educate, motivate, and alert people with diabetes. The FGM or CGM is medically recommended for patients with frequent, severe, or nocturnal hypoglycemia, especially in those who are unaware of it. Several studies indicated that consistent use of CGM results in better glycemic control. A meta-analysis on fourteen RCTs by Floyd et al. showed a significant reduction in HbA1c and duration of hypoglycemia with CGM use. Similarly, a cochrane review of 22 RCTs revealed a reduction in HbA1c with higher compliance to CGMS when compared to self-monitoring of blood glucose (SMBG).

In the end, proper biological rationale and enough evidence convince us to endorse the concept of GV as an important risk factor that is directly involved in the pathogenesis of the vascular complications of diabetes. Overall, it is persuading enough to propose that regulating glycemic variability is necessary to achieve proper glycemic control in diabetes patients. Collectively, GV and CGMS could help in redefining reasonable interventions in the resource limited healthcare environment of countries such as India.

**Quality of Life**

Of late quality of life (QOL) has emerged as an important parameter in the general disease management routine. The QOL is defined as a multidimensional construct incorporating an individual’s subjective perception of physical, emotional, and social wellbeing. It includes both a cognitive component (satisfaction) and an emotional component (happiness). In general, QOL is low in diabetes patients and it is positively correlated with duration of the disease. Past research on QOL in diabetes has revealed that patients desired to improve the way they feel. Complications associated with diabetes affects the QOL of patients. Moreover, acute and bothersome side effects and lifestyle restrictions prevent the patients from motivating to comply with the treatment even though it promises long-term benefits. Therefore therapeutic policies should aim at reducing the complications and also improve treatment adherence and compliance. Benefits of diabetes therapy could be properly reaped through the maximum convenience of the dosing regimen and maximal QOL benefits. Martinez et al suggest that QOL in patients could be enhanced by including interventions that could overcome the negative attitude towards treatment adherence and by promoting medical prescription knowledge. Furthermore, balance between treatment burden and health outcomes could be achieved with the wide variety of interventions available in the current market.

In general patient compliance is poor in diabetes irrespective of the treatment regimen (oral antidiabetic agents or insulin). Moreover, physicians should notice that failure to achieve target glycemic levels could be because of inadequate self-management rather than less effectiveness of the prescribed medication. In such cases, patient counseling to improve treatment adherence should be preferred rather than increasing the dose or changing the medication. Insulin-based therapy is generally associated with decreased QOL, therefore, it should be carefully considered before various combinations of oral medications are used. To sum up, QOL in diabetes is affected by two categories of factors: the disease derived factors such as duration and complications and therapy derived factors such as adverse events, cost, life style restrictions imposed by the treatment. Therapeutic factors generally influence the compliance to treatment and when the compliance is decreased, diabetic complications increase resulting in the deterioration of QOL in a cyclic process. Hence, medications used to treat diabetes should reduce the complications and also contain the features to enhance adherence.

International diabetes guidelines has mentioned the importance of QOL during the course of treatment. The American diabetes association (ADA) recommends to use a patient-centered communication style that incorporates active listening, elicits patient preferences and beliefs, and assesses literacy, numeracy, and financial barriers. They also suggest that a successful medical evaluation depends on beneficial interactions between the patient and the care team. Individualization of treatment based on patients’ preferences, values, and goals is also recommended.

QOL is generally assessed using a broad questionnaire that
translates an individual subjective perception into numerical scores. Accuracy and reliability of a QOL tool depends on the extent to which it addresses the factors pertaining to the local population such as language, socio-economic elements, culture, race and religious beliefs. Several instruments/questionnaires are available to assess QOL. While instruments such as World Health Organization – BREF (WHO-BREF), EuroQol five dimensions questionnaire (EQ-5D) and Short Form – 6D (SF – 6D) are used for general QOL assessment, questionnaires such as Diabetes Quality Of Life Measure (DQOL), Diabetes-Specific Quality Of Life Scale (DSQOLS) and Diabetes – 39 (D - 39) are specifically used to measure QOL in diabetics. As India is a diverse country with enormous cultural and socio-economic disparities, QOL assessment tools created for other ethnic populations might not derive complete and proper information. Therefore, India specific QOL measurement tool is the need of the hour. In this regard, Nagpal J et al. has developed Quality Of Life Instrument for Indian Diabetics (QOLID), to assess the QOL of Indian diabetes patients. It comprises of eight domains and 34 items (questions) evaluating the physical health, socio-economic and psychological status of a patient. The first three domains role limitation due to physical health, physical endurance, and general health could be classified as health related quality of life (HRQOL); they evaluate the general health and wellbeing of an individual. The remaining five domains treatment satisfaction, symptom botherness, financial worries, emotional/mental health and diet advice tolerance reflect the diabetes specific quality of life (DSQOL). Further work is mandated to validate this instrument across a wider geographical and socio-economic spectrum and in different community settings.

To summarize, QOL should be considered en route to achieve optimal glycemia in a diabetes patient. From this viewpoint, following are some of the important attributes of any antidiabetic therapy: it should be simple to follow and affordable, it should have convenient dosing regimen and least side effects, it should not impose too many lifestyle restrictions and overall, it should improve the way an individual feels about oneself.

Collectively, the glycemic pentad as a new concept deserves to have its position in the diabetes management course. It is imperative that a global antidiabetic strategy should be aimed at reducing the four components of glycemic pentad i.e., FPG, PPG, HbA1c, and glucose variability and improving the fifth element, quality of life.

Achieving Goals of Glycemic Pentad with Anti-Diabetic Therapy

Anti-diabetic agents

Several varieties of antidiabetic agents are currently available. On the basis of mode of administration, anti-diabetic therapy can be broadly categorized into injectable and non-injectable or oral therapy. Insulin and its analogues and glucagon like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs) belong to the injectable category. Oral antidiabetic (OADs) category is overwhelming, with a variety of drugs that have different modes of action. Insulin secretagogues such as sulphonylureas (SU), meglitinides and DPP-4 inhibitors stimulate the β-cells of pancreas to secrete insulin. Insulin sensitizers including biguanides, thiazolidinediones, and DPP-4 inhibitors prevent hepatic glucose production and increase glucose uptake in the peripheral tissues such as muscle and adipose tissue. Two other classes of drugs, alpha-glucosidase inhibitors (AGIs) and SGLT-2 inhibitors function at the level of glucose absorption and excretion respectively. While AGIs delay the intestinal glucose absorption by inhibiting enzymes responsible for complex carbohydrate breakdown, SGLT-2 inhibitors prevent glucose reabsorption in the kidney by regulating the activity of glucose transporters.

Attaining optimal glucose levels is the foremost objective of any antidiabetic therapy. Decision to begin or alter a therapy is based on the prevailing glycemic levels. When monotherapy fails to produce ambient glycemic levels, multiple drugs with different modes of action can be considered. Factors such as safety, efficacy, additional benefits in reducing complications, ease of use, and expense are important considerations while choosing an OAD. Furthermore, HbA1c levels also provide a direction towards decision making; while high HbA1c levels (≥8.5%) desire to be treated with fast acting agents or combination therapy, levels close to target indicate the use of agents with lesser potential and/or slower onset of action. Overall the treatment regimen should be planned in such a way that all of the five goals of glycemic pentad are attained both at the convenience of physician and patient.

The list of different antidiabetic agents, their mode of action and ability to reduce different components of glycemic triad is listed in Table 1. Regardless of the mode of administration or action, sole aim of any anti-diabetic therapy is to maintain glucose homeostasis with minimal adverse events and maximal convenience or ease. Since Indians constitute a special category of diabetes population with distinct dietary habits and socio-economic and cultural backgrounds, choice of antidiabetic therapy should not only rely on the effectiveness of the agent but also on the cost, ease of administration and other confounding factors.
Table 1: Summary of antidiabetic agents. List of different antidiabetic agents with their mode of action, abilities to reduce components of dysglycemia and cost**

<table>
<thead>
<tr>
<th>Class of drugs</th>
<th>Mode of action</th>
<th>HbA1c (%) reduction</th>
<th>FPG reduction</th>
<th>PPG reduction</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Insulin secretagogue</td>
<td>0.8 – 2.0</td>
<td>+++</td>
<td>++</td>
<td>✓</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Insulin secretagogue</td>
<td>0.5 – 2.0</td>
<td>+</td>
<td>+++</td>
<td>✓</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Insulin secretagogue</td>
<td>0.5 – 1.0</td>
<td>+++</td>
<td>++</td>
<td>✓✓</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Insulin sensitizer</td>
<td>1.5 – 2.0</td>
<td>+++</td>
<td>+</td>
<td>✓</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Insulin sensitizer</td>
<td>1.4 – 2.6</td>
<td>+++</td>
<td>+</td>
<td>✓</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Insulin secretagogue and insulin sensitizer</td>
<td>0.5 – 0.8</td>
<td>+</td>
<td>+++</td>
<td>✓</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Delay carbohydrate absorption in intestine</td>
<td>0.5 – 0.7</td>
<td>0</td>
<td>+++</td>
<td>✓</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Prevent glucose re-absorption in kidney</td>
<td>0.7 – 1.0</td>
<td>++</td>
<td>++</td>
<td>✓✓</td>
</tr>
</tbody>
</table>

**References:35,36,37,38,39; 0 = neutral; + = mild; ++ = moderate to marked; +++ = marked; ✓ = cheap; ✓✓ = quite cheap; ✓✓✓ = expensive; ✓✓✓✓ = very expensive

Insulin vs. Oral Antidiabetic Agents

It is an undisputed fact that insulin is the effective therapeutic agent for the control of diabetes which cannot be re-placed by any other antidiabetic agents in critical cases (i.e. HbA1c > 9.0%). However, several factors hinder the routine use of insulin in diabetes patients. Inconvenience to life-style caused due to strict timings and multiple doses,36 fear of hypoglycemic episodes,37 concerns over weight gain and mitogenic potential,38 fear of injections and needles39 are perceived as some of the barriers for insulin use. Mandatory regular monitoring of blood glucose levels during insulin therapy is also one of the reasons for less treatment adherence.36 Major drawbacks of insulin treatment include negative perception and noncompliance.40 Furthermore, patient self-management during insulin therapy requires adequate knowledge on storage, syringe and vial compatibility, needle size, injection site and technique and dosing.40 All of this could have significant impact in the Indian population where majority of patients don’t give adequate emphasis on health care awareness.

When QOL and patient-perceived difficulties are considered, OADs score better over insulin treatment.31 Ample availability of different OADs that can effectively attain glucose homeostasis helps in delaying the initiation of insulin therapy and therefore could increase a patients’ quality of life. Particularly, triple fixed combination therapy involving agents with different modes of action could help in achieving target glycemic goals when mono and dual therapy have failed. However, it has to be strictly noticed that OADs are not replacement for insulin treatment and insulin should be appropriately prescribed as and when necessary.

Fixed Dose Combination Therapy

Increasing body of evidence suggest that glycemic targets in patients not taking insulin could be effectively attained with a combination of different antidiabetic agents with distinct modes of action.42 Apart from that, high dose monotherapy could cause more side effects than low dose combination therapy.42 Usually, guidelines recommend the use of combination therapy of two or more OADs with distinct modes of action when glycemic goals are not achieved with metformin.2 Fixed dose combinations (FDC) or polypill(s) have emerged as important players in the management of not only diabetes but also other diseases. They contain fixed doses of more than one active pharmaceutical ingredient. The FDCs are simple to use, can be effective in controlling aberrant glucose levels, and have the tendency to enhance adherence and persistence to therapy.43 Use of FDCs could effectively overcome several barriers for treatment adherence such as pill burden, dosage frequency, flexibility and ease during administration and medication costs.43 Optimal glycemia can be obtained with triple FDCs in a safe, well-tolerated and economic manner.44

Landmark trials such as DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) has proven that intensive glucose lowering from the early stages of diabetes is associated with lesser risk of diabetes associated complications.11, 45 In many cases, this requires using fixed dose combinations as monotherapies are not effective at regulating all aspects of dysglycemia. Current guidelines also propose a paradigm shift in the treatment approach, where combination therapy is recommended when HbA1c levels are elevated in the initial stages of diagnosis.46 As discussed above, achieving the targets of all variables in glycemic pentad is important in the holistic diabetes management. However, such goals can only be attained with combination therapy. For instance, metformin could only control fasting glucose levels. Sulphonylureas could regulate PPG effectively and to some extent PPG. It has to be noted that in Indian scenario agents effectively downsizing postprandial glucose excursions are also crucial. Therefore a combination therapy controlling fasting, inter-meal and postprandial hyperglycemia is essential for obtaining optimal glucose levels in the Indian population; in fact, this is true in all those people who consume heavy meals containing high amount of carbohydrates and in people with high PPG levels.

Several FDCs are available in the market. The FDC of metformin and sulphonylurea is a established combination among
the Indian market. The FDCs of metformin or sulphonylurea with other antidiabetic agents are also routinely available. Of the contextual interest is the triple fixed dose combination of metformin, glimepiride, and voglibose. This combination has different drugs optimizing glucose levels through distinct mechanisms; metformin is an insulin sensitizer, glimepiride is an insulin secretagogue and voglibose delays glucose absorption in intestine.

**Fixed Dose Combination of Metformin, Glimepiride, and Voglibose Might be Appropriate to Achieve all Goals of Glycemic Pentad**

Glycemic pentad acknowledges a multidimensional approach in treating diabetes. It suggests that the therapy should not only aim at clinical features (FPG, PPG, HbA1c, and GV) but also consider the socio-economic and psychological status of the patients. Among the clinical aspects, the major factor that sets Indians (Asians) apart is the postprandial hyperglycemia which is due to intake of high carbohydrate content in the diet. Hence, an antidiabetic agent that could effectively reduce these excursions and therefore reduce the GV is essential. The antidiabetic therapy has to be affordable and it should be relatively simpler to follow. The FDCs have repeatedly proven their effectiveness in attaining these elements of disease management. Therefore, an FDC of metformin, glimepiride, and voglibose appear to have all the necessary characteristics to fulfill this criterion.

Metformin and glimepiride are the most commonly prescribed diabetic agents in India. Safety and efficacy of these molecules was proved repeatedly. They are known to reduce the fasting glucose levels and HbA1c and to some extent postprandial glucose. Hypoglycemia and weight gain are the usual adverse events associated with SUs. However, glimepiride use is associated with less hypoglycemic episodes when compared to other SUs except glipizide. Furthermore, glimepiride is associated with weight neutralizing/reducing effects and therefore it might be advantageous. When compared to various other sulphonylureas, glimepiride has highest extra pancreatic activity and lowest ratio of increase in plasma insulin and decrease in blood glucose activity. Combination of metformin and glimepiride was found to be effective when compared to metformin plus DPP-4 inhibitors in a systematic review and meta-analysis of safety and effectiveness variables. Efficiency of voglibose is far bigger and its tolerability is also high when compared to other AGIs including acarbose and miglitol. Furthermore, voglibose is able to improve insulin sensitivity, increase high-density lipoprotein (HDL) and apolipoprotein A-I levels and reduce insulin and triglyceride levels in the body. In addition, voglibose administration elicits changes in the intestinal microbiota and reduces body weight, total cholesterol and triglyceride levels.

Voglibose is also associated with increase in GLP-1 levels in the circulation which could further help in attaining glucose homeostasis. Apart from controlling PPG and hyperlipidemia, voglibose is known to reduce oxidative stress markers and soluble intercellular adhesion molecule 1, which is an inflammatory marker. Moreover, voglibose is equally effective as sitagliptin at improving endothelial dysfunction in type 2 diabetes patients. Pharmacokinetic properties of metformin, glimepiride, and voglibose are provided in Table 2.

Combined use of voglibose and sulphonylureas might be effective in controlling postprandial plasma glucose and delay the onset of vascular complications in patients with type 2 diabetes. Even IDF guidelines suggest that the AGIs could be effective in combination with metformin or sulphonylurea. Therefore, addition of voglibose to metformin and glimepiride combination would effectively reduce the postprandial glycemic excursions along with FPG and HbA1c. As a result, the overall glycemic variability could also be reduced significantly. GV parameters such as mean amplitude of glycemic variations (MAGE) and standard deviation (SD) around the mean glucose levels were found to be similar or better with metformin use when compared to insulin or meglitinides. In an open label prospective study on T2D patients, Matsumoto et al have demonstrated that voglibose is able to effectively reduce the daily glycemic excursions and functional burden of the β cells. Furthermore, when compared to sitagliptin, voglibose significantly reduced the slope of postprandial elevation of glucose after every meal and also increased the time taken to attain maximal glucose levels post dinner. All these evidences clearly suggest that metformin and voglibose are effective at managing glycemic excursions.

