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The Clinician and the COVID -19 Pandemic – Keeping Track, Keeping Pace and Keeping the Faith

Nithya J Gogtay1, Arun D Bhatt2

As this editorial is being written, the highly anticipated new James Bond movie No Time to Die has been released. Its title probably resonates with the multitude of health care workers [HCWs] who have put their lives on the line since the beginning of the pandemic and continue to do so amidst the challenge of new waves, deadlier strains, frazzled colleagues and family and beleaguered healthcare systems hoping each day for a glimmer of light at the end of a long and dark tunnel. It is useful at this point to address some key issues faced by clinicians and clinician researchers and dwell on potential solutions that may in some manner mitigate this and learnings for the future.

A critical area has been that of a mountain of evidence including studies with alternative systems of medicine. In 2010, at the rate of 75 trials and 11 systematic reviews a day, a question was asked by a few authors as to whether we could at all keep track of evidence.2 Eleven years later, the COVID-19 pandemic compounded this manifold. While there are success stories of high quality studies,3,4,5 several smaller studies with low sample sizes have led to wasteful research and wasted resources.6 Hydroxychloroquine [HCQ] which found appeal with national platforms including articles in the preprint stage and often disseminates flawed research.6 It becomes next to impossible for the clinician to appreciate the true quality and utility of media messages.6 Not just this, the average person has stayed on top of this mounting information as television and radio channels broadcast peer reviewed [and otherwise] information into the homes of people. This has brought greater difficulty for the practicing clinician already reeling under pressure of treating COVID -19 patients not knowing how to address patient and caregiver concerns particularly with sketchy and often conflicting evidence.

A third area is doing research during the pandemic. An example would be taking written informed consent wearing personal protective equipment [PPE], explaining benefit-risk of unproven interventions as also taking consent for placebo controlled trials, retaining participants in ongoing COVID and non COVID trials, keeping abreast of COVID specific guidelines from the ethics committees and regulatory bodies and finally sustaining clinical research itself as an enterprise. All this amidst desperate participants and caregivers and the need to maintain the highest standards of science and ethics at all times and be in readiness for audits and inspections. In addition, studies with use non pharmacological interventions such as masks are not easily implementable and yet need to be done.10

The primary challenge was really managing participant expectations in a trial with a 3:1 randomization and which was double-blind. Some questions from participants are listed here - What are the chances I have got placebo? Why are you excluding me because I have antibodies? Is it my fault I got COVID to be excluded from your trial? Why did I get COVID-19 disease despite being vaccinated? Can you break the blind quickly as I am a COVID warrior as I have volunteered when no one else in the country came forward? When a Serious Adverse Event [SAE] occurred in the study [shown later to be not causally related to the investigational product and at the point where due process was still being followed], participants said they felt betrayed that they were not informed about it.11 Following study completion, as the names of these participants did not feature in the COWIN app,12 a fresh set of issues cropped up. “I wish I had never taken part in your clinical trial. I wish I had waited for the Emergency Use Authorization and got my vaccine from the system”. These were among the kinder calls and comments.

A fifth and perhaps less addressed area is that of mental health. Studies on burn out among physicians conducted during the pandemic have shown high levels of emotional exhaustion, depersonalization, anxiety, and fear of risk to themselves and their families. Many HCWs hesitated to go home to their families for fear of infecting them. Several were torn between the obligation to be a caregiver to the patient and family responsibilities.13,14

Hindsight they say is always hundred percent. How could we have done better? Or could we have done better at all? While is it not easy to keep track and keep pace with evidence, there are a few tools that can help.