The Diabetes Prevention Program (DPP) and its Outcomes Study (DPPOS) revealed that the investment made on lifestyle interventions and metformin to prevent diabetes in high-risk adults is highly beneficial. Long-term use of metformin stabilized body mass index (BMI) and improved body composition in adolescent obese and insulin resistant subjects. Evaluation of overall treatment satisfaction with Diabetes Treatment Specific Questionnaire, status version (DTSQs) revealed no significant differences between combination of metformin plus glimepiride or empagliflozin. Furthermore, though a population based mathematical model Zhang et al has found that the use of SUs as second line of therapy resulted in similar outcomes such as life years (LYs) and quality.
adjusted life years (QALYs) as DPP-4 inhibitors or GLP-1 RAs or insulin. In addition SU based therapies incurred significantly low cost per QALY and prolonged the time required for insulin treatment. Similarly, voglibose along with standard care resulted in cost saving and prolonged life expectancy in glucose intolerant Japanese patients. Together these evidences suggest a beneficial role of metformin, glimepiride, and voglibose in improving the QOL. Considering all these facts, it is rationale to put the triple combination of metformin, glimepiride, and voglibose at the forefront of diabetes management in India.

Summary of safety and efficacy studies on the combination of metformin, glimepiride, and voglibose is available in Table 3. Availability of limited number of studies assessing the safety and efficacy of this triple FDC demands the necessity for further high quality studies. However, it is evident from the already available information that this triple combination is safe to use and effective at reducing FPG, PPG, and HbA1c (Table 2). Pankivn VI et al. also reported a significant weight reduction in the group of patients treated with this FDC when compared to the dual combination of metformin and glimepiride. This combination is well tolerated in general, yet, some patients might experience temporary side effects such as abdominal pain, headache, diarrhea, flatulence, sweating and hot flushes.

Consensus Statement on the Position of Glycemic Pentad in Diabetes Control and the FDC of Metformin, Glimepiride, and Voglibose in the Management of Diabetes In India

**Objectives**

Research on diabetes has been endorsing the importance of GV and QOL in the management of diabetes along with FPG, PPG, and HbA1c. Even though some guidelines have been acknowledging the significance of QOL in diabetes control, GV has been largely ignored. Furthermore, Indian diabetes patients are different from western people due to their varied dietary and cultural habits. So diabetes management there require slight modifications, particularly in regulating postprandial hyperglycemia through a cost-effective and easy to follow regimen. Various OADs are available in the market. Even though this gives quite many opportunities to physicians, often it creates confusion among health care professionals working at primary health care centers where most of the Indian diabetes population is treated. Therefore, there is a need for a simple medication which could offer easy and economical alternative to treat diabetes.

**Methodology**

An expert group, Glycemic Pentad forum, consisting of 51 leading medical experts from different regions of India in the field of diabetology were convened into 5 groups to bring a consensus on the position of glycemic pentad in diabetes control and the FDC of metformin, glimepiride and voglibose in the management of diabetes in India. Each group met independently in different cities of India, reviewed the relevant literature, expressed their opinions on the position of glycemic pentad and shared their personal experiences with the use of triple FDC of metformin, glimepiride, and voglibose in clinical practice. A final consensus statement is generated after the key points in different meetings were shared among the forum and an approval is given by all members of the forum.

**Key Points from the Consensus Meetings**

Consensus on the position of glycemic pentad in the management of diabetes in Indians

Recent advances in the field of diabetology incited a further leap to diabetes management and added two more dimensions - glycemic variability (GV) and quality of life (QOL) - to already existing glycemic triad and the composite of these 5 elements is now identified as Glycemic Pentad. Glycemic variations are the physiological consequences of circadian rhythms of hormones involved in glucose control and also due to postprandial spikes in glucose levels. Clinical evidences suggest that patients with high GV are prone to high risk of retinopathy. Patients with painful neuropathy had high GV when compared to patients with painless neuropathy. Also, high GV is associated with increased carotid media thickness. Even though the fluctuation reduction with insulin and GLP-1 added together (FLAT-SUGAR) study has provided some evidences on the benefits of controlling GV,
Table 3: Efficacy and safety studies on metformin, glimepiride and voglibose combination. A list of safety and efficacy studies that were carried out on the combination of metformin, glimepiride, and voglibose either as FDC or as triple therapy

<table>
<thead>
<tr>
<th>Author et al., Type of study</th>
<th>No. of subjects (n); duration of study</th>
<th>Drug dosage</th>
<th>Efficacy and safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hari K. et al., 2014; 20 Non-randomized, open, non-comparative, mono-centric study.</td>
<td>n = 20; 4 months</td>
<td>Metformin 500mg (SR#) + Glimepiride 1/2mg + Voglibose 0.2mg OD. (FDC)</td>
<td>Significant reduction in FPG (181±10.2 mg/dl to 168±2.97 mg/ml; P &lt; 0.0001), PPG (239±11.2 mg/dl to 140±4.22 mg/dl; P &lt; 0.0004) and HbA1c (9.07 ±0.346 to 6.51±0.129; p &lt; 0.0001). All of the patients tolerated the drug and no adverse events were reported.</td>
</tr>
<tr>
<td>Faruqui AA, 2016; 27 Non-randomized, open, non-comparative, mono-centric study.</td>
<td>n = 50; 3 months</td>
<td>Metformin 500mg (SR#) + Glimepiride 0.5mg + Voglibose 0.2mg BD. (FDC)</td>
<td>Significant decrease in HbA1c value 10.6 ± 1.3 vs. 6.6 ±0.4 (P &lt; 0.0001), FPG levels 208.33mg/dl vs. 118.06 (P &lt; 0.0001), and PPHG levels 360.14 mg/dl vs. 186.36. (P&lt;0.0001). None of the patients complained about adverse events including nausea, vomiting, and headache at the given doses of medication.</td>
</tr>
<tr>
<td>Rao C. et al., 2013; 28 Non-randomized, open, non-comparative, mono-centric study.</td>
<td>n = 20; 3 months</td>
<td>Metformin 500mg (SR#) + Glimepiride 1/2mg + Voglibose 0.2mg BD. (FDC)</td>
<td>Significant decrease in HbA1c (8.86± 0.7111 gm/dl vs. 8.0 ± 0.66 gm/dl), fasting (137±17.64 mg/dl vs. 116.8 ± 6.129 mg/dl, P &lt; 0.0001) and post prandial blood glucose level (237.8 ± 59.22 mg/dl vs.173.4 ± 27.6 P &lt; 0.0004) was observed from baseline.&lt;br&gt;This triple combination was well tolerated.</td>
</tr>
<tr>
<td>Jindal A. et al., 2014; 29 Open label study</td>
<td>n = 30; 6 months</td>
<td>Metformin 500mg BD + Glimepiride 2mg BD + Voglibose 0.2mg TDS</td>
<td>Significant reduction (p&lt;0.001) in FPG, PPG and HbA1c over a period of 6 months. Side effects such as abdominal pain, headache, diarrhea, flatulence, sweating, and hot flushes are observed.</td>
</tr>
<tr>
<td>Murti K. et al., 2016; 30 Prospective, open-label, comparative study</td>
<td>n = 75; 10 months</td>
<td>Dual therapy group: Metformin 500mg + Glimepiride 1mg Triple therapy group: Metformin 500mg + Glimepiride 1mg + Voglibose 0.3mg</td>
<td>Increase in HbA1c was high in group I (1.5 [1.1; 1.9] % (p &lt; 0.05) than group II (0.1 [0.09; 0.6] % (p &gt; 0.05) after 12 weeks of treatment. Decrease in HbA1c was observed from baseline to end of study in both dual and triple therapy groups, it was larger in triple therapy group.</td>
</tr>
<tr>
<td>Pandey VI et al., 2016 Prospective, comparative study</td>
<td>n = 45; 12 weeks</td>
<td>Group I: Metformin + Glimepiride + Voglibose 0.2mg TDS. Group II: Metformin + Glimepiride +</td>
<td>Decrease in HbA1c value 10.6 ± 1.3 vs. 6.6 ±0.4 (P &lt; 0.0001) was observed from baseline. TDS. Body weight reduced significantly by 2.1 kg in group I while no response was observed in group II. Safety was proven in terms of functional states of liver and kidney.</td>
</tr>
</tbody>
</table>

FDC: Fixed dose combination; # SR: sustained release; OD: Once daily; BD: Twice daily; TDS: Three times in a day

Further high quality research is recommended to strongly establish these facts. GV is of two types: 1. Intra-day variations which are vertical glycemic fluctuations within a day. 2. Inter-day variations which are observed as time wise glycemic fluctuations between different days. Several evidences suggest that GV is an important predictor of hypoglycemia whereas HbA1c could not provide any such information. Therefore, it is imperative to acknowledge the importance of controlling glycemic variations in diabetes patients.

Off late QOL has emerged as an important element in the management of diabetes and also in the overall health care of an individual. It predicts an individual’s capacity to manage disease and maintain long-term health and well-being. Poor QOL worsens the life of an individual in a positive feedback loop. In diabetic patients, poor QOL leads to diminished self-care which results in deregulated glycemic control. This leads to increase in the risk of diabetes associated complications which in turn affect the QOL of an individual again. Therefore, it is sensible to address the issue of QOL of a patient during the diabetes treatment.

Considering all these facts, it is convincing to incorporate glycemic variation and quality of life as new dimensions in the overall diabetes management program and therefore glycemic pentad as a fresh concept has utmost significance in the holistic control of diabetes. Hence, it is rational to identify the better combination therapy that could score well in regulating all five domains of glycemic pentad.

Consensus on the role of triple FDC of metformin + glimepiride + voglibose in regulating glycemic variability

Post meal hyperglycemia, particularly post breakfast hyperglycemia is the major factor influencing the glycemic excursions in Indian diabetes patients and are important in regulating glycemic variation and the overall glycemic control and quality of life. Furthermore, for the same amount of carbohydrate intake, Asians have higher postprandial glucose values when compared to Caucasians.

Even though the carbohydrate content in the breakfast is lower than lunch and dinner, post breakfast glucose spikes are observed to be higher in the Indian diabetes patients (personal experience from
Continuous glucose measurement is important to understand the dynamics of blood glucose levels. Since this technique is expensive to some individuals, 7 point glucose measurements are recommended to be performed routinely with intermittent AGP.

Choice of any antidiabetic drug should be individualized based on the patients’ phenotype, history, affordability, and acceptance.

Changing the timing of medication based on AGP is more beneficial in improving the glycemic control rather than increasing the dosage of the medications.

In the Indian scenario, where consumption of carbohydrates is high, alpha glucosidase inhibitors are the best choice of drugs after metformin and glimepiride.

Alpha glucosidase inhibitors could be preferred over bolus insulin in controlling post meal hyperglycemia when hypoglycemic episodes are considered. This is mainly because it is very difficult to the patient to plan their carbohydrate intake based on the insulin dose on a daily basis.

Voglibose could decrease glycemic variations by controlling postprandial glucose excursions and also effectively reduce the risk of hypoglycemia. Voglibose (alpha glucosidase inhibitors) is under used in Indian population when compared to other Asian countries.

Voglibose can be prescribed to regulate uncontrolled postprandial glucose peaks in those patients who are already on metformin, glimepiride, and basal insulin. Moreover, addition of voglibose at night could reduce the need for SU or bolus insulin who have the tendency to cause nocturnal hypoglycemia.

In patients who are predisposed to gastroparesis or bloating, start with low dose of voglibose (0.2 mg) and up-titrate it to maximal dose (0.3 mg) after the patient is acclimatized to the treatment. Voglibose should be restricted in patients with active hepatic disease.

Metformin and glimepiride has been a successful combination in the diabetes management scenario of Indian setup. On the similar note, it is also a well-accepted fact that the effect of this combination reduces after sometime due to various physiological consequences and therefore it compels the inclusion of a new agent.

Triple fixed dose combination (FDC) of metformin, glimepiride, and voglibose is effective in reducing glycemic variability and HbA1c in Indian diabetic patients. The results are very conspicuous when data from triple FDC are compared to metformin + glimepiride dual combination.

In order to control post dinner hyperglycemia in patients who have nocturnal hypoglycemia after sulphonylurea (SUs) use it is recommended to down titrate the SU dose and incorporate voglibose into the treatment regimen. This combination can also be prescribed as up-titration to the ongoing medication or as a replacement therapy in the patients who are already on a different triple drug combination.

Twice daily dose of this FDC after breakfast and dinner is sufficient to prevent the glycemic excursions in a day. However, as and when required, elevated blood glucose levels post lunch or evening snack could be handled with voglibose alone.

The ideal time to take the triple drug is 15 - 30 minutes before the meal. However, when practical inconvenience is considered, it can also be taken just before the meal, at the time or after the consumption of a meal. Even if the patients miss the appropriate timing, it is recommended that they take it sometime rather than missing the dose completely.

This combination provides an extended temporal window for the patients and the physician before an insulin dose is initiated. However, it is not a substitute for insulin therapy. Patients who have very high HbA1c or PPG levels and require insulin therapy should be given appropriate treatment.

Effective treatment regimens should include GLP-1 receptor agonists and DPP-4 inhibitors along with voglibose in order to achieve over all good glycemic control. Glitpins are a good option when patients have both high FPG and PPG values whereas when only PPG values are more, voglibose is a better choice.

Overall the triple FDC of metformin, glimepiride, and voglibose is effective in attaining good glycemic control in diabetic patients. While glimepiride controls FPG and to some extent PPG, metformin regulates nocturnal glucose levels and voglibose majorly prevents PPG excursions. As a result, this combination could effectively regulate overall glycemic levels. However, high quality studies comparing the efficacy of triple fixed dose combination with dual therapy of metformin and glimepiride or any other antidiabetic therapies are recommended so as to fairly demonstrate the additive benefits of this triple combination in the control of diabetes.

Consensus on the role of metformin, glimepiride and voglibose FDC in achieving good QOL scores in Indian diabetic patients

Use of the triple drug combination of metformin, glimepiride, and voglibose could result in the overall improvement of QOL in diabetes patients. However, compelling evidences that substantiate this concept has to be generated in the due course through systematically designed QOL studies.

Triple FDC of metformin, glimepiride, and voglibose is associated with improving overall glycemic control, increasing
compliance, reducing pill and cost burden on the patient. Therefore, all these elements collectively enhance the QOL of an individual.

Generally, Indian population are reluctant to reduce high carbohydrate content in their diet. In those people, this FDC provides an excellent option for maintaining ideal glucose levels without compromising much on their food habits. As a result, diet satisfaction is improved and QOL is enhanced.

Since triple therapy reduces the pill and cost burden, it has fairly good chances of increasing the treatment adherence and compliance, therefore, it will result in overall good glycemic control and better QOL.

Usually, increase in pill number put a psychological burden on the patient that the disease has worsened. However, with the triple combination therapy, this aspect can be easily circumvented.

Simplified therapy is one of the fundamental characteristics to improve compliance. The FDC of metformin, glimepiride, and voglibose provide such uncomplicated option to the patient, which ultimately leads to improved QOL.

The FDC of metformin, glimepiride, and voglibose is associated with decreasing hypoglycemia episodes and HbA1c levels, which in turn improves the psychosocial behavior of a patient.

Voglibose as a combination with metformin and glimepiride is a better choice drug in comparison to DPP4 inhibitors or SGLT2 inhibitors when compliance, convenience and cost effectiveness are considered.

Compliance to treatment and diet adherence of patients can also be increased by showing their own AGP data.

Patients should be advised on strict diet plan before the onset of any anti-diabetic therapy as frequent changes in diet and lifestyle patterns often leads to confusion in both physicians and patients. In some cases, it might also lead to severe hypoglycemia as well. As a result, the QOL is also affected.

**Overall consensus on the use of the triple FDC of metformin, glimepiride, and voglibose in attaining goals of glycemic pentad in Indian diabetic patients**

Triple combination of metformin, glimepiride, and voglibose is an important armamentarium in the control of glycemic pentad. The drug combinations could effectively regulate FPG and PPG, and therefore the other two elements in glycemic pentad HbA1c and glycemic variations are also well controlled. As the improvement in glycemic control reduces the burden of diabetes associated complications, it improves the QOL of an individual. Therefore, all objectives of glycemic pentad could be collectively achieved with a single therapy. Hence this combination definitely has a bigger role to perform in the overall diabetes management of Indian population.

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Concept and Identification of “Soft Bipolarity” in Patients presenting with Depression: Need for Careful Screening by Physicians

Pooja Patnaik Kuppili¹, Priyanka Yadav², Raman Deep Pattanayak³

Abstract

The bipolar spectrum is a broader concept, which questions the strict dichotomous categorical division of erstwhile manic-depressive illness into two discrete categories viz. bipolar disorder and major depressive disorder, thereby overlooking a wide ‘spectrum’ of patients which lie ‘in between’ the two extremes. The presence of underlying bipolar ‘spectrum’ or ‘soft bipolarity’ often goes undetected in patients presenting with major depression. This sub-group of patients may not stabilize with indiscriminate use of anti-depressant drugs, and without proper management, it may be associated with continued non-responsive symptoms, increased suicidality and poorer prognosis. There is a need to suspect and identify such cases of soft bipolarity/spectrum by early screening of patients with major depression presenting to medical settings. The review paper covers the current concepts and understanding of bipolar spectrum disorders which is aimed to facilitate early identification, management and referral of cases detected to have soft bipolarity in the general medical settings.

Introduction

Mood disorders are characterized by a fundamental disturbance of mood or affect towards either depressive side or elation, along with the corresponding changes in the activity level, thought etc. In terms of years lived with disability, depression is the second leading cause of global burden.¹ By the year 2030, depression is projected to be the leading cause of global disease burden worldwide, highlighting the public health significance of mood disorders. Depression and bipolar disorders together account for around 47% of the DALYs (disability-adjusted life years) contributed by mental and substance use disorders.² At least 10% of the patients visiting primary care physician may have major depression.³ Physicians working in primary and secondary care settings are often the first point of contact for depressive symptoms. Large scale recent studies have found that the depressive severity was not different, and symptomatic presentations did not differ substantially between primary care and specialty settings.⁴ Major depressive disorder is more similar than different among patients at primary and specialty settings. Many a times, their treatment is initiated in the general medical settings, especially where psychiatric services are not readily available. Therefore, it becomes imperative that physicians in primary and secondary health care settings are updated and sensitized about the various key aspects of mood disorders in their clinical practice.

One such scenario is the presence of underlying bipolar ‘spectrum disorders’ or ‘soft bipolarity’ which often goes undetected in patients presenting with depression. The review paper covers the current concepts and understanding of ‘spectrum’ and ‘soft bipolarity’ which is aimed to facilitate early identification, management and referral, if necessary.

Relevance for the Physicians

Less than 25% of antidepressants are prescribed by psychiatrists or other mental health specialists. More than 70% of antidepressants are prescribed by the general physicians across most of the world.⁵ The situation is not different in India in the background of wide mental health gap, with antidepressants being widely prescribed without the consultation of mental health specialists. The figures are alarming considering the propensity of antidepressants

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causing a “switch” to mania in persons with underlying predisposition to bipolarity, leading to significant socio occupational dysfunction.

Hence the concept of soft bipolarity is of greater importance and relevance to the physicians to promote judicious use of antidepressants considering the double whammy of wide mental health gap leading to physicians providing care to depressed patients and vigorous marketing strategies employed by the pharmaceutical companies.

Understanding the Concept of ‘Spectrum’ Disorder (and ‘Soft Bipolarity’)

The spectrum is a term borrowed from physics, where the visible light after passing through the prism appears as a rainbow spectrum of colors. From a medical/psychiatric perspective, the spectrum concept includes the broad areas of psychiatric phenomenology relating to a given ‘classical’ form of disorder, but in addition, also goes on to include:

- Core, subthreshold and subclinical symptoms of the classically described disorder
- Atypical symptoms related to the prototypic configuration
- Associated features including signs, isolated symptoms, symptom clusters & behavioral patterns related to core symptoms
- Temperamental and/or personality traits

Spectra of symptoms may be prodromal, precursors of a full disorder or sequelae of a previous full disorder. From a medical perspective, there is a need to pay attention to these spectrum conditions, as this approach for bipolar spectrum disorders may help us in identifying at-risk population, lessen morbidity and providing a rationale for the use of a single group of drugs for a continuum/spectrum of disorders.6,7

The bipolar spectrum is a broader concept, and questions the strict categorical division of erstwhile manic-depressive illness by the third edition of DSM-III into two discrete categories viz. bipolar disorder and major depressive disorder. This strict dichotomy overlooks a wide ‘spectrum’ of patients which lie ‘in between’ the two extremes.

Bipolar spectrum is thus a broad inclusive term for bipolar disorders (including those beyond classical mania as well). So we can understand bipolar spectrum to encompass sub-threshold, short duration hypomanic symptoms, or depression arising in the background of cyclothymia, hyperthymic temperament, familial bipolarity or hypomania arising due to treatment.7-9 Depressed patients often fail to report past history of subthreshold hypomanic symptoms that are usually associated with intact, or even enhanced functioning.10 The clinic visits are made mainly with prominent depressive symptoms each time, which may pose a hindrance for the diagnosis of bipolar spectrum. In medical settings, since the focus is on treatment of physical illnesses, it may prevent proactive questioning about past hypomanic symptoms. Also, the lack of awareness of spectrum concept amongst physicians may lead to an oversight of important clinical indicators which may point towards bipolar spectrum while treating depression.

Currently the entity of bipolar spectrum is not separately specified under any of the traditional nosological systems such as International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM). The DSM, however, allows and specifies the diagnosis of one of the spectrum disorder viz. bipolar II disorder. For making a diagnosis of Bipolar II, it is necessary to have a current or past hypomania (as opposed to mania in BP-I) lasting at least four days in addition to major depression.11

Prevalence of ‘Spectrum’/‘Soft’ Bipolarity

The lifetime prevalence of Bipolar disorder - I (BP-I; defined as presence of depression and atleast one manic episode) is 1% in general population surveys.12 However, when we focus on the entire spectrum of bipolar disorders, the prevalence is much higher. The prevalence for the bipolar disorder II (BP-II; defined as presence of depression and atleast a hypomania) was found to be 1.67% in a large-scale epidemiological survey in U.S.13 The secondary analyses from these landmark studies revealed that if we consider the prevalence of entire bipolar ‘spectrum’ disorders, it was found to be about 6.4% in the community setting implying that the sub threshold cases are atleast five times more common than BP-I and BP-II.14 The findings were further replicated in U.S National Comorbidity Survey-Replication study with the lifetime and 12-month prevalence estimates being 1.0% and 0.6% for BP-I, 1.1% and 0.8% for BP-II, and as high as 2.4% and 1.4% for sub-threshold BPD.15 In terms of clinic prevalence, on applying the broader criteria for ‘spectrum’ bipolarity, it was seen that upto half of the patients with current diagnosis of depression may be bipolar spectrum disorders.10 Timely and accurate diagnosis may facilitate improved management and outcome for these patients.

These alarming figures thereby highlight the importance of focusing not only on the ‘classical’ bipolar disorder, but also a wide variety of difficult-to-recognize / easy-to-overlook bipolar spectrum disorders for its diagnostic relevance, and clinical as well as public health importance.
Box 1: Bipolar spectrum disorders: Akiskal and Pinto (1999)

Bipolar I - Depression and mania
Bipolar II - Depression and discrete hypomania
Bipolar III - Depression and treatment-emergent hypomania
Bipolar IV - Depression (late-life) in context of hyperthymic temperament

*Hypomania: a milder form of mania usually lasts few days with no marked dysfunction; #Hyperthymic temperament is proposed to be characterized by an excessively positive disposition, along with a set of attributes, similar to, but more stable than, the hypomania.

Key Diagnostic Schema of Bipolar Spectrum/Soft Bipolarity

Key diagnostic schema of BSD were given by researchers, notably Klerman, Akiskal & Pinto and more recently, by Ghaemi and co-researchers. Akiskal and Pinto in their landmark paper on ‘bipolar spectrum disorders’ have described the various subtypes of bipolar disorder from I to IV (Box 1). Additionally, the types I 1/2, II 1/2, III1/2, V and VI have been proposed as well.

More recently, Ghaemi et al proposed diagnostic criteria for bipolar spectrum disorders as follows:

A. At least one major depressive episode
B. No spontaneous hypomanic or manic episodes
C. Either of the following, plus 2 items from criterion D, or both of the following
   1. A family history of bipolar disorder in a first degree relative
   2. Antidepressant-induced mania or hypomania
D. If no items from criterion C are present, 6 of the following 9 criteria are needed.
   1. Hyperthymic personality (at baseline, non depressed state)

Box 2: Clinical Signs pointing towards “soft bipolarity”

2. Recurrent major depressive episodes (>3)
3. Brief major depressive episodes (on average, < 3 months)
4. Atypical depressive symptoms (DSM-IV criteria)
5. Psychotic major depressive episodes
6. Early age of onset of major depressive episode (< 25 years)
7. Post partum depression
8. Antidepressant “wear off” (acute but not prophylactic response)
9. Lack of response to 3 or more antidepressant trials

The closely related concept of soft bipolarity was first given by Akiskal and Mallya. The chief attributes of soft bipolarity are same as bipolar spectrum (only difference being that the Bipolar I subtype is excluded from rubric of soft bipolarity while included in bipolar spectrum). The severity of elated phases never reaches level of manic or manic mixed states, and remains at clinical or sub-threshold hypomanic level. Patients with soft bipolarity are often referred to as “pseudo-unipolar depression”, and may go undetected for years. The clinical signs or pointers of soft bipolarity are shown in box 2.

Perugi and Akiskal later on have further expanded soft bipolarity encompassing a variety of conditions ranging from mood, anxiety, impulse control, and eating disorders with underlying cyclothymic-anxious-sensitive disposition, mood reactivity and interpersonal sensitivity, though this concept is more of research significance as of now.

Screening for Soft-Bipolar/Bipolar Spectrum

The screening of patients for depression has been discussed in more detail in a previous review paper in JAPI. Asking just a few more questions focusing on any periods (few days to few weeks, even few hours at times) with elated mood, feeling over-energetic, overactive and decreased need for sleep etc may help delineate the subgroup of patients with bipolar spectrum who present to the physicians with current depressive symptoms.

A two-question screen for mood lability may help identify bipolar II disorder patients if there is positive response to at least one question indicating mood lability. The questions are as follows:

“Are you a person who frequently experiences ups and downs in mood over life?”
“Do these mood swings occur without cause?”

Along with these presence of atypical symptoms, reversed vegetative symptoms like hyperphagia and hypersomnia during depression instead of loss of appetite and sleep, past history of elevated mood and increased activity, family history of bipolarity or treatment induced mood symptoms should be enquired about, using questions such as: “Have you had periods of feeling so happy or energetic that your friends told you were talking too fast or that you were too ‘hyper’ than your usual self?”
Mood Disorder Questionnaire is one of the most commonly used screening tool. It has 17 questions pertaining to hypomanic symptoms, presence of several of these symptoms in the same time duration and the impact of these symptoms. When structured diagnostic interviews were applied to patients on antidepressant treatment attending family physicians 30% of the patients were found to be having bipolar disorder.23

The Bipolar Index is another assessment tool which evaluates across five domains namely signs and symptoms, age of onset, course of illness, response to treatment, and family history and researchers have found that a score ≥50 had good sensitivity and specificity for identifying bipolar disorders.24

Screening using the relevant clinical questions or instruments should be done in all patients presenting with major depressive episode in a busy outpatient setting.25

**Treatment Principles and need for Referral**

Some general principles for managing the suspected cases of soft bipolar or bipolar spectrum disorders are as follows:19,26

- **Family members should be psychoeducated about identification and delineation of the early symptoms of hypomania** (decreased need for sleep, increased energy, euphoria etc)
- **In case of a definite ‘switch’ from depression to hypomania, the dose of antidepressant drugs must be immediately reduced or stopped.**
- **In cases with Bipolar II or III, the decision may have to be made to initiate the long-term treatment with mood stabilizer (such as lithium, valproate etc) or an atypical antipsychotic drug, in order to prevent future affective episodes.**
- **In known bipolar I patients, antidepressants should be prescribed very judiciously and for short-term under the cover of mood-stabilizing medication, especially if depressive symptoms are mild.**
- **Use of tricyclic antidepressants in patients with suspected “pseudo-unipolar” depression should be avoided as they carry a higher risk for a ‘switch’ than the Selective Serotonin Reuptake Inhibitors (SSRIs) and Bupropion.**
- **Ensure a regular sleep-wake cycle to all patients with ‘soft bipolarity’, as sleep-deprivation can precipitate mania/hypomania in predisposed individuals.**

The cases with suspected clinical pointers of spectrum/soft bipolarity should be identified and sent for an expert opinion. These should be referred to a psychiatrist for further evaluation and management.

**Implications for Under-Recognition and Under-Treatment**

As the diagnosis may be more easily clinched on cross-sectional presentation of patient rather than the longitudinal history, therefore the hypomanic or subthreshold symptoms are often missed. Patients are often left in the “shadow” due to the current nosological status of bipolar spectrum not being particularly emphasized. The role of a thorough history to rule out past history of any hypomania or elated mood state cannot be overemphasized.

Misdiagnosing bipolar spectrum as pure depression has its own share of risks as majority of these patients get treated with antidepressants alone.27 There exists a risk of incomplete or inadequate remission, anti-depressant-induced switch, anti-depressant induced rapid cycling and mixed state, and destabilization of mood. Injudicious use of antidepressants in cases with underlying bipolarity may also lead to continued subthreshold symptoms, and increased risk of suicidality, poor prognosis and adverse psychosocial outcomes.28,29

While majority of the patients remain under diagnosed, there is a definite risk of over diagnosis and unnecessary exposure to mood stabilizers and antipsychotic medication. Caution is also needed regarding the potential risks of over diagnosis, which is also detrimental.

**Conclusion**

To conclude, the concept of spectrum and soft bipolarity is of increasing importance to the general physicians in the recent times owing to their clinical and public health burden. The patients with bipolar spectrum often fall prey to unscrupulous prescribing of antidepressants which may lead to devastating consequences. Hence, there is a definite need for the physicians to be wary of the clinical profile of full spectrum of bipolarity.

Some of the “soft pointers” towards bipolar spectrum should be kept in mind while assessing depressed patients. Though screening instruments are available, the feasibility of screening instruments in the busy outpatient setting is again a matter of concern. In case of switch, the antidepressant must be stopped immediately. Patients with signs of soft bipolarity may be referred to mental health professional conforming to the principle of medical ethics of non-maleficence- “Primum non nocere”.

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Statistical Evaluation of Diagnostic Tests – Part 2 [Pre-test and post-test probability and odds, Likelihood ratios, Receiver Operating Characteristic Curve, Youden’s Index and Diagnostic test biases]

NJ Gogtay, UM Thatte

Introduction

In the previous article on the statistical evaluation of diagnostic tests – Part 1, we understood the measures of sensitivity, specificity, positive and negative predictive values. The use of these metrics stems from the fact that no diagnostic test is ever perfect and every time we carry out a test, it will yield one of four possible outcomes – true positive, false positive, true negative or false negative. The 2 x 2 table (Table 1) gives each of these four possibilities along with their mathematical calculations when a new test is compared with a gold standard test.

From the example, it follows that
Odds = p/1-p, where p is the probability of the event occurring. Probability, on the other hand, is given by the formula
p = Odds/1+Odds

Bayesian Statistics, Pre-Test Probability and Pre-Test Odds

A clinician often suspects that a patient has the disease even before he orders a test [screening or diagnostic] on the patient. For example, when a patient who is a chronic smoker and presents with cough and weight loss of a six-month duration, the suspicion of lung cancer has already entered

Understanding Probability and Odds and the Relationship between the Two

Let us understand probability and odds with the example of a drug producing bleeding in 10/100 patients treated with it. The probability of bleeding will be 10/100 [10%], while the odds of bleeding will be 10/90 [11%]. This is because odds is defined as the probability of the event occurring divided by the probability of the event not occurring. Thus, every odds can be expressed as probability and every probability as odds as these are two ways of explaining the same concept.