1Professor and Head, Department of Clinical Pharmacology, KEM Hospital, Mumbai, Maharashtra; 2Consultant, Clinical Research and Drug Development, Mumbai, Maharashtra
Trials/Studies that are open label, single arm, observational in nature are extremely unlikely to prove the efficacy of a new or a repurposed intervention. Similarly, announcement or approval by the regulator of the conduct of a clinical trial may lend hope but is no guarantee of the efficacy or safety of the intervention or vaccine. As a result, our clinicians are hard pressed for time and this was compounded during the pandemic leading to paucity of Real World Evidence [RWE] from India. Academia -industry collaboration and investment in RWE studies would go a long way in good quality data collection, adopting Electronic Health Records [EHRs] as a matter of routine and delivering research that finally matters to the patient. As regards research, clinician researchers would do well to understand the huge effect of participants’ expectations. These are beliefs about the nature and the possibility of improvement after an intervention. Expectations are verbalized and can be measured and addressed. Total knee arthroplasty in osteoarthritis offers a good example here about addressing expectations. Tolk J and colleagues randomized patients scheduled to undergo total knee arthroplasty into two groups – the control which received the routine preoperative orientation and who long do you withhold vaccination in them just to answer questions of science needs to be addressed through a pragmatic approach. Finally, a global crisis like this pandemic does beget change. Learnings have been many and even unimaginable until last year. We thought we could not practice medicine from home but we did. We thought we could not work from home but we did. The mRNA vaccines [a novel technology] reached a large population quickly and clinical trials were completed and reported in record time. Virtual clinical trials where patient visits to the trial site are partly or entirely avoided may become the new normal.

So where do we go from here? As we continue navigate the thick, tall tail of the pandemic, keep the faith we must. A test of this pandemic for many of us has been searching for some significance and meaning to our existence as our lives were upended when we lost colleagues, loved ones and family members. Perhaps the answer lies in the sixth stage of grief as described by David Kessler in his book Finding Meaning– meaning is what you make happen.

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BP: Blood pressure

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Ivermectin and Hydroxychloroquine for Chemo-Prophylaxis of COVID-19: A Questionnaire Survey of Perception and Prescribing Practice of Physicians vis-à-vis Outcomes

Shambo Samrat Samajdar1*, Shatavisa Mukherjee2, Tanuka Mondal3, Jyotirmoy Paul4, Santanu K Tripathi5, Ajay Chakrbarty6, Bibhuti Saha7, Debasish Bhattacharrya8, Rohan Tripathi9

Abstract
Background: Chemoprophylaxis (CP) along with masking and physical distancing seem an undeniable alternative. Considering the significant but uncertain role of CP for the current COVID-19 pandemic situation, we aimed to determine the various aspects of CP prescribing practices among physicians across India.

Methods: An online survey was conducted among prescribing physicians across India where physicians were assessed for their prescribing practices on COVID-19 CP. Responses to the questionnaire were obtained via telephone, email and WhatsApp messages. Responses were duly analyzed thereafter.

Result: Ivermectin was the preferred choice in 44% individuals followed by hydroxychloroquine in 34% individuals. Odds of COVID contact among those using HCQ and / or IVR prophylaxis was less than 1 of which IVR was found more protective. The present study also made a survey among 309 community dwellers, where odds of contacted COVID among those with any prophylaxis was 0.46 times than those without any prophylaxis.

Conclusion: The HCPs found IVR to have a greater risk reduction than with HCQ; while the combination showed the greatest reduction and lack of CP use was associated with a high risk of SARS-CoV-2 infection.

Introduction

Over the period of past 17 months, the world has witnessed more than 160 million cases of infection, as on date, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and nearly 2% (>35 lac) had fatal outcome. As we were exposed to the world has witnessed more than 160 million cases of infection, as on date, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and nearly 2% (>35 lac) had fatal outcome. The risk for healthcare workers (HCW) in those who provide endotracheal intubation or adorning insufficient personal protective equipment (PPE) is high due to prolonged exposure to infected patients which is even greater in those who provide endotracheal intubation or adorning insufficient personal protective equipment (PPE). Unfortunately, the latest factor that has compounded the pandemic worry is the incidence of mucormycosis, which has been found in more than 76% patients treated with corticosteroids. Also, 80% of the patients diagnosed with mucormycosis are diabetics, and India is the home to alarming 8.9% diabetics of the total adult population.