Table 1: A 2 x 2 table of depicting the results of a new test vis à vis a gold standard test

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True Positive (TP)</td>
<td>False positive (FP)</td>
<td>a</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negative (FN)</td>
<td>True Negative (TN)</td>
<td>c</td>
</tr>
</tbody>
</table>

Positive predictive value = a/(a + b)

Sensitivity = a/(a + c)

Specificity = d/(b + d)

Negative predictive value = d/(c + d)
the physician’s mind. Thus, the clinician has already, mentally, identified some “pre-test” probability of the patient having the disease; lung cancer in this case.

Clinical decision-making, by and large, requires a combination of clinical acumen along with a correctly performed and interpreted screening or diagnostic test. When the physician allocates a “pre-test probability”, what he is applying is a field of statistics called Bayesian statistics. Herein, the knowledge of prior beliefs is used and quantified as a numerical value ranging from 0-100%. This value is then used for subsequent calculations. Bayesian statistics allows us to interpret screening and diagnostic tests in their clinical context.

Logically, the next question would be - what are the ways in which these pre-test probabilities can be allocated? These are listed below

- Subjectively based on informed opinion, consensus guidelines or experience in treating the disease in question
- An understanding of the evolution of the disease and matching it with how the disease has actually evolved in the patient
- Objectively based on available evidence [prevalence data for example]

In the example presented, the treating physician may assign a pretest probability of 60% or even higher based on his clinical acumen and what he sees in practice. How is this calculated? Let us say that the clinician is a lung cancer specialist and he sees 100 patients in three months who are chronic smokers with persistent cough and weight loss. Sixty of them eventually return a diagnosis of lung cancer based on one more tests. The pretest probability for a new patient with a similar history and complaints who presents to him in the fourth month would thus be 60%.

Mathematically, this is calculated as

Pre-test probability =
Number of patients with complaints actually diagnosed to have the disease
Total number of patients who present with the same complaints

[In this case, it would be 60/100 or 60%].

Pretest odds, however, would be 0.6/0.4 or 1.5 (the probability of the event occurring divided by the probability of the event not occurring).

The clinician next orders a test, which he hopes, will confirm [or refute] his diagnosis. The test result and the pre-test probability together will now be used to calculate the post-test probability as described below.

**Post-test Probability and Post-Test Odds**

Since the result of a diagnostic test can be either positive or negative, post-test probabilities are either positive or negative. Mathematically,

- Post-test probability = Pre-test probability x Likelihood ratio (see below for explanation), while
- Post-test odds = Post-test probability/1 – post-test probability

**The Likelihood Ratio**

[A Summary Statistic]

Likelihood ratios [LR] combine both sensitivity and specificity into a single measure and are an alternate way of evaluating and interpreting diagnostic tests. They help in making a choice of a diagnostic test or sequence of tests. LR essentially tell us how many times more [or less] a test result is to be found in diseased compared to non-diseased people. LRs are of two types – positive and negative. A positive Likelihood ratio is given by

\[
\text{Likelihood ratio }_{\text{positive}} = \frac{\text{Sensitivity [TP]}}{1 - \text{Specificity [FP]}}
\]

while a negative Likelihood ratio is given by

\[
\text{Likelihood ratio }_{\text{negative}} = \frac{1 - \text{Sensitivity [FN]}}{\text{Specificity [TN]}}
\]

Let us understand this with an example. When physical examination is carried out in patients with suspected acute appendicitis, there-is-rebound tenderness at or about the McBurney’s point, pain on percussion, rigidity, and guarding. The positive likelihood ratio for the diagnosis of appendicitis would be the ratio of those with appendicitis who have tenderness at McBurney’s point [sensitivity] by those without appendicitis who have tenderness at McBurney’s point [false positive or 1- specificity]

\[
\text{LR+} = \frac{\text{Sensitivity [TP]}}{1 - \text{Specificity [FP]}}
\]

The negative likelihood ratio LR- would be

\[
\text{LR-} = \frac{1 - \text{Sensitivity [FN]}}{\text{Specificity [TN]}}
\]

The number of patients with appendicitis who have localized tenderness at the McBurney’s point

The number of patients without appendicitis who have localized tenderness at the McBurney’s point

The negative likelihood ratio LR- would be

\[
\text{LR-} = \frac{1 - \text{Sensitivity [FN]}}{\text{Specificity [TN]}}
\]

If we were to express both these mathematically, based on the 2 x2 table, these would be as given below

\[
\text{Likelihood ratio positive or LR+} = \frac{\text{Sensitivity [TP]}}{1 - \text{Specificity [FP]}}
\]

The probability of obtaining a positive test result in patients with disease [TP]

\[
\text{The probability of obtaining a positive test result in patients without the disease [FP]}
\]

On the other hand, a negative likelihood ratio or LR- would be
The probability of obtaining a negative test result in patients with disease [FN]

The probability of obtaining a negative test result in patients without the disease [TN]

Since different tests for the same disease have different sensitivities and specificities, each test would yield a different likelihood ratio for the same disease. Let us understand this with an example. The diagnosis of prostate cancer can be made by both digital rectal examination [DRE] and Trans rectal ultrasonography [TRUS]. Manyahi JP and colleagues in their study found the sensitivity of DRE to be 66.7%, and the specificity to be 88.6%. The values for TRUS were 58.3% and 85.7% respectively. The LR + for DRE thus would be 5.8 [0.667/1-0.886], while that for TRUS would be 4.1[0.583/1-0.857]. The LR- for the two tests similarly would be 0.38 [1-0.667/0.886] and 0.49 [1-0.583/0.857] respectively.

LRs range from 0 to infinity. LRs more than 1 argue for the presence of the disease and numbers further away from 1 strengthen this argument. They, thus rule in the disease. LRs between 0 and 1 argue against the diagnosis of interest. Values of 1 or close to 1 indicate that the test may lack diagnostic value. LR- values below 1 indicate that the result is likely to be associated with the absence of the disease.

While LRs are good measures of diagnostic accuracy, these are seldom used in clinical practice as they require a knowledge of probabilities and involve calculations. Nomograms such as the Fagan’s nomogram [https://mclibrary.duke.edu/sites/mclibrary.duke.edu/files/public/guides/nomogram.pdf] are available for ease of use of LRs, but may not always be available for a quick bedside diagnosis. The logarithm of the likelihood ratio [log likelihood ratio statistic] is used to compute a p value and then compared with the critical p value of 5% that we use routinely use to check for statistical significance of a LR that is calculated.

**Clinical Application – putting Together Probability, Odds and the Likelihood ratio**

Having understood the concepts of probability and odds, pre-test and post-test probabilities and the likelihood ratios we need to put all of them together to see how they actually help in clinical decision making; the sequence for which is given below

- Calculate Pre – test probability (p)
- Derive Pre-test odds as p/1-p
- Conduct the test [screening or diagnostic] with an appreciation of its sensitivity and specificity
- See the result – positive or negative
- Calculate Post-test odds = Pre-test odds x Likelihood ratio
- Calculate Post-test probability = Post-test odds/(1+ post-test odds)
- Make a decision regarding the diagnosis

Let us understand this with the same hypothetical example. Let us say that a 60-year old male is more likely to have lung cancer than someone with 20 pack years of smoking presents with cough and weight loss of 6 months’ duration. The treating physician knows from literature that the pre-test probability of lung cancer is 60% in those with 20 pack years or more in the 50-75 age group.

- Thus, pre-test probability = 60% or 0.6

We now convert pre-test probability into pre-test odds

- Pre-test odds = 0.6/ 1-0.6 or 0.6/0.4 or 1.5

We now conduct a CT scan [low dose] which returns a diagnosis of lung cancer. In other words, the test is “positive”. Literature tells us that low dose CT has an approximate sensitivity of 80% and a specificity of 90%. Thus, the positive likelihood ratio would be

- LR + = Sensitivity [0.8]/ 1-specificity [1-0.9] = 8 [this LR + indicates that the test result is more likely in someone with lung cancer than someone without]

We now calculate the post-test odds as pre-test odds x likelihood ratio

- Thus, post-test odds = 1.5 x 8 = 12

Finally, we want to convert the post-test odds into post-test probability

- i.e., 12/1 + 12 = 12/13 or 0.92 or 92% [indicating a high probability that the patient has lung cancer]

**What if the CT scan results had been negative?**

Here, the pre-test probability of 0.6 and the pre-test odds of 1.5 would have remained unaltered. However, we would now need to calculate the negative LR or LR-

- Negative Likelihood ratio [LR-] = 1- sensitivity/specificity
- Or 1-0.8/0.9 = 0.22

Now, the post-test odds would be pretest odds x LR-

- Or 1.5 x 0.22 = 0.33

Post-test probability would be

- 0.33/1 + 0.33 = 0.25 or 25% [a much lower probability of the patient having lung cancer]

Based on these single summary statistics [92% or 25%], the physician will take the next step towards management. However, as stated earlier, because LRs involve tedious calculations that include conversion of odds to probabilities and thus are rarely used in clinical practice.
Receiver Operating Characteristic [ROC] Curve and its Interpretation

The ROC curve is a plot of the sensitivity or true positive rate on the y-axis and 1 minus Specificity or the false positive rate on the x-axis. Figure 1 depicts the various components of the ROC curve and these are described below.

The point where the x and y axis begin [0,1] depicts 0% sensitivity and 100% specificity. Both sensitivity and specificity are 0 [0,0] where the x axis ends. The upper end of the y axis would be the ideal test with 100% sensitivity and 100% specificity [1,1]. If we were to draw yet another x-axis at the top parallel to the one below, its outer end would depict 100% sensitivity and 0% specificity [0,1] [Figure 1]. The line that connects the beginning of the lower x-axis to the end of the upper x-axis is called the line of equality or random chance line where x [false positive] = y [true positive]. Thus, any ROC curve that appears below this line indicates that the test performs worse than random guessing.

Each point on the ROC curve represents a sensitivity-specificity pair corresponding to a certain decision threshold. An ideal test would be one that has 100% sensitivity and 100% specificity and thus the curve will pass through the upper left corner [Figure 1]. Since no test is really ideal and we tradeoff between sensitivity and specificity, the closer the curve is to the upper left corner, the better is its accuracy. The area under the ROC curve, is taken as 1 and is a useful metric for evaluating the performance of a test. The closer the value of the AUC is to 1, the better is the discriminatory ability of the test [Table 2 and Figure 1]. Since the curve is based on the metrics of sensitivity and specificity alone, the ROC curve is independent of disease prevalence.

Applications of the ROC curve-
Any ROC curve helps serve the following four purposes:

a. Finding the cut off that least misclassifies diseased and non-diseased individuals
b. Assessing the discriminatory ability of the test
c. Comparing the discriminatory ability of two or more diagnostic tests for assessing the same disease
d. Comparing two or more observers performing the same test [inter-observer variability]

The Youden's index [a Summary Statistic]

It is useful to summarize the information from a ROC curve into a single statistic or index. One of the commonly used indices in the Youden’s index “J”. This index gives the maximum vertical distance from the line of equality to point [x, y] [Figure 1]. In other words, the Youden index J is that point on the ROC curve that is furthest away from the line of equality [the diagonal line] and maximizes the difference between the sensitivity [true positivity rate] and the false positivity rate [1-specificity].

It is calculated by deducting 1 from the sum of the test’s sensitivity and specificity expressed not as percentage but as a part of a whole number. In other words, it is (sensitivity + specificity) – 1. For a test with poor diagnostic accuracy, Youden’s index equals 0, and a perfect test will have a Youden’s index of 1.

Diagnostic Odds Ratio [A Summary Statistic]

The Diagnostic odds ratio [DOR] is yet another summary statistic for diagnostic accuracy, that is used for the evaluation of the discriminative abilities of diagnostic procedures as also for the comparison of diagnostic accuracies between two or more diagnostic tests. DOR of a test is defined as the ratio of the odds of positivity in individuals with disease relative to the odds of positivity in individuals without disease. It is calculated similar to the odds ratio as seen in an earlier article as a cross product from the 2 x 2 [Table 1] and given by the formula

$$DOR = \frac{TP \times TN}{FP \times FN}$$

DOR as seen with its calculation depends significantly on the
sensitivity and specificity of a test. A test with a high specificity and sensitivity [i.e., low rates of false positives and false negatives] will have a high DOR. It is also important to remember here that the same DOR may be achieved with different combinations of sensitivity and specificity. As an illustration, the DOR of 4 can have four combinations of sensitivity and specificity [Table 4].\textsuperscript{13}

### Statistical Tests to be Used when Diagnostic Tests are Compared

When two screening or diagnostic tests are conducted on the same patient, the results would amount to "paired" data and since the outcomes are either positive or negative, these constitute "binary outcomes. The McNemar's test is used for this type of comparison. When these two tests are conducted on independent populations, then we use the chi-square or Fisher's exact test.\textsuperscript{16}

### Understanding Biases when Using Diagnostic Tests - Spectrum Bias and the Imperfect Gold Standard Bias

An important and often overlooked aspect of diagnostic tests evaluation is spectrum bias. In general, patients who present later in the course of a disease are easier to diagnose than those who present early, as with the latter, signs maybe subtle and difficult to pick up. Spectrum bias is a form of selection bias that results when a test is used for a disease that has a wide spectrum of severity.\textsuperscript{17} Thus, values of sensitivity and specificity obtained for any test are driven by the population that is being studied and different populations would yield different values of the two metrics.

Let us understand this with an example. If we are evaluating a test for detecting patients with diabetes, we could have in our "disease" population, patients with very mild diabetes at one end to severe or even uncontrolled diabetes at the other end of the spectrum. Any diagnostic test study that limits the diabetic patients to the "sickest of the sick" will overestimate the sensitivity of a test, while similarly, another study that uses only the "wellest of the well" [those who are truly non-diabetic; for instance, the very young] will overestimate specificity.\textsuperscript{18}

Another bias is the "imperfect gold standard" bias.\textsuperscript{19} When a new test [also called as the index test] is being tested, it is compared with an existing "gold standard" or reference test. An ideal gold standard test would be one that "rules in" ALL patients with disease and "rules out" ALL those without. Unfortunately, gold standards are rarely perfect and can themselves misclassify those with and without disease leading to what we call an "imperfect gold standard". Let us understand this with the example of malaria diagnosis. The current gold standard is the peripheral smear. In the hands of trained and expert technicians, the test sensitivity is 50 parasites/ml of blood and results are made available within 30 minutes.\textsuperscript{20} The use of this "gold standard" will logically result in declaring parasitemias of less than 50parasites/ml as falsely negative. The polymerase chain reaction [PCR], on the other hand, that detects specific nucleic acid sequences of the parasite has a much higher sensitivity at 5 parasites/ml. However, it is time consuming, technically demanding,

### Table 3: A 2 x 2 table depicting the calculation of the diagnostic odds ratio as a cross product ratio

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>Test negative</td>
<td>FN</td>
<td>TN</td>
</tr>
</tbody>
</table>

### Table 4: Diagnostic odds ratios for varying combinations of sensitivity and specificity\textsuperscript{13}

<table>
<thead>
<tr>
<th>Specificity [%]</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>95</th>
<th>99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity [%]</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>50</td>
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<td>2</td>
<td>2</td>
<td>2</td>
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<td>9</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>70</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>21</td>
<td>44</td>
<td>231</td>
</tr>
<tr>
<td>80</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>16</td>
<td>36</td>
<td>76</td>
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<td>14</td>
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<td>149</td>
<td>231</td>
<td>396</td>
<td>891</td>
<td>1881</td>
<td>9801</td>
</tr>
</tbody>
</table>

### Reporting of Studies using Diagnostic Tests - The STARD and QUADAS Checklists

STARD stands for “Standards for Reporting Diagnostic Accuracy Studies” and is a checklist of n = 30 items developed by the STARD steering group; an independent group of researchers who formulated this checklist in an attempt to ensure both completeness and transparency of reporting by authors and also for editors and peer reviewers to assess adequacy and quality of information. Authors need to use this checklist in manuscripts that report studies that involve screening or diagnostic tests and reporting their accuracy. STARD can be viewed at [http://www.stard-statement.org/].\textsuperscript{14} The Quality Assessment of Diagnostic Accuracy Studies (QUADAS - 2) tool is a 14-item checklist to help in the evaluation of diagnostic accuracy studies primarily for use in preparing and presenting systematic reviews.\textsuperscript{15}
expensive and also detects non-viable parasites that may be present even after successful antimalarial treatment and can confuse the treating physician. Thus, with its inherent limitations of much lower sensitivity [relative to the PCR], the peripheral smear still remains the “gold standard” [albeit imperfect] for the diagnosis of malaria. Some other biases include uninterpretable or indeterminate test bias and inter-observer bias.

Conclusions

Few topics in the medical field are more important than screening and diagnostic tests as these are ordered nearly every day as an important aid to clinical decision making. Diagnoses are made based on a combination of patient history and physical examination. Tests are often ordered to confirm initial impressions or rule out alternatives, and it is estimated that 10% of all diagnoses are not considered final until clinical laboratory testing is complete. The utility of any test must be assessed bearing in mind its discriminatory ability [to distinguish between health and disease], the nature and severity of the disease under question, the ease of availability of the tests and risks associated with their use, understanding the several diverse metrics [with their limitations] that go into interpreting the results, cost considerations and finally impact on patient management based on the results of the test.

Research studies that publish findings using diagnostic tests must be critically appraised using the STARD criteria as also an appreciation of whether the population on whom the test was used is similar or different from the one that a physician actually sees in his practice. Finally, laboratorians who carry out diagnostic testing, clinicians who treat patients and clinician-researchers who interpret evidence need to work in tandem. This enables better linkage of results of the diagnostic testing with the patient. When coupled with continued monitoring of the effectiveness of these tests, we would ensure both optimal outcomes for an individual patient as also decisions that would drive health policy for nations.

Acknowledgements

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References

The Forgotten Blow

Sandip Ghosh¹, Biswajit Majumder², Pranabananda Goswami³, Sougat Chakraborty⁴, Viral Tandel¹, KN Sudeep¹

A sixty-year-old male patient presented to the cardiology department with non-specific pain chest for last four months. His vitals were stable and JVP normal. Cardiovascular system examination revealed double apical impulse with lateral retraction without any murmur. ECG showed non-specific ST-T changes [A]. A large opacity with well-defined outer margins and a broad medial margin silhouetting the left heart border was seen in the chest X-ray [B]. Echocardiographic examination revealed a large pseudoaneurysm arising from lateral wall of left ventricle with a narrow neck with the ratio of orifice to the maximum diameter of the aneurysm to be <0.5 [C]. Color Doppler showed turbulent bidirectional flow across the neck of the aneurysm [D]. Coronary angiography was normal. On further enquiry the patient gave a history of a blunt trauma to chest 30 years back while working in his shop. CT scan of thorax showed a large [67 mm X 102 mm X 70 mm] thin walled well defined lesion with calcified margins seen close to the left lateral wall of left ventricle with vascular type of enhancement [E, F]. Subtracted black blood and white blood axial MRI images of mediastinum showed a pseudoaneurysm with turbulence [G, H]. Left ventricular pseudoaneurysm form subsequent to cardiac rupture and is contained by the overlying pericardium and scar tissue.¹² True aneurysms are dyskinetic areas of thinned full thickness myocardium.² The ratio of the maximum internal diameter of the orifice to the maximum internal diameter of the cavity is usually less than 0.5 in the cases of a pseudoaneurysm, and between 0.9 and 1.0 in the cases of a true aneurysm.⁴ Most cases are a sequel of myocardial infarction, prior cardiac surgery and bacterial endocarditis but may rarely occur subsequent to trauma. Congestive heart failure, dyspnea and chest pain are the most frequently reported symptoms.² Though a few cases of delayed presentation of LV pseudoaneurysm after blunt trauma have been reported,³⁴ but presentation thirty years after a blunt trauma chest is very rare. Management consists of surgical repair of the pseudoaneurysm with patch as mortality rate is very high in untreated cases.³ However, our patient refused any surgical intervention.

References

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Pleuro-pulmonary Cryptococcosis without Pleural Effusion

Kamal Gera¹, Nevin Kishore², Andleeb Abrari³, Kanika Singh⁴

A 59-year-old woman, never smoker, presented with complaints of dry cough, breathlessness and right-sided pleuritic chest pain for past 2 months. She had a history of oral corticosteroid intake for 5 years for undiagnosed rheumatological condition. She had no other co-morbidities and tested negative for HIV serology. Her physical examination was unremarkable. Complete blood counts, ECG, urine analyses and renal as well as hepatic functions were also within normal limits. The chest radiograph posterior-anterior view showed inhomogeneous opacities in right mid zone peripherally (Figure 1). Contrast enhanced computed tomography (CECT) of the thorax revealed areas of patchy consolidation in right upper lobe along with pleural involvement but without pleural effusion (Figures 2 A, B). Mantoux test with 1 TU failed to elicit any induration or erythema. CT-guided transthoracic biopsy was done from this peripherally located lesion, which on histopathology, showed features consistent with cryptococcosis (Figures 3 A, B, C). Subsequently, cryptococcal antigen was detected in serum. MRI brain and spine did not show any CNS involvement by cryptococcosis. Finally, a diagnosis of pleuro-pulmonary cryptococcosis was made on the basis of 1) histopathological findings and 2) detection of cryptococcal antigen in serum. The patient was started on oral fluconazole 200 mg twice a day and that led to significant clinical improvement in 2 weeks.

Pulmonary cryptococcosis is an uncommon form of cryptococcosis occurring predominantly in immunocompromised patients. Radiological manifestations mainly include pulmonary nodules, mass lesions, cavitation and consolidation.¹ However, pleural involvement by cryptococcosis is further rarer and is usually accompanied by pleural effusion.² In a recent retrospective study to evaluate thoracic CT findings in patients with pulmonary cryptococcosis, it was observed that pulmonary nodules / masses were the most common manifestation (65/72 patients, 90.3%). On the other hand, pleural involvement in the form of pleural effusion was seen in only 8/72 (11.1%) patients.³ However, pleural involvement without pleural effusion has been documented only once previously in a 50-year-old female from Japan who presented with multiple left pleural nodules.⁴ In our patient too, pulmonary and pleural cryptococcosis occurred but without pleural effusion, making it a rarely observed clinical entity. A high index of suspicion is therefore required to diagnose cryptococcosis in such places where prevalence of pulmonary tuberculosis far exceeds the occurrence of cryptococcosis.

References

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Chikungunya Fever Presenting as Life Threatening Thrombotic Thrombocytopenic Purpura

Vimal Kumar, Rujul Jain, Arvind Kumar, Neeraj Nischal, Pankaj Jorwal, Manish Soneja, Sudheer Arava, Naveet Wig

Abstract
It is well known for Chikungunya fever to present as myriad of skin rash along with usual joint pain and fever, but probably this is the first case report of Chikungunya fever presenting as severe life threatening thrombotic microangiopathy, thrombotic thrombocytopenic purpura leading to multiple areas of skin necrosis, peripheral digital gangrene, haemolytic anemia, renal failure and severe thrombocytopenia with bleeding. This complication was most likely due to inhibitor autoantibody formation against ADAMTS13 triggered by chikungunya virus leading to thrombotic thrombocytopenic purpura. Patient was treated with plasmapheresis and other supportive care which she responded. Her symptoms subsided, and she is symptom free and leading normal life in her follow up visits.

Introduction
Chikungunya fever is caused by Chikungunya virus, vector being Aedes mosquito. This disease usually presents with fever, joint pain and various types of skin rash. We describe in this case, a very unusual presentation of Chikungunya fever presenting as thrombotic thrombocytopenic purpura which to our best knowledge has not been reported so far in a patient of Chikungunya.

Case Report
A 24-year old married female, hailing from North-west Delhi, who was an employee in a motorcycle showroom, with no prior illness or any known medical condition presented with illness of 5 days. Her illness started with fever which was high grade (103°F) and associated with chills but no rigors, followed by multiple episodes of vomiting and profuse watery diarrhea, along with severe joint pain involving both large and small joints of the body. Although her fever and abdominal symptoms subsided after two days of illness, she continued to have severe joint pain, and on the 4th day of illness, she developed dark purple-reddish rash involving bilateral hand and feet, bridge of the nose. She also noted similar skin rash on genital area and lower back. She also noticed dark crusted lesions on lips and vulva. She also had complaints of dysphagia after the appearance of these rashes, some degree of headache and a history of decreased urine output for two days.

There was no history of syncope, altered sensorium, seizures, blurring of vision or weakness of any part or any sensory loss at presentation. There was no history of bleeding from any site during presentation, no history of cough, expectoration or shortness of breath. There was no history of travel outside the town in last 6 months or exposure to pets or other animals in the recent past. Patient gave no history of substance abuse. She was a divorcee and had one child of two-year age born of normal vaginal delivery. There was no significant medical history in any close family member.

At presentation, she was vitally stable, although tachycardia was present. She didn’t require any respiratory or hemodynamic support. General physical examination revealed pallor, cyanosis of all digital tips, purpuric rash all over bilateral hand and feet and bridge of the nose, petechial rashes all over bilateral upper and lower limb, necrotic black rash on natal cleft, right shin and right groin area (Figure 1). Generalized erythema was present all over the body but more pronounced over the trunk. Hemorrhagic rash with crusting was seen over mucocutaneous junction of lips and vagina. Paresthesia was present all over both hand and feet and with severe tenderness in large and small
joints of hands and feet. At the time of presentation, her central nervous system examination and other systemic examination were within normal limits.

Her initial work up revealed anemia, thrombocytopenia, deranged renal profile and slightly prolonged coagulation profile (Table 1).

All workup for common causes of acute febrile illness (dengue, peripheral smear for malaria, leptospirae, scrub typhus, including chikungunya) were negative on day 6 of the illness (Table 2). With high degree of clinical suspicion of chikungunya in this patient, the test for chikungunya was repeated and the result came out to be positive on day 9 signifying acute infection. Her coagulation profile normalized on its own in two days and DIC (Disseminated intravascular coagulation) was ruled out by further testing.

During hospital stay, her thrombocytopenia further worsened and platelets fell further to 6000/μL and she started having epistaxis and melena, for which she required platelet and packed RBC transfusion.

Her peripheral smear showed schistocytes, LDH was raised. Unconjugated hyperbilirubinemia was present and her direct/indirect coomb’s test was negative signifying non-immune haemolytic anemia.

She started developing progressive gangrene of the digital tips of left hand and of the tip of lower limb digits (Figure 2). Urgent arterial doppler ultrasound of all limbs was performed which showed no occlusion of any large arteries. Her sensorium started dipping in the form of confusion and she also complained of severe headache, a CT head was done to rule out intracranial bleed secondary to thrombocytopenia, it came out to be normal study. Hemolytic-uremic syndrome (HUS), was ruled out although there was history of diarrhea, but the renal involvement was only transient (for 24-48 hours) and not a prominent feature, the microvascular thrombosis was more prominent and rapidly progressive. A clinical diagnosis of Chikungunya induced thrombotic thrombocytopenic purpura (TTP) was made based on clinical and lab features of non-immune haemolytic anemia with thrombocytopenia with evidence of microvascular thrombosis, immediate testing for ADAMTS13 activity was not possible due to unavailability of test in the hospital and because of financial constraints of the patient. A recently developed clinical tool PLASMIC score\(^1\,^2\) which predicts the ADAMTS13 activity <10% and studies have shown better prediction of TTP as compared to clinical assessment when applied in appropriate clinical setting when ADAMTS13 activity turn-around time is more or unavailable in resource limited settings, was calculated after day 4 of admission which came out to be 7, categorizing the patient in high risk group.

Other conditions mimicking Fig. 1: Different kind of rashes in the patient at presentation
Table 1: Laboratory workup

<table>
<thead>
<tr>
<th>Test</th>
<th>At admission</th>
<th>Day 4</th>
<th>Day 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dl)</td>
<td>8.9</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>29.1</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Platelet Count (µL)</td>
<td>79,000</td>
<td>6000</td>
<td>47000</td>
</tr>
<tr>
<td>TLC (per mm3)</td>
<td>8900</td>
<td>8300</td>
<td>4300</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>127</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.7</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>1.99</td>
<td>5.8 (7.4')</td>
<td>8.4</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>2.1</td>
<td>2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Uric Acid (mg/dl)</td>
<td>3.0</td>
<td>3.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>135</td>
<td>139</td>
<td>136</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.7</td>
<td>2.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Bilirubin (T) (mg/dl)</td>
<td>3.5</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Indirect Bilirubin</td>
<td>1.3</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Total Protein (gm/dl)</td>
<td>4.2</td>
<td>4.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>2.0</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Globulin(gm/dl)</td>
<td>2.2</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>SGOT (&lt;50) IU/L</td>
<td>17</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>SGPT (&lt;50) IU/L</td>
<td>13</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>286</td>
<td>286</td>
<td>146</td>
</tr>
<tr>
<td>PT/INR (PT in seconds)</td>
<td>23.8/2.18</td>
<td>14/1.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: *gm/dl–gram per decilitre; *mg/dl- milligram per decilitre; *meq/L- milliequivalent per litre; *IU/mL- international units per millilitre; *corrected for albumin; *per µL - micro litre; *per mm 3-per cubic millimetre; *IU/L- international units per litre

Table 2: Fever workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 4</th>
<th>Day 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue IgM (Day 6)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Chikungunya IgM (Day 6; Day 8)</td>
<td>Negative</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Smear for malaria parasite (Day 6)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Leptospira (Day 6)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Scrub typhus (Day 6)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Widal test (Day 7)</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Fever workup

<table>
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<tr>
<th>Test</th>
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<th>Day 12</th>
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<tbody>
<tr>
<td>Dengue IgM (Day 6)</td>
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<tr>
<td>Smear for malaria parasite (Day 6)</td>
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</tr>
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<td>Leptospira (Day 6)</td>
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<td></td>
</tr>
<tr>
<td>Scrub typhus (Day 6)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Widal test (Day 7)</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

seasonal trend in incidence is seen. The disease usually presents as acute febrile illness with asthenia, arthralgia, myalgia and rash, unlike dengue fever the infection is usually symptomatic with less than 15% having asymptomatic infection with seroconversion. 4

Usually the disease is self-limiting and non-life threatening in majority of patients, and the complications tend to occur in extremes of age group and patients with co-morbidities like diabetes mellitus, hypertension, cardiovascular or renal disease, immunosuppressed individuals. The complications include encephalitis, myocarditis, hepatitis, multi-organ failure and bleeding although rare with chikungunya but can occur and more likely to occur with patients with co-infection with dengue virus.

It is not uncommon for the disease to present with unusual complications. Some of the major unusual complications described in literature areguillian-barre syndrome, 5 transverse myelitis, 6 disseminated intravascular coagulation. 7 The mechanism postulated for such complication might be molecular mimicry of some viral elements with the host elements, but it is not fully understood as of now.

Thrombotic thrombocytopenic purpura (TTP) is severe life-threatening disease with mortality rate of around 90% without timely treatment with plasma exchange therapy. It is described as a classic pentad of thrombocytopenia, microangiopathic haemolytic
anemia, neurological symptoms, kidney failure and fever, although classic pentad of symptoms is rarely seen together. Differential diagnosis of TTP is wide and mainly includes ruling out other thrombotic microangiopathies and conditions like DIC, rheumatic diseases, malignancy or pregnancy related complications (Table 6). It is caused by acquired or inherited deficiency of ADAMTS13 (A disintegrin and metalloprotease with a thrombospondin type I motif, member13) leading to its reduced activity (<10%). ADAMTS13 is a plasma protease which cleaves ultra large molecules of von Willebrand factor (VWF) synthesized by endothelial cells. This normal cleavage to smaller fractions prevents these large molecules to accumulate. When the activity of this protease is reduced, ultra large VWF molecules accumulate on endothelial surface where platelets attach and accumulate leading to thrombosis of vessels.