Thus far, prevention of SARS-CoV-2 is a better alternative to contain the pandemic. Though the vaccines have been developed and are a ray of hope, there are many logistic and other challenges in vaccinating a meaningful proportion of the population at risk within a short time. Another threat are the Concerns about newer neutralization escape mutants are being reported from several parts of the world. Further, the prolonged Covid-19 pandemic has already shown its potential to shatter global fiscal and societal predicament.

Overall it appears that the disease is unlikely to vanish soon and therefore to resume the daily activities and live life amidst the various restrictions, a rational, multi-pronged strategy needs to be adopted. Chemoprophylaxis (CP) along with masking and physical distancing seem an undeniable alternative. CP seems a particularly useful strategy for the frontline HCWs, including healthcare professionals, the ones who need to be on site for earning their livelihood and the care-takers of infected family members. Two drugs ivermectin (IVR), which is an anti-parasitic drug with lower drug interaction potential and hydroxychloroquine (HCQ) have been used as chemoprophylactic agents. No less than eight RCTS and observational studies have demonstrated statistically significant decreases in the transmission of COVID-19 among human subjects with IVR. Based on available evidence and the guideline recommendation from the international BIRD conference, ivermectin has been proposed to be positioned in the prevention of COVID-19. However, when available published
individuals, and 75 were just prescribed vitamin C/multivitamin. For self-chemoprophylaxis, 50% prescribing professionals used HCQ, 31.67% used IVR, and 11% used none (only vitamin C/multivitamin). The aggregate choice of drug for CP is represented in Figure 1.

On an average 10 patient were advised HCQ in a month, compared to 23.67 who were advised IVR instead. Majority of the prescribers believed that IVR or HCQ chemoprophylaxis should be given to all health care workers at higher risk of transmission, e.g., doctors, nurses, other health staff along with those with occupational or behavioral risk of (unknown) transmission, e.g., policemen etc. An interesting finding reflects that out of an average of 99 patients put on HCQ chemoprophylaxis, an average of 10 persons suffered from COVID-19. Of an average of 154 patients put on IVR chemoprophylaxis, an average of only 3.67 persons suffered from COVID-19. Noticeably despite being in self-chemoprophylaxis, 15% (n=9) prescribers still contacted COVID-19, though were mostly mild in severity grading. Odds of COVID contact among those using HCQ and/or IVR prophylaxis is less than 1 of which IVR was found more protective. Chi-square value for trend is statistically significant.

The present study also made a survey among 309 community dwellers. Out of 309 population 109 people were with any CP. Among them only 11 people contacted COVID. Out of 200 people without any CP, 39 people contacted COVID. Odds of contacted COVID among those with any prophylaxis is 0.46 times than those without any prophylaxis. Association between use of prophylaxis against COVID and getting infected with COVID is statistically significant and as the value is less than 1, so use of any prophylaxis is protective among community dwellers (Table 2).

Most prescribers added to their prophylactic therapy advised personal protection measures like mask, hand hygiene, physical distancing etc. Some noted adverse reactions to HCQ/IVR therapy were gastrointestinal complications (nausea, vomiting, abdominal discomfort etc.) and cardiac complaints (palpitations, arrhythmia, tachycardia etc.).

### Discussion

Considering the crucial need of CP, HCQ was recommended by the COVID-19 National Task Force of India for all HCW, other frontline workers involved in COVID-19 activities, and asymptomatic household contacts of RT-PCR-confirmed cases. Cohort and retrospective studies have demonstrated that HCQ CP by HCW at high risk, significantly reduced the rate of RT-PCR positivity compared to no-CP. However, a later meta-analysis concluded that the use of HCQ did not reduce the risks of developing COVID-19, hospitalization, or mortality. Besides, the analysis also revealed that HCQ increased the risk of adverse events. On the contrary, results of meta-analyses of 4 RCTs and 5 observational studies of IVR have found significantly reduced risks of contracting COVID-19 with the regular use of ivermectin.