Majority of TTP cases (95%) are acquired due to formation of an inhibitory autoantibody to

<table>
<thead>
<tr>
<th>Vasculitis workup</th>
<th>Viral markers</th>
<th>APLA workup</th>
<th>Hypercoagulability workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Negative β2 GP</td>
<td>Negative S. Homocysteine</td>
</tr>
<tr>
<td>ANCA</td>
<td>Negative</td>
<td>Negative Lupus-anticoagulant</td>
<td>Negative Factor V leiden mutation</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Negative</td>
<td>Negative Anti-cardiolipin IgG and IgM</td>
<td>Negative Factor IV</td>
</tr>
<tr>
<td>RF</td>
<td>1:128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D-Echo</td>
<td>EF- 61.8%, No vegetation/clot seen, no pericardial effusion, all valve morphology and opening normal; Normal study</td>
<td>Day 10</td>
<td>At discharge</td>
</tr>
<tr>
<td>Arterial Doppler all limbs</td>
<td>All major vessels show normal flow, no occlusion or decreased flow.</td>
<td>Normocytic normochromic cells with 2-5% schistocytes, corrected retic-2.5%, few spherocytes; Platelets-60,000</td>
<td>Normocytic normochromic cells with occasional schistocytes(&lt;1%), corrected retic-3.06%</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Microcytic hypochromic cells with target cells, acanthocytes,(MCV-72FL) 2% schistocytes, retic-0.3%, few activated lymphocytes Platelets&lt;10,000</td>
<td>Day 4</td>
<td>Platelets-1.5lac, few clumps seen</td>
</tr>
</tbody>
</table>

Table 3: Work up for hypercoagulable states
infection with chikungunya virus which probably triggered an autoantibody response to form inhibitory autoantibody towards ADAMTS13 protease and led to severe decrease in its activity (<10%) which led to accumulation of ultra large molecules of VWF and platelet accumulation leading to occlusion of small arterioles and capillaries, culminating into skin necrosis, digital tip gangrene formation and microangiopathic haemolytic anemia.

Plasmapheresis is the mainstay of treatment, which removes the inhibitory autoantibody formed and replenishes the activity of ADAMTS13 protease eliminating the thrombotic complications of the disease. Steroids can be used in addition to plasmapheresis in very severe cases. The number of sessions needed is judged on individual patient response, usually minimum of 5 sessions over a period of one week is given and further more sessions are added according to clinical response. Our patient improved in 5 sessions given over a period of one week and no further sessions were deemed required as all parameters improved and was stable thereafter.

So, in the list of unusual presentations of chikungunya fever, thrombotic thrombocytopenic purpura can be added. Early recognition of this complication with initiation of timely plasmapheresis will reduce morbidity and mortality in such cases.

References


In the treatment of Tuberculosis

Presenting
An Innovation with patented novel drug delivery process

**Risorine**
Rifampicin 200mg + Isoniazid 300mg + Piperine 10mg Capsule

Rifampicin powered by Bio-enhancer Piperine

Clinical efficacy at par with standard regimen
- 93% sputum conversion at the end of 4 weeks
- 92% Cure rates after 24 weeks

Improved GI tolerance during 6 months treatment
- Reduced risk of drug induced hepatotoxicity
- Improved patient compliance – Reduced risk of relapse

Ensures Better Bioavailability of Rifampicin

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Rifampicin Powered by Bioenhancer Piperine

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Pyrazinamide 500/750/1000 mg
The (2) category power

**Mycobutol**
Ethambutol 400/600/800/1000 mg
The Trusted Ethambutol

**Mycocox**
(MgRw)
Multifocal Tuberculosis Presenting as Metastatic Tumour

Nitin M Rathod¹, Deepak Patkar², Amit Choudhari³, P Revanth⁴

Abstract
A middle aged female presented with multiple lesions in the bone mimicking as multiple metastasis. In such cases detection of lesion should be confirmed by soft tissue diagnosis and appropriate culture. In our case, the lesions were responsive to anti-tuberculous treatment.

Case Report
A 50 years old lady came with complaints of back-ache since one year, which had worsened in the past 2 months. The pain was dull aching, localized to her lower back region and non-radiating. There was no tingling or numbness in the limbs, nor any bladder or bowel disturbances. Patient gave no history of weight loss, fever, cough or any other mass lesion in the body. There was no history of diabetes, hypertension or ischemic heart disease. There was no history of Koch’s or Kochs contact.

General examination of the patient did not reveal any significant abnormality except for localised tenderness over the dorso-lumbar spine. Patient was afebrile. Her blood pressure was 130/80 mm Hg. She was conscious, oriented to time, place and person, and no focal neurological deficit was seen. She was being treated by 5 different orthopaedic consultants over the past one year with analgesic and muscle relaxants with temporary relief. Plain X-ray of her dorsal spine did not reveal any pathology. Her vitamin-D levels were marginally low, which had been corrected but still there was no improvement in her pain symptoms.

Investigations revealed:
Hb- 11.4 gm/dl, WBC - 8200/ cumm, ESR -110/1 hr, CRP- 241 mcg/L, procalcitonin - 0.85 (mild risk for bacterial infection), Creatinine 0.7 mg/ dl, Alkaline Phosphate 125 IU/L (N- 35 – 104), Uric acid 5.4 mg%, Calcium 9.3 mg/dl, Phosphorus 4.7 mg/dl. BT/CT/ PT/ INR were normal. T3/T4/TSH were normal. Thyroglobulin was 230 ng/ml (N-1.6 – 60 ng/ml).

Serum Protein Electrophoresis showed no evidence of Myeloma

2-D echo examination showed LVEF of 60 %, good biventricular systolic function. No regional wall motion abnormality noted.

Viral markers were negative.

The chest x-ray showed mild prominence of vascular markings, otherwise the rest of the lung fields were normal. Considering unbearable localised back pain, high ESR with high CRP and normal X-ray, MRI dorso-lumbar spine was advised to evaluate the aetiology of back pain.

MRI of the dorso-lumbar spine revealed altered marrow signals in D3, D10, D12 vertebrae, D3 and D10 vertebral body and left half of the left pedicle and spinous process of the D12 vertebrae (Figure 1). The above findings showed possibility of a neoplastic process such as metastasis.

To evaluate further a PET scan of the whole body was done which showed FDG avid lesions in the left lobe of thyroid, nodes in the right sub-pectoral region as well as in the mediastinum with multiple FDG avid osseous lesions. Small nodules are seen in the left lobe of the thyroid measuring 20x12 mm. Osseous lesions in the left femoral shaft and in the ribs (Figure 2). Lesions were seen in D3, D10/12 vertebral bodies and spinous process of D12. Anterior mediastinal nodes of 21 mm size were also noted. The possibility of a thyroid primary, (follicular probably with metastatic lung parenchyma and osseous lesions) was given.

FNAC of the left lobe of thyroid was performed to further gain knowledge into the disease process. 15 smears of FNAC of left lobe of thyroid showed colloid granulation tissue which suggested organisation of an inflammatory process. Repeat tru-cut biopsy of the left thyroid lesion was also performed which also showed...
FNAC and Tru-cut biopsy findings from the thyroid gland and femoral bone, a trial of Anti Koch therapy (AKT) was given to patient over 2 months under medical supervision. Patient was taking sedative analgesics (Tramadol) along with other anti-inflammatory drugs for relief of pain, within 15 days the requirement of analgesics reduced to half and after 2 months of AKT, she didn’t require any analgesic. Patient’s clinical parameter as well as lab reports improved. Her ESR and CRP which was 110 mm and 241 mcg/l reduced to 37 mm and 53 mcg/l respectively.

Discussion

Tuberculosis of the bone is a well-recognized clinical condition that can be diagnosed and managed by physicians and orthopaedic surgeons, often with an excellent outcome. Tuberculosis with multiple-bone involvement is extremely rare in immunocompetent patients and in those with normal pulmonary findings. Nevertheless, since patients with multifocal skeletal tuberculosis may present with vague multiple somatic symptoms, Physician and orthopaedic surgeons should maintain a high degree of suspicion in order to diagnose this condition. Multiple disease processes such as infection, autoimmune diseases, granulomatous processes as well as metabolic diseases like hyperparathyroidism may cause appearance of multiple FDG avid lesions at multiple sites on PET scan. In case of infective process some appropriate culture should also be performed to grow organisms responsible for diffuse lesion. This case report underlies the need for specific tissue diagnosis.

Conclusion

The detection of multiple lesions on PET does not always indicate a neoplastic process. The detection of these lesions should be followed by some form of tissue diagnosis to confirm the real nature of lesion.

References

Isolated Supravalvular Aortic Stenosis with Infective Endocarditis presenting as Pyrexia of Unknown Origin

Deepak Kumar Mishra¹, Vishal Khullar², Shalima Gautam¹, Tamanna Khullar³

Abstract
Supravalvular aortic stenosis is a less common form of left ventricular outflow tract obstruction (LVOTO); commonest being the valvular aortic stenosis followed by valvular and subvalvular forms respectively. Most of the supravalvular aortic stenosis is associated with Williams syndrome; isolated supravalvular aortic stenosis is further rarer. We present a case of isolated SVAS with infective endocarditis (1.6) as the cause of pyrexia of unknown origin (PUO).

Case Report

A 25 years female presented with ECG features suggestive of LVH. She was running fever since 6 weeks. Fever was moderate grade intensity and used to occur with chills. There was associated history of weight loss and decreased appetite. She was prescribed paracetamol and oral antibiotics outside without any improvement. Patient was admitted for evaluation. She was tachycardic with BP of 130/90 mm Hg in right arm and BP of 116/88 mm Hg in right lower limb. There was moderate valvular aortic regurgitation. Other valves were normal. 2D echocardiography revealed diastolic murmur at the aortic area which was maximum in sitting with more radiation to right side of precordium. S4 was palpable at apex. She had harsh ejection systolic murmur peaking late in systole with maximum intensity on right upper parasternal region and with more radiation to right side of clavicle as compared to left. There was no radiation to apex. There was an early diastolic murmur at the aortic area occupying more than half of diastole which was maximum in sitting with leaning chest position. S4 was audible at apex. ECG showed LVH. X-ray was normal. 2D echocardiography revealed severe LVH, mild LV dysfunction with EF 45 %, supravalvular aortic stenosis with peak gradient of 100 mm Hg. There was moderate valvular aortic regurgitation. Other valves were normal. She had a vegetation at the site of origin of brachiocephalic trunk. Blood investigations ESR was 50 mm for 1st hr. Blood counts were normal. Blood cultures grew streptococcus viridians with colony count of 50,000/ cu.mm. Other blood parameters were normal. CT angiogram showed narrowing of ascending aorta including the sinotubular junction and part of ascending aorta (Figures 1-3). The patient was started on inj. Ceftriaxone 1gm IV 12 hrly for 6 weeks and inj. Gentamicin 40 mg OD for 2 weeks. The patient responded well to the antibiotics course. Two weeks after the therapy conventional cardiac catheterization as done which confirmed the findings of echo and CT angiography. Coronaries were dilated but there were no luminal obstruction. She was taken up for definitive surgery: Dacron patch repair with aortic root enlargement (Figures 4 and 5) and aortic valve replacement (18 mm ATS valve) which went uneventful and was discharged on 7th postoperative day. The patient is doing well in follow-ups with INR in therapeutic range.

Discussion

PUO has varied definition depending on the duration of fever and the type of set up i.e nosocomial, neutropenic or in HIV / AIDS patients Commoner cardiac condition manifesting as fever are infective endocarditis, pericarditis, left atrial myxoma, Takayasu arteritis, cardiac sarcoidosis, myocardial tuberculosis/ granulomas. Infective endocarditis is a dreaded disease with an incidence of 1.7 – 6.2 cases per lac patient year. Males are twice as commonly affected as females.¹,² Common predisposing factors are rheumatic heart disease, congenital heart disease, prosthetic heart valve patients and intravenous drug users/ abusers. It has acute (fulminant) presentation or subacute presentation. The mortality as studied in Indian patients are as high as 23 % as mentioned by Garg et al³ and Choudhary et al.¹

Commoner organisms are Streptococcus viridians, Enterococci, Pseudomonas, Staphylococcus, HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, kingella), salmonella in HIV/ AIDS pts, fungi, atypical organisms like Coxiella, Bartonella etc.

Criteria for diagnosing IE have evolved since the Von Reyn criteria initially described for infective endocarditis followed by Duke’s criteria to recent modified Duke’s criteria. Serum procalcitonin level greater than 2.3 ng/ ml has been predicted to diagnose I.E with almost 85 % specificity.³

With the introduction of new guidelines for antibiotic use for the prevention of IE introduced by ACC/ AHA in 2008⁶ all the recommendation which were class 1 were changed to class 2a and it clearly mentions that rheumatic valvular heart disease doesn’t require any antibiotic prophylaxis as long as antisepsis is not breached.

And these indications are :
1. Patients with previous prosthetic cardiac valve, prosthetic material used for cardiac repair.
2. Patients with previous IE.
3. Patients with congenital heart disease: unrepaired cyanotic, palliative shunts / conduits, completely repaired with prosthetic material, device closure for 6 months. Repaired congenital heart disease with residual defects.

¹Intervention Cardiologist, ²Consultant Cardiothoracic Surgeon, ³Consultant, Dept. of Non-invasive Cardiology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra

Received: 29.11.2014; Accepted: 30.03.2017
4. Cardiac transplant recipients with valve regurgitation due to structurally abnormal valve.

The exact incidence of isolated supravalvular aortic stenosis (SVAS) is not known. SVAS in association with Williams-Beuren syndrome (chromosome 7) is commoner than the isolated forms. Williams syndrome is either familial or sporadic. Syndromic association include bicuspid aortic valve, Mitral valve prolapse, coarctation aorta, pulmonary stenosis, extracardiac manifestation like diabetes mellitus, hypercalcemia, hypothyroidism, typical Elfin facies (God like), denture abnormality, hearing abnormality, gastrointestinal problems, skin abnormalities, genitourinary problems, psychosomatic complaints and attention deficit hyperkinetic disorders. Our patient had no other feature suggestive of William syndrome except SVAS.

SVAS can present as breathlessness, angina, presyncope, Syncope. It can either progress (mostly in initial five years) or remain the same unlike the pulmonary stenosis component which usually regresses.\(^7\),\(^8\)

One peculiar thing about SVAS is that the risk of sudden cardiac death is low unlike other forms of LVOTO. But this risk increases significantly if pulmonary stenosis is also present along with right ventricular hypertrophy.\(^9\)

Treatment option for SVAS is mostly different forms of surgical correction depending upon the different types of obstruction: hourglass, multiple stenosis, diffuse hypoplasia. It can be either end to end resection, vertical incision with Dacron patch repair, etc. Balloon angioplasty has poor result in such pts. as media of aorta has plenty of smooth muscle in the disease (mutation of Elastin ELN gene on chromosome 7). On the contrary, balloon angioplasty has good result for other vessels like pulmonary arteries.

Our patient was treated with intravenous antibiotics: Inj. ceftriaxone 1 gm IV BD for 6 weeks and Inj. Gentamicin 1mg/kg for 2 weeks. The vegetation at brachiocephalic trunk was due to selective streaming of jet towards the right side of aorta and its branches (Coanda effect). This phenomena also describes the selective radiation of systolic murmur to right side of trunk in SVAS.
Cardiac catheterization (Figures 1, 2) was done to corroborate the 2D echocardiography and CT Angiogram (Figure 3) findings. The patient had severe aortic regurgitation also and severe left ventricular hypertrophy with mild left ventricular dysfunction (EF 45%). So patch repair of aorta (Figures 4, 5) along with prosthetic aortic valve size no 18 mm was done.

The operation was uneventful; so was the recovery and the patient was discharged on 7th postoperative day and is doing well in follow up.

Conclusion

Infective endocarditis complicating supravalvular aortic stenosis can be a rare but potentially treatable cardiac cause of PUO.

References


Listeria in Adults – Truly Rare or Rarely Diagnosed in India?

Arjun Rajalakshmi1, Ram Gopalakrishnan2, P Senthur Nambi3, P Vishnu Rao4, V Ramasubramanian2

Abstract

Listeria monocytogenes is a facultative anaerobic intracellular Gram positive rod causing infection in pregnant women, extremes of age and immune-compromised hosts. In clinical specimens, the organisms may be gram-variable: laboratory misidentification of L. monocytogenes isolates as diphtheroids, streptococci, or enterococci is not uncommon and the isolation of a diphtheroid from blood or CSF should always alert the clinician to the possibility that the organism may be L. monocytogenes. The disease has rarely been reported in India in non-pregnant adults. We herein report four cases of L. monocytogenes infection in immune-compromised adults.

L. monocytogenes infection in immune-compromised adults.

Case 1

A 62 year old lady presented with fever, headache, vomiting and altered mental status of 1 day duration. She had been diagnosed to have retroperitoneal fibrosis due to IgG4 related disease four years ago for which she was on mycophenolate motefil (MMF) 360 mg twice daily and prednisolone 15 mg daily. On examination, she was confused, had neck stiffness and right lateral rectus palsy. General and other system examination was otherwise unremarkable. WBC count was 18,200 cells/cumm (89 % polymorphs). Contrast enhanced MRI revealed mild leptomeningeal enhancement. Cerebrospinal fluid (CSF) examination showed WBC of 425 cells/µL (lymphocytes- 92% neutrophils 8%), glucose of 26 mg/dl (corresponding blood glucose was 196 mg/dl), protein of 230 mg/dl and negative Xpert MTB, cryptococcal antigen and HSV PCR. Gram stain of CSF (Figure 1) and blood (Figure 2) revealed gram positive bacilli. CSF

Introduction

Listeria monocytogenes infection is commonly reported in the Western literature as an important cause of bacteremia and meningitis in neonates, pregnant women, the elderly and patients with impaired cell mediated immunity.1 The disease has rarely been reported in India in non-pregnant adults. We herein report four cases of L. monocytogenes infection in immune-compromised adults.

Fig. 1: Patient 1, CSF showing L. monocytogenes (arrow)

Fig. 2: Patient 1, blood gram stain smear showing L. monocytogenes (arrow)

1Fellow, 2Senior Consultant, 3Consultant, 4Fellow, Apollo Hospital, Chennai, Tamil Nadu

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and blood cultures inoculated in blood agar (Figure 3) grew *L. monocytogenes*. Ampicillin 2 gm IV q4h and gentamicin was added for synergy in the initial week and subsequently ampicillin alone for a total of 4 weeks. On subsequent enquiry, she was found to be consuming raw vegetables in the form of salads and juice after refrigeration, which could have been a source of *Listeria*. She improved over a week and was well at two month follow up at which time the initial CSF fungal and mycobacterial cultures were negative.

**Case 2**

A 65 year old lady with well controlled diabetes presented with acute onset fever, headache, vomiting and altered sensorium of 1 day duration. She was not on any immune-suppressants. There was neck stiffness and remainder of the examination was unremarkable. Her WBC was 11,000 cells/cumm. (polymorphs 70%). Liver and renal parameters were normal. Chest x-ray and brain imaging were normal. CSF cell count was 240 cells/µL (polymorphs 60% lymphocytes 40%), protein was 120 mg/dl, sugar was 50 mg/dl (blood glucose was 160 mg/dl). She was started on ceftriaxone 2 gm IV q12h and ampicillin 2 gm IV q4h. Gram stain, AFB, fungal stain and Xpert MTB were negative. Blood culture did not reveal any growth. CSF culture grew *L. monocytogenes* (Figure 4). He was treated with ampicillin 2 gm IV q4h for initial 2 weeks and was switched to oral amoxicillin 1gm thrice daily for another 2 weeks, as he was unwilling for further IV therapy. He improved and was waitlisted for liver transplant.

**Case 4**

A 58 year old lady with diabetes, chronic kidney disease and sarcoidosis for which she was on tapering dose of steroids (5 mg of prednisolone at presentation) was admitted with fever and dry cough for 10 days. She gave no history of consumption of salads, raw milk or refrigerated or uncooked vegetables. Physical examination was unremarkable. WBC count was 19,890 cell/cumm (polymorphs 76%) and toxic granules were present in the peripheral smear. Chest x-ray was normal. Blood culture grew *L. monocytogenes*. She was initiated on ampicillin 2gm IV q 4h and steroids were stopped. She received 3 weeks of parenteral ampicillin. She improved and was discharged.

**Discussion**

*L. monocytogenes* infection occurring in neonates, immunosuppressed patients, pregnancy, extremes of age, cancer, corticosteroid therapy, CRF, AIDS, organ transplant recipients is not uncommon. However there is no clinical way to separate *Listeria* infection from many other infectious diseases that can lead to fever and constitutional symptoms. *L. monocytogenes* is a facultative anaerobic, catalase positive, oxidase negative, short gram-positive rod that grows readily on blood agar producing incomplete β-hemolysis. In clinical specimens, Gram stain has a low sensitivity, the organisms may be gram-variable: laboratory misidentification of *L. monocytogenes* isolates as diphtheroids, streptococci, or enterococci is not uncommon and the isolation of a “diphtheroid” from blood or CSF should always alert the clinician to the possibility that the organism may be *L. monocytogenes*. Apart from blood agar, special media used are Brain Heart Infusion (BHI) and Mueller-Hinton agar which are selective for growing *Listeria monocytogenes*. Polymerase Chain Reaction (PCR) assay targeting hlyA gene which encodes Listeriolysin-O and other target genes are available. Of the six *Listeria* species, only *L. monocytogenes* is pathogenic for humans.

*L. monocytogenes* is ubiquitous and is found in soil, decaying vegetation, water, sewage, as part of the fecal flora and even in processed foods stored at 4°C. Many foods such as raw vegetable, raw milk, cheese and meat (including fresh, frozen and processed) are contaminated with *L. monocytogenes*. In a susceptible host, consumption of uncooked food, unboiled milk, cheese and meat are the risk factors. Those who are colonised with *L. monocytogenes* in their gut are at increased risk of invasive infection following gastrointestinal infection with another pathogen and also following colonoscopy.

Being an intracellular pathogen, clearance of this infection is dependent mainly on cell mediated immunity as evidenced by the strong clinical association of listerial infections with conditions associated with impaired cellular immunity like pregnancy, HIV, lymphomas, transplant recipients and corticosteroid use. Tumor necrosis factor α used to treat rheumatoid arthritis and Crohn’s disease can be complicated by listeriosis. Elderly, alcoholism, cirrhosis and iron overload state are other risk factors. Listeriosis is not commonly encountered in HIV infection, possibly because of the use of trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis*.

Clinical syndromes caused by *L. monocytogenes* include infection in pregnancy, neonatal infection, bacteremia, CNS infection, endocarditis, localized infection and febrile gastroenteritis. Diagnosis is by isolating...
L. monocytogenes from normally sterile clinical specimens through standard microbiologic techniques. Pregnancy is usually associated with a decline in cell mediated immunity, especially in the third trimester and hence listerial infections are more common during this period. L. monocytogenes has a predilection for placenta, where it can multiply and cause fetal infection and abortions. In neonates it is among the three major microbial etiologies of meningitis.

Bacteremia without an overt focus is the most common manifestation of listeriosis after the neonatal period. It presents with non-specific fever and myalgia which may be preceded by a prodrome of diarrhea, thus mimicking other systemic febrile illnesses. Patient 3 in our case series presented with febrile illness and cough and had a positive blood culture.

CNS infection can present as meningitis, encephalitis, brainstem encephalitis, brain abscess and myelitis. Listeria is the commonest cause of bacterial meningitis in the immune-compromised host in adults older than 50 years and is second only to S. pneumoniae in the elderly. Patients 1 and 2 in our series had meningitis. Patient 1 had a typical history of consuming raw food and medication induced cell mediated immune compromise. Patient 2 was an elderly lady and age was apparently her only risk factor. CSF mononuclear cells predominate in one-third of patients with Listeria meningitis and can mimic tuberculous meningitis, as in our case. In contrast to organisms commonly causing bacterial meningitis, L. monocytogenes not only causes meningitis but has a tropism for brain parenchyma and causes brain abscess. Focal neurological findings are found in 35-40 % and movement disorders in 15-20 % of patients with listerial meningitis. L. monocytogenes has predilection from brainstem causing rhombencephalitis: 40 % of these patients develop respiratory failure and mortality is high.

Cirrhosis is usually not considered as a risk factor for listeriosis; however cirrhosis is associated with impaired cell mediated immunity and as in our second case, there are case reports of spontaneous bacterial peritonitis with bacteremia due to L. monocytogenes. L. monocytogenes causing spontaneous bacterial peritonitis (SBP) in cirrhotics, especially in alcoholics, is likely related to increased gut translocation and impaired cell mediated immunity. Listeria monocytogenes is an uncommon cause of peritonitis, with less than 50 cases reported in the medical literature. Most cases were reported from Spain possibly related to consumption of diet rich in raw fruits, vegetables and dairy products. In Syria, where our patient 2 resides from, there are reports of higher rates of contamination of raw milk with Listeria spp, up to 10.96% in one study.

Due to inadequate food borne disease surveillance, very limited information is available on the prevalence of food borne listeriosis in India. On literature search, we found 42 case reports of human listeriosis from India all of which were in either pregnant women or neonates. There are very few reported cases in non-pregnant adults. It is unclear why human listeriosis is less commonly reported in India. Possible reasons include: refrigeration of food is not as widely practiced, salad and raw vegetable consumption is less common, widespread use of antibiotics for acute febrile illness may reduce diagnostic yield from cultures and laboratories may misidentify or discard Listeria as a contaminant.

All four of our patients had a good outcome with timely antibiotic therapy. The preferred agent is penicillin or ampicillin, while gentamicin is added for synergy for the initial 2 weeks in the treatment of bacteremia in those with severely impaired T-cell function and in all cases of meningitis, encephalitis, brain abscess and endocarditis. The best alternative agent is trimethoprim-sulfamethoxazole, especially for patients with anaphylactic beta-lactam allergy. Cephalosporins which are usually recommended for SBP, are bacteriostatic for L. monocytogenes while chloramphenicol is associated with failure and relapse and hence both are not recommended.

Treatment duration is 2 weeks for bacteremic patients, 3 weeks for meningitis, 6 weeks for brain abscess and rhombencephalitis and 4-6 weeks for endocarditis. Listerial gastroenteritis is self-limited and treatment is not warranted.

Preventing listeriosis requires proper food hygiene: thoroughly washing raw vegetables, cooking vegetables and meat and avoiding soft cheese and unpasteurised milk. In immune-compromised groups, trimethoprim-sulfamethoxazole given for pneumocystis prophylaxis will be effective in preventing listeriosis as well.

Conclusion

Listeriosis is not uncommon in India and is probably under-diagnosed. The disease should be considered in the differential diagnosis of meningitis and sepsis in cell mediated immune compromised hosts, especially those with impaired T cell mediated immune response. Cultures of blood and other involved fluids readily grow Listeria, and the laboratory should be alerted to this possibility. Ampicillin should be part of the empiric regimen for meningitis in these patients and outcome is generally very good with early and appropriate antibiotic therapy as in our patients.

References

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Bilateral Acute Anterior Uveitis and Conjunctivitis following Intravenous Zoledronic Acid

Samrat Chatterjee¹, Deepshikha Agrawal¹

Abstract

The ocular side-effects of bisphosphonates have the potential to escalate with their widespread use. We report a patient of osteoporosis who was treated with zoledronic acid infusion. He developed ocular pain, redness, watering, photophobia and swelling of both the eyes. He was diagnosed with acute anterior uveitis and conjunctivitis and treated with topical 1% prednisolone acetate and 1% atropine sulphate. The signs of inflammation abated by one week and the steroids were tapered over the next six weeks. There were no further recurrences. Patients must be educated about the ocular side-effects of bisphosphonate therapy, monitored closely after intravenous infusion and advised to seek ophthalmic consultation promptly if any ocular symptoms or signs develop.

Introduction

Bisphosphonates are widely used in the treatment of hypercalcemia and osteoporosis. They have been reported to cause adverse ocular inflammation like conjunctivitis, episcleritis/scleritis, anterior uveitis, orbital inflammation, and optic neuritis or other cranial nerve palsies. These manifestations are part of an acute phase reaction mediated by peripheral blood γδ T cells which cause release of pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor. However the low incidence of such complications means that a physician or an ophthalmologist may infrequently encounter such an event. Thereby these patients pose a diagnostic and therapeutic challenge. We report a patient with bilateral conjunctivitis and anterior uveitis following treatment with zoledronic acid, a potent bisphosphonate, for osteoporosis secondary to prostrate malignancy.

Case Report

A 70-year old man had been diagnosed to have high risk adenocarcinoma of the prostrate in 2012. He underwent bilateral orchiectomy and radiotherapy at a distant tertiary cancer treatment facility. In December 2015, he was diagnosed with osteoporosis when he complained of low back ache and was advised yearly zoledronic acid. The first dose was given at the time of diagnosis as an infusion of 4 mg in 100 ml of normal saline. Following administration of the drug he was discharged the same day. Next day during his return journey, he experienced flu-like symptoms and mild pain in both the eyes which progressed in quick succession to swelling, redness, watering and blurring of vision. At presentation two days later, his flu-like symptoms had subsided but he was in pain and anxious. His vision in both the eyes was 20/64, N12 and this was not improving with refraction. The ocular movements were full and pupillary reaction normal. The lids of both the eyes were edematous with fresh keratic precipitates were observed on the corneal endothelium in both the eyes. There was anterior chamber reaction in the right eye and fibrinous reaction in the anterior chamber without hypopyon in the left eye (Figures 1C and D). There was early nuclear sclerosis in lens of both the eyes with brown iris pigments on
the surface. Intra-ocular pressure was 18 mm Hg in both eyes. The fundus examination was normal without any vitreous cells.

A diagnosis of acute non-granulomatous anterior uveitis with conjunctivitis in both the eyes was made. He was treated with topical 1% prednisolone acetate two hourly and 1% atropine sulphate three times daily. After a week the symptoms had subsided and his best corrected visual acuity improved to 20/20, N6 in both the eyes. The inflammation in the conjunctiva and anterior chamber had subsided (Figure 2). The topical steroid was tapered over six weeks and the atropine discontinued. There were no further recurrences.

Discussion

The incidence of uveitis following intravenous zoledronic acid is faster compare to oral administration, the former occurring within the first week, with a median of three days, while in the latter it is delayed by several days to months.4 In our patient the onset was within two days after infusion similar to what is seen in an acute phase reaction.5,6 Our patient had been discharged the same day of receiving the infusion and as the symptoms began during his return journey there was a delay in his seeking medical advice, resulting in significant worsening of conjunctivitis and uveitis.

The conjunctivitis and uveitis caused by bisphosphonate are nonspecific and the uveitis may be unilateral or bilateral and range from mild to severe with tendency to form posterior synchia.5,6 The presence of pigments on the lens surface in our patients indicate the onset of posterior synchiea formation (Figures 2C and D). As both these entities present without characteristic features, etiological diagnosis depends on a carefully elicited drug history.

Bisphosphonate induced uveitis is treated with topical corticosteroids and cycloplegic drugs.1,3,4,6 Oral bisphosphonates need to be discontinued. Due to contrarian reports in literature it is unclear at present whether re-treatment with the same or an alternate bisphosphonate, would result in recurrence of ocular side-effects. Fraunfelder et al reported the recurrence of scleritis in the same eye of five patients, who were re-treated with the bisphosphonate pamidronate,2 while Patel et al did not observe any recurrence in three patients re-challenged with multiple infusions of zoledronic acid 18 months apart without any prophylactic topical corticosteroid.6

Patients treated with intravenous formulations needs close observation during the first week. Treatment is usually uneventful with topical corticosteroids and cycloplegics although there are differing opinions about re-treatment with bisphosphonates in patients who experience ocular adverse effects.

Conclusion

Ophthalmologists need to be sensitized to bisphosphonate induced uveitis as the drug is extensively prescribed. The diagnosis of bisphosphonate induced uveitis requires careful history taking. The physician needs to inform patients on bisphosphonates about ocular adverse effects and seek ophthalmic consultation promptly.