In the current study, we found that IVR was preferred by physicians for self-prophylaxis and for general population along with HCW at risk of developing the infection. Similar to the recently published meta-analysis, we found a reduced risk of contracting SARS-CoV-2 infection in subjects who received IVR prophylaxis compared to those who received HCQ. Among HCPs, who self-prescribed CP majority opted for IVR, followed by HCQ or combination; very few did not use either CP. Clearly, those who used CP had reduced RR of infection compared to those who did not. The HCPs found IVR to have a greater risk reduction than with HCQ; while the combination showed the greatest reduction and lack of CP use was associated with a high risk of SARS-CoV-2 infection.

It is also worth considering that HCQ is a lysosomotropic drug may influence the functions of proteins involved in antigen presenting pathways and in
B-cell activation involved in antibody responses and may influence vaccine efficiency negatively. Trained immunity is known to enhance the innate immune response and thereby facilitates the defense against infections. HCQ forestalls the trained immunity and therefore may not be beneficial for clearing viral infections like SARS-CoV-2 and contends against its use as a CP for COVID-19. No negative influence of IVR on immune response has been documented yet, rather worldwide dataset has only strengthened the correlation of its prophylactic effect against SARS-CoV-2, also supported by several recent findings reported in literature. Until, vaccine availability improves along with its reach, CP with IVR seems a promising alternative.

This study was conducted when no vaccine for COVID 19 was available. Role of CP in COVID 19 vaccine beneficiaries is extremely debatable. It is important to consider well designed studies to understand the CP and vaccination interaction. Though this survey helped gathering information from a varied cohort, it was a small sample of physicians. Additionally, inconsistency in recall precision may have affected our results. Further compliance could have also affected our results in terms of the risks of contracting the SARS-CoV-2 infection among those prescribed CP apart from the missing follow-up data, which was not captured by our questionnaire.

To affirm these findings and avoid recall bias an appropriately designed randomized controlled study with a larger sample size is warranted.

References


Dr. Siddharth Shah Memorial Oration – 2023

Recommendations are invited from members for the following assignments so as to reach, Hon. General Secretary – API, Dr. Mangesh Tiwaskar by 31st December 2021.

Category (i) Dr. Siddharth Shah Memorial Oration – 2023

Persons are selected from the recommendations received from members of the API. The orator in the discipline of medicine should preferably be a member of API. The recommendations for the above assignments must be accompanied with reasons for recommending a particular person showing the value of his/her research and eight copies each of three of his/her best publications. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer. The recipient of the above oration should deliver a lecture at the Annual Conference in January, 2023, at Ahmedabad.

Those who have received Oration / Lectureship in a given category are eligible for application for the other two categories.

The members of the Governing Body of API / PRF and the Members of the Faculty Council of ICP are not eligible to receive Oration.

The prescribed nomination form for the above oration is available on the website “apiindia.org”.

The completed application form for the “Dr. Siddharth Shah Memorial Oration” should reach to Dr. Mangesh Tiwaskar, Hon. General Secretary of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Malahaxmi Station West, Mumbai – 400 011 not later than 31st December 2021. Tel. No. 022 6666 3224 • e-mail: api.hdo@gmail.com

Dr. Mangesh Tiwaskar
Hon. General Secretary
Transthyretin - A Novel Biomarker for Insulin Resistance and Atherosclerosis Risk in Prediabetics

Ayushi Singhal¹, Ajay Chauhan²*, Parul Goyal³, Anil Taneja⁴

Abstract

Objective: The aim of the study was to compare serum levels of Transthyretin in prediabetics and controls and to correlate levels of same with HOMA-IR and mean CIMT.

Method: It was a case control study in which 60 prediabetic patients and 60 controls (age, sex, BMI matched) were employed. Plasma levels of glucose (fasting and postprandial), glycated hemoglobin (HbA1c), and serum levels of insulin (fasting) were measured in both cases and controls. HOMA-IR values in both the groups were calculated using fasting plasma glucose and serum insulin levels. Serum Transthyretin levels were measured using ELISA. The values obtained were compared between cases and controls. In cases, obtained serum levels of Transthyretin were correlated with HOMA-IR values and mean CIMT (measured in cases only using B-mode ultrasonography).

Results: Median (IQR) of serum levels of insulin (fasting in μIU/ml) in cases (11.3 (10.175-13.505)) was significantly higher than that of controls (5.73 (4.3-7.1)). HOMA-IR median (IQR) in cases and controls was 3.12 (2.73-3.595) and 1.21 (0.918-1.505) respectively. Median (IQR) for serum levels of Transthyretin was also significantly higher in cases as compared to controls [46.74 (30.43-81.225) and 22.38 (16.628-27.89) respectively]. Significant positive correlations were observed between serum levels of Transthyretin with both HOMA-IR and mean CIMT (with correlation coefficients being 0.288 and 0.536 respectively). Univariate linear regression analysis showed that with increase in serum Transthyretin by 1 mg/dl, mean CIMT increases by 0.001 mm.

Conclusion: Individuals with impaired glucose tolerance have been found to have increased risk of atherosclerosis as compared to normoglycemics after excluding other risk factors. Assessment for the risk of same with the help of novel markers can help in diagnosis and intervention at an early stage and thereby preventing risk of further complications.

Introduction

Diabetes Mellitus is a state of hyperglycemia, due to either an inadequate production of insulin or insulin resistance. Its predecessor state where plasma glucose is found to be elevated above normal levels but below that of clinical disease is regarded as prediabetes. As per American diabetes association (ADA), prediabetes encompasses fasting plasma glucose of 100-125 mg/dl, 2-hour postprandial blood glucose of 140-199 mg/dl or HbA1c of 5.7-6.4%.¹

Metabolic changes occurring due to diabetes leading to multiple organ dysfunction is a common knowledge. However, it has been observed that majority of diabetics already have complications when diagnosed. So, following the adage “catch it early” to decrease not only the progression to frank diabetes but also various micro and macrovascular complications and hence the mortality; knowledge about various aspects of the disease in prediabetic stage is essential.² One of the most devastating among all complications is atherosclerosis, characterised by vessel wall narrowing secondary to inflammatory process. It initially remains asymptomatic and silently progresses over decades before actual clinical manifestations (usually occur in middle and late adulthood).³

CVDs, one of the major complications of atherosclerotic process, contributes to world’s largest disease burden and are a leading cause of morbidity and mortality in individuals with diabetes and prediabetes.⁴ In prediabetes, various etiologies are associated with increased risk for CVD including insulin resistance, hyperglycemia, dyslipidemia, hypertension, systemic inflammation, and oxidative stress.⁵ Various novel biomarkers also increase in insulin resistance states and may have a role in these atherosclerotic changes. One among them is Transthyretin (a small globular transport protein with homo-tetrameric structure) synthesized mainly by liver (in serum) and choroid plexus of brain (in cerebrospinal fluid).⁶ Assessment of these atherosclerotic changes in both peripheral and coronary arteries is by measuring intima-media thickness (IMT). Most commonly used among these is Carotid Intima-Media Thickness (CIMT), usually performed by a B-mode ultrasonographic scan as it is a noninvasive, inexpensive, reproducible method.⁷ So identification of raised levels of Transthyretin at initial stages of insulin resistance and its association with CIMT can help in early intervention and thereby decreasing the risk of atherosclerosis progression.

Materials and Methods

The study was conducted after taking ethical clearance from the institutional ethics committee of ABVIMS and Dr.
RML Hospital in the Departments of Medicine, Biochemistry and Radiology.