References

Rescue PTCA in a Patient with Single Coronary Anomaly

Parveen Kumar\textsuperscript{1}, Hemant Chaturvedi\textsuperscript{2}, Ramakrsihna\textsuperscript{1}, Sanjeev Sharma\textsuperscript{3}

Abstract

We present a case of rescue percutaneous coronary intervention (PCI) using right radial approach in a rare case of single coronary artery originating from the right sinus. Although these anomalies and stenosis of anomalous vessels have earlier been reported, treatment of atherosclerotic lesions by PCI has rarely been reported. There is a definite risk during PCI in patients with a single coronary ostium because dissection with the guiding catheter would result in a catastrophic event. Additionally, technical difficulties may occur due to the ostial configuration and course of the branch to be stented.

Introduction

There is a definite risk during PCI in patients with a single coronary ostium because dissection with the guiding catheter would result in a catastrophic event. Additionally, technical difficulties may occur due to the ostial configuration and course of the branch to be stented. Here we present a case of rescue PCI performed in a patient with single coronary artery.

Case Report

A 52 years old non-diabetic, normotensive male presented with complaints of sudden onset chest pain of one-hour duration and diagnosed at a peripheral hospital as Acute Anterior wall ST elevation myocardial infarction (STEMI) and managed with thrombolysis. He developed progressive breathlessness following that episode. He was intubated and kept on ventilator. Later he was shifted to our centre for further management. On examination he had stable vitals, afibrile with bilateral basal crepts on auscultation. Two-dimensional echocardiography revealed regional wall motion abnormalities in Left anterior descending (LAD) artery territory with moderate left ventricle dysfunction with no mitral regurgitation. After proper informed consent, patient underwent coronary angiography via right radial route which revealed single coronary artery arising from right aortic sinus which further divided into Right coronary artery (RCA) and Left main (LM) coronary artery. LM has 80\% thrombotic culprit lesion (Curved arrow) and bifurcates into left anterior descending artery (LAD) and left circumflex (LCx) artery.

Fig. 1: Selective coronary angiogram using guide JR 3.5 showing single coronary artery arising from right aortic sinus which further bifurcates into Right coronary artery (RCA) and Left main (LM) coronary artery. LM has 80% thrombotic culprit lesion (Curved arrow) and bifurcates into left anterior descending artery (LAD) and left circumflex (LCx) artery.

Fig. 2: LM into LAD was wired with workhorse coronary wire.

Fig. 3: LM lesion was predilated with 2.5x12mm and 3x10mm balloon.

Fig. 4: Final coronary angiogram after stenting the LM lesion with third generation everolimus eluting stent.

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vessel with minor plaque in mid to distal part. He further underwent rescue percutaneous transluminal coronary angioplasty (PTCA) with stenting to proximal to mid Left main with a 3.5 X 18 mm third generation Everolimus drug eluting stent (Figure 3). Final angiogram showed good end results with TIMI III flow without any complications (Figure 4). He was subsequently extubated next day and discharged in a stable condition on fourth day.

Discussion

Several classification systems for coronary artery abnormalities exist. Lipton et al., classified coronary variations based on origin and anatomical course relating to the ascending aorta and pulmonary trunk. Type L represents an RCA originating from the left main stem and type R indicates that the left coronary artery originates from the RCA. These types are then classified as I-III. Class I follow the anatomical course of either an RCA or LCA. Class II indicates one coronary artery arising from the proximal part of the normally located opposite coronary artery. In class III, the left anterior descending (LAD) and left circumflex (LCx) arise separately from the proximal part of a normal RCA. Classes II and III are then designated as anterior (type A) to pulmonary artery or posterior (type P) to aorta, or interarterial (type B) if it courses between the ascending aorta and the pulmonary trunk. Type B morphology has been associated with a high risk of clinical consequences when associated with an intramural course. Angelini et al., proposed a slightly different classification according to the anatomical course within the interventricular sulcus and atrioventricular groove, as well as the location of penetrating side branches. According to Lipton’s classification, our patient had R II P subgroup (single coronary artery from the right sinus with LCA arising from the proximal part of RCA and a posterior course to aorta). Lipton’s classification has been modified by others, adding to this classification the “S” septal (through the interventricular septum) and “C” combined types. R II P subgroup is rare. Though there are several case reports of PCI in single coronary artery, most are through the femoral route. To the best of our knowledge, this case report is one of a few similar cases described in the literature. We did not have much difficulty during PCI as we were using right radial artery approach and Judkin’s right catheter. For right coronary cannulation, we always start with a JR curve. Other catheters like internal mammary artery (IMA), Multipurpose, and Amplatz left (AL) can also be used according to the situation.

Conclusion

The present case merits mention because of several points. Intervention in a single coronary artery through radial approach has been rarely reported and in type R II, it is rarer. Radial PCI is as good as femoral PCI for anomalous coronaries, provided operator has experience in radial interventions. Meticulous attention should be given to pressure damping while doing PCI in cases with both coronaries originating from single ostium. We should take non-selective shoot if there is no coronary originating from either sinus (left/right).

References

1st time in India

Volibom
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell
Discovery of Anticoagulant Warfarin

Jayant Pai-Dhungat

In the 1920s there was an outbreak of an unrecognized, strange, cattle bleeding disease, in Northern United States and Canada. After investigations by veterinary pathologist, it was found to be due to ingestion of spoiled silage from sweet clover (M. Officinalis), which caused cattle deaths whereas ingestion of fresh sweet clover had no ill effects. Sweet clover flourishes in poor soil and provides a rich source of protein, enriches the soil and makes a good fodder. However, Spoilage is likely to occur in sweet clover silage since its small leaves dry quickly, leaving succulent stems that are damaged by organisms. In case of spoiled sweet clover, the harmless ingredient coumarin is converted into bis-hydroxycoumarin (dicoumarol) which is toxic due to its anticoagulant property.

The identity of anticoagulant substance in spoiled sweet clover remained a mystery until 1940. At the University of Wisconsin, the lab chemist Karl Paul Link set out to isolate and characterize this agent. After five years, Link’s student, Harold Campbell recovered 6mg. of crystalline anticoagulant. Later, another student took over the project and initiated a large scale extraction in 4 months. Through degradation experiments, they established the molecular structure of the agent and named it Dicoumarol.

Dicoumarol is a product of plant molecule Coumarin. Coumarin is harmless when ingested and is present in many plants. It produces notably sweet smell of freshly cut grass or hay and plants like sweet grass. It is present in green leafy vegetables like Amaranths. It was once used to scent tobacco and snuff, as the hay-like aroma of dried sweet woodruff intensifies and persists for years. Coumarin can be manufactured from trans-cinnamic acid, a compound isolated by Austrian chemist Joseph Loschmidt (1821-1895). Coumarin can also be produced from aldehydes such as cinnamic aldehyde which is found in the bark of cinnamon and is used in manufacture of perfumes due to its pleasant odour.

Name WARFARIN is an acronym for the patent holder-Wisconsin Alumni Research Foundation with the suffix ‘in’ from coumarin. Although it was first developed by Link, the name Warfarin was given because of most involved in the discovery of Dicoumarol were students of the University of Wisconsin. Warfarin is a synthetic derivative of Dicoumarol. It was first registered for use as a rodenticide in US in 1948, and was immediately popular due to its self baiting. The WARF financially supported the research and assigned the patent. Warfarin acts by depleting vitamin K, and affecting its recycling in the body. Its action can be reversed by replacing vitamin K.

In 1951, a US army inductee, unsuccessfully attempted suicide with rodenticide pills of Warfarin. His survival with vitamin K led to the start of clinical trials in patients with thrombo-embolic syndromes. It was approved by FDA in 1954, and has come in wide use till today. An early recipient of warfarin was US President Eisenhower who was prescribed the drug after he suffered myocardial infarction in 1955.
Innovative Therapy with Caspofungin  

Rajeev Soman¹, Vidylultala Koparkar², Anjali Shetty³, Camilla Rodrigues⁴  
¹Consultant Internal Medicine and Infectious Diseases, ²Infectious Diseases Fellow, ³Consultant Microbiology, P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra  

Dear Sir,  

Candida meningitis is a rare but highly consequential disease. As per the guidelines, initial therapy is with Liposomal Amphotericin B (LAmB) with or without 5Flucytosine.¹ Step down treatment is with fluconazole. Caspofungin has poor penetration into meninges, and hence is usually not used for treating candida meningitis.  

We report the successful treatment of CSF shunt associated Candida meningitis refractory to standard treatment with LAmB and 5-Flucytosine (5FC). Caspofungin was instilled intraventricularly and also used systemically in addition to the standard therapy, which resulted in cure.  

A 68 year old gentleman suffered subarachnoid and intra-ventricular hemorrhage due to a basilar artery aneurysm, which was clipped. He needed multiple changes of external ventricular drain and Ommaya reservoir due to blocks. This led to nosocomial Candida albicans meningitis which was worsening despite 10 days of treatment with LAmB and 5FC to which the organism was susceptible. The susceptibilities were as follows. 5FC <1, AmB = 1, Fluconazole <1, Voriconazole <0.12, Caspofungin <0.25, Micafungin <0.06 mcg/ml.  

Encouraged by our past experience of treating permanent hemodialysis catheters and chemotherapy ports with Echinocandin Lock Therapy² and finding precedence in the literature of the use of intraventricular caspofungin in a case of Scedosporium brain abscesses in a 2 year old child³ we used caspofungin lock for the Ommaya reservoir.  

We instilled at first, 5 mg caspofungin into the Ommaya reservoir to target a concentration of 2500 mcg/ml in the reservoir and planned a dwell time of 24 hours. However the patient required letting out 150 ml of CSF every 12 hours, to relieve the intra-cranial pressure. Hence we instilled 10 mg of caspofungin with a daily dwell time of 12 hours and administered the remainder of 60 mg caspofungin intravenously. This was based on a case report of refractory Candida meningitis in an immunocompromised patient cured by addition of intraventricular caspofungin after failure with intravenous and intraventricular AmB and systemic fluconazole.⁴  

We had reservations about this approach as the caspofungin preparation for intravenous use contains glacial acetic acid and has a pH of 5. Besides, we wondered whether the paradoxical effect of high concentrations of caspofungin would lead to resistance in the Candida organism.⁵ We could not measure caspofungin levels in the blood or CSF in order to assess the inhibitory quotient obtained in the CSF. However CSF samples obtained 3 days into treatment and several times later were found to have been rendered sterile.  

The patient developed ARDS and cytopenias due to LAmB and 5FC which had to be changed to intravenous caspofungin and oral fluconazole. Treatment was continued for 20 days after which the Ommaya reservoir and VP shunt were removed and a fresh VP shunt was inserted on the contralateral side. The patient has a VP shunt and a basilar artery clip in situ, hence oral fluconazole has been continued as chronic suppressive therapy. Patient is well at follow up 1 year later.  

Conclusion  

In patients with candida meningitis who are refractory to usual treatment, additional intraventricular caspofungin may be an important therapeutic modality.  

References  


Coronary Artery Ectasia – The Need for an Expanded Classification  

Arun Gopalakrishnan, Sanjay Ganapathi, Krishna Kumar Mohanan Nair, Harikrishnan Sivadasanpillai, Ajitkumar Valaparambil  

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Sir,  

We read with interest the article by Kerr et al on coronary artery ectasia and congratulate the authors for their work.¹ We would like to share a few perspectives on the related entity of coronary aneurysms, and on the limitations of the classification used by the authors.  

While coronary aneurysms and ectasia are possibly differing manifestations of the same pathophysiologic process, isolated coronary artery ectasia is rare. The higher prevalence of coronary artery ectasia in the index study is not unexpected as it was a single center study which primarily included patients who presented with coronary events. Coronary aneurysms are of two types, saccular and fusiform. Saccular aneurysm refers to an aneurysm with the transverse dimension of the involved segment greater than longitudinal dimension (along the axis of the vessel) while fusiform aneurysm is an aneurysm with the longitudinal dimension at least twice its transverse dimension.²  

It would be relevant to mention our experience in an earlier study where we had tried to classify our cases of coronary artery ectasia based on the proposed classification by Markis. We had noted that not all patients could be classified into one of the four groups, like those with diffuse ectasia in one vessel, localized ectasia in two vessels or localized ectasia in two or three vessels.³ This formed the basis of the revised classification which is given below for reference (Table 1). Localized ectasia was defined as ectasia involving less than 50% of the length of the vessel.  

This modification facilitates easy classification of all different types of
Table 1: Revised classification of coronary artery ectasia by Harikrishnan et al

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Diffuse ectasia in two or three vessels.</td>
</tr>
<tr>
<td>Ia</td>
<td>Diffuse in three vessels</td>
</tr>
<tr>
<td>Ib</td>
<td>Diffuse in two vessels, localized (discrete) in one vessel</td>
</tr>
<tr>
<td>Ic</td>
<td>Diffuse in two vessels</td>
</tr>
<tr>
<td>Type II</td>
<td>Diffuse ectasia in one vessel and</td>
</tr>
<tr>
<td>Ila</td>
<td>Localized in one vessel</td>
</tr>
<tr>
<td>Ilb</td>
<td>Localized in two vessels</td>
</tr>
<tr>
<td>Type III</td>
<td>Diffuse ectasia in one vessel</td>
</tr>
<tr>
<td>Iva</td>
<td>One vessel involved</td>
</tr>
<tr>
<td>Ivb</td>
<td>Two vessels involved</td>
</tr>
<tr>
<td>Ivc</td>
<td>Three vessels involved.</td>
</tr>
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ectasia unlike the original classification by Markis et al.2,3

References

Vitamin D and Muscle Weakness

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Sir,

Although ubiquitous, vitamin-D deficiency is still unrecognized and under-diagnosed. Proximal muscle weakness is a common symptom of vitamin-D deficiency and occurs before biochemical signs of its deficiency appears. Therefore, vitamin-D deficiency should be kept in the differential diagnosis for the muscle weakness, as it is reversible and easily treated with vitamin-D supplementation.

A 53 years old woman and a 46 years old male presented in our out-door clinic in May and July 2014 because of difficulty in getting up from squatting position. About 15 month before presentation, the family members noticed the difficulty in getting up from the sitting position, which was progressive. For last 6 months, they had to use hands and or needed help of the others to get up. They denied generalized aches, other symptom or any drug intake. On physical examination, muscle bulk and muscle tone were normal, muscle power was 3/5 in the flexor and extensor of the hip and they were unable to get up from squatting position unaided.

Their complete hemogram, fasting plasma glucose, liver function tests, renal function tests included electrolytes, vitamin B12, thyroid function tests, rheumatoid factor, anti-nuclear anti-body, muscle creatinine phosphokinase (CPK) and CXR were normal. Corrected serum calcium was 7.8 mg/dl and 8.4 mg/dl respectively with normal alkaline phosphatase levels. Their serum 25-hydroxyvitamin-D levels were extremely low (4.5 ng/dl and 5.8 ng/dl). Keeping in view their risk factors: dark skin color, wearing whole body clothes, low sun exposure and poor dietary intake, a diagnosis of proximal muscle weakness due to severe vitamin-D deficiency was made. Treatment with oral cholecalciferol 60,000 IU weekly for eight weeks followed by 60,000 IU monthly was initiated. They were able to stand up unaided now and their serum 25-hydroxyvitamin-D levels were 33 ng/dl and 31.5 ng/dl at 3 month follow-up.

About 30% of patients with hypovitaminosis-D presents with proximal muscle weakness and is often unrecognized because patients don’t complain of muscle weakness until they are unable to rise from sitting position.1 A serum 25-hydroxyvitamin-D <20 ng/dl causes increased body sway and level <10 ng/dl leads to difficulty in rising from sitting position and inability to ascend stairs.2 The powerful type II muscle fibers that are essential for muscle strength are atrophied in vitamin-D deficiency. Skeletal muscle contains vitamin-D receptors that modulate various transcription factors in muscle cells, mediating muscle cell proliferation and differentiation into mature type II muscle fibers.2 Only in minority of patients with vitamin-D related muscle weakness has raised CPK and muscle biopsy shows non-specific muscle fiber atrophy and no sign of inflammation. Ultimate evidence of the diagnosis rests on the response to therapy. Muscle strength strikingly improves when 25-hydroxyvitamin-D level increases from 4 ng/dl to 16ng/dl and continues to improve as the level increases to more than 40 ng/dl as seen in our patients.1,3

We conclude that in patients with proximal muscle weakness and finding of typical biochemical alterations in high risk individuals should limit exhaustive and costly neuromuscular work up. In such patient, a therapeutic trial of vitamin-D is warranted.

References

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