Study Design: Cross sectional observational study

Study Group: 60 consecutive patients of prediabetes and 60 control subjects from Medicine OPD, wards and Emergencies after fulfilling all inclusion and exclusion criteria were included and matched for age, sex and ethnicity.


Calculation of Sample Size

Primary Objective
To compare serum levels of Transthyretin in prediabetics and controls.

To achieve this, input for statistical sample size calculation was taken from the study by Pandey GK et al\(^8\) (2015). Minimum required sample size with 90% power of study and 5% level of significance is 30 patients in each study group. To reduce margin of error, total sample size taken was 120 (60 patients per group).

Formula used:
For comparing mean of two groups

\[
N \geq \frac{2(SD)^2 \times (Z_\alpha + Z_\beta)^2}{(\text{mean difference})^2}
\]

Where \(Z_\alpha\) is value of \(Z\) at alpha error of 5% and \(Z_\beta\) is value of \(Z\) at power of 90% and \(S\) is SD of another group.

Calculations of sample size for Transthyretin

Pooled standard deviation (SD) = \(\sqrt{(S_1^2 + S_2^2)/2}\)

Where \(S_1\) is SD of 1 group and \(S_2\) is SD of another group.

Calculations of sample size for Transthyretin

Pooled standard deviation = 200.03

\[
N \geq \frac{2(200.03)^2 \times (1.96 + 1.28)^2}{(169)^2}
\]

\(\geq 29.41\) =30 (approx.)

Exclusion Criteria

- Known hypertensive
- Known diabetics
- Known cases of chronic liver disease
- Known cases of non-alcoholic fatty liver disease
- Known cases of myelodysplastic syndrome
- Patient on maintenance hemodialysis
- Known cases of coronary heart disease
- Known case of cerebrovascular accidents (CVA) or transient ischemic attacks (TIA)
- Pregnant females
- Known cases of inflammatory bowel disease
- Known cases of Alzheimer’s disease
- Known cases of senile systemic amyloidosis.
- Known smokers and alcoholics

Methods

All the cases and controls underwent:

Clinical Examination
- Anthropometric measurement:
  The study participants were called to the Department of Medicine and asked to fill a pre-determined questionnaire which included baseline data about age, sex, race, ethnicity and family history of diabetes or hypertension. Then they underwent a detailed clinical examination including measurement of height (using stadiometer), weight (using a weight measurement scale) and waist circumference (using a standard measuring tape). BMI was calculated as weight in kilograms divided by height in meters squared.
- Resting systolic and diastolic blood pressure were recorded twice using an automated sphygmomanometer after a 5-min rest and mean of the two values (both systolic and diastolic) blood pressure was considered.

Laboratory Investigations

Around 10 ml of fasting blood sample was collected after venepuncture. Samples were taken in EDTA vial for HbA1c measurements and hemogram profile and fluoride vials for plasma insulin. Plain (Red) vials were used to take samples for biochemical profile and separately for Transthyretin.

Investigations done on the patients were:
- Fasting plasma glucose
- 2-hour postprandial plasma glucose
- HbA1c measurement by Immunoturbidimetry method on Vitros dry chemistry analyser by NSGP guidelines.
- Fasting Plasma insulin levels, measured by Chemiluminescence Immuno Assay (CLIA) on Vitros ECiQ by Orthoclinical Diagnostics.

All the samples were analysed on a fully automated clinical chemistry analyser in Department of Biochemistry.

- Samples for serum Transthyretin were centrifuged and stored in aliquots at -20°C in Department of Biochemistry until batch analysed by ELISA (Enzyme linked Immunosorbent Assay).
- Basal insulin resistance of the individual was calculated using HOMA-IR (Homeostatic model assessment of insulin resistance) using formula:

\[
\text{HOMA} – \text{IR} = \left(\frac{\text{FPI} \times \text{FPG}}{405}\right)
\]

Where, fasting plasma glucose is in mg/dl.

Transthyretin

Kits for transthyretin (prealbumin) were imported from IMMUNDIAGNOSTIK AG, Germany (Reference Number K 6331).

Principle of test

Test was done by ELISA. Standards, controls and samples containing prealbumin (Transthyretin) were added to wells of a microplate coated with polyclonal anti human prealbumin antibodies. During 1st incubation step, antibodies immobilised on the walls of the microtitre wells captured prealbumin in the samples. After washing of unbound components, a peroxidase conjugated anti prealbumin detection antibody is added to each well. In 2nd incubation period detection antibody is bound
Table 1: Demographic and anthropometric characteristics among cases and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases (n = 60)</th>
<th>Controls (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>45.68 ± 8.78</td>
<td>44.48 ± 7.44</td>
<td>0.439</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td>0.855</td>
</tr>
<tr>
<td>Males</td>
<td>46.67% (n= 28)</td>
<td>48.33% (n= 29)</td>
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<tr>
<td>Females</td>
<td>53.33% (n= 32)</td>
<td>51.67% (n= 31)</td>
<td></td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>25.33 ± 2.65</td>
<td>24.93 ± 2.22</td>
<td>0.387</td>
</tr>
<tr>
<td>Waist Circumference (mean ± SD)</td>
<td>84.57 ± 7.3</td>
<td>82.62 ± 8.7</td>
<td>0.287</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mean ± SD)</td>
<td>116.23± 6.66</td>
<td>116.93 ± 8.13</td>
<td>0.541</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mean ± SD)</td>
<td>74.97 ± 5.17</td>
<td>73.43 ± 4.97</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Table 2: Biochemical parameters among cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=60)</th>
<th>Controls (n=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>110 (106-115.25)</td>
<td>86 (79-91.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>168 (156-184.25)</td>
<td>125 (117-130)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6 (5.9-6.2)</td>
<td>4.9 (4.6-5.125)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting Serum Insulin Levels</td>
<td>11.3(10.175-13.505)</td>
<td>5.73 (4.3-7.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR Index</td>
<td>3.12 (2.73-3.595)</td>
<td>1.21 (0.918-1.505)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum Transthyretin</td>
<td>46.74(30.43-81.225)</td>
<td>22.38(16.628-27.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3: Descriptive statistics of mean carotid intima media thickness (mm) of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± Sidev</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean carotid intima media thickness (mm)</td>
<td>0.61 ± 0.1</td>
<td>0.60(0.5-0.7)</td>
<td>0.4-0.8</td>
</tr>
</tbody>
</table>

Fig. 1: Correlation of serum Transthyretin level (mg/dL) with fasting plasma insulin level (µIU/ml)

Fig. 2: Correlation of serum Transthyretin level (mg/dL) with mean CIMT (mm)

Results

Aim of the study was to assess the serum levels of Transthyretin in patients with prediabetes, compare the same in normoglycemics and to correlate its levels with CIMT and HOMA-IR in prediabetics. It was an observational case-control study and a total of 60 patients and 60 controls were enrolled. Matching with respect to age, sex, blood pressure and BMI was ensured. The following observation was made (Tables 1, 2 and 3).

Median (IQR) of fasting plasma insulin level (µIU/ml) in cases (11.3(10.175-13.505)) was significantly higher as compared to controls ((5.73(4.3-7.1)) (Table 2). Fasting plasma insulin levels (µIU/ml) were ≥9 in 83.33% of cases as compared to controls in whom it was 1.67% of the total. HOMA-IR Index showed median (IQR) values of 3.12 (2.73 ± 3.595) in cases and 1.21 (0.918 ± 1.505) in controls with a statistically significant difference (p value < 0.0001) (Table 2). Moreover around 91.67% of cases and 1.6 % of controls had HOMA-IR > or equal to 2. Median (IQR) of Transthyretin level (mg/L) in cases was 46.74 (30.43-81.225), which was significantly higher as compared to controls (22.38(16.628-27.89)) (p value <0.0001) (Table 2). Mean value of mean CIMT (mm) of study subjects was 0.61 ± 0.1 with median (IQR) of 0.6(0.5-0.7) (Table3). The correlation of Transthyretin with HOMA-IR Index, Fasting Plasma Insulin and mean CIMT was found to be statistically significant with a correlation coefficient of 0.228, 0.295 and 0.536 respectively and p value of 0.026, 0.023 and <0.0001 respectively (Figure 1 and 2). Univariate linear regression analysis showed that with increase in levels of Transthyretin by 1 mg/L, mean CIMT significantly increased by 0.001 mm (Table 4).

to captured prealbumin leading to formation of capture antibody human prealbumin peroxidase conjugate. Tetramethylbenzidine was used as a peroxidase substrate. Finally, an acidic stop solution added to terminate the reaction. The intensity of yellow colour is directly proportional to prealbumin (Transthyretin) concentration of sample. A dose response curve with optical density at 450 nm was used to determine the transthyretin values.

Values measured were in ng/ml. After applying dilution factor, values were converted to mg/dl, as per reference range (18-45 mg/dl).

3. Ultrasonographic Examination: (only performed in cases)

All cases underwent high-resolution B-mode ultrasonography with a 7.5 MHz linear probe, in Department of Radiology, ABVIMS and DR. RML Hospital, New Delhi. CIMT was measured as distance between two echogenic lines (representing intima and media). All scans and image measurements were carried out by the same investigator, blinded to the risk factor status of the participants.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using Independent t test/ Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-Square test. Spearman rank correlation coefficient was used to assess the correlation of mean carotid intima media thickness with Transthyretin (mg/dL). A p-value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.


Discussion

The study showed evidence of increased levels of Transthyretin in prediabetics as compared to controls and a significant positive correlation of Transthyretin with mean CIMT, HOMA-IR Index (marker of insulin resistance) and fasting plasma insulin.

In diabetic and prediabetic individuals, insulin resistance along with impairment of insulin signaling, hyperinsulinemia and hyperglycemia lead to decrease in vascular compliance by increasing glycosylation and oxidation of lipoproteins like LDL and VLDL (Very Low-Density Lipoprotein). The atherosclerotic vascular changes are characterized by arterial wall lesion, endothelial dysfunction and leads to vessel wall hypertrophy which later contributes to increased risk of strokes, MI and TIA.9

Risk factors leading to prediabetic state are often associated with increased expression of inflammatory cytokines and also infiltration of immune cells in adipocytes which leads to an insulin resistance state and problems linked with this state like dyslipidemia, hypertension, hypercoagulability and atherosclerosis. By exerting inflammatory process RBP4 (novel adipokine) and its binding protein Transthyretin exert their effect in the pathogenesis of insulin resistance, atherosclerosis and thus CVD.10

Till date only few studies suggest role of Transthyretin in insulin resistance states and as a predictor of assessing atherosclerosis risk in individuals with insulin resistance. A very similar observation as in our study was done by Pandey GK et al (2015)11 where they reported significantly raised circulating levels of TTR (µg/ml) in T2DM (832 ± 310); followed by those with IGT (TTR: 720 ± 214) as compared to those with NGT (TTR: 551 ± 185; P <0.001).

Although unlike our study they didn’t observe any significant correlation of Transthyretin levels with insulin resistance. Although Kwanbunjjan K et al12 found a positive association of RBP4 and Transthyretin levels with insulin resistance, concluding their role in stroke and heart disease.

Conclusion

- Transthyretin has a role in atherosclerotic process through its influence on insulin sensitivity and lipid metabolism. It can be considered as a surrogate marker of predicting early atherosclerosis and thereby cardiovascular risk and also helps in early intervention and preventing further complications. It can also improve the predictive value to diagnose early atherosclerosis when combined with other markers. As Transthyretin levels positively correlate with mean CIMT, so it can be used in early detection and intervention of vascular complication.

References


9. Pollin SK, Hanis C, Wolfson J,templates for presentation of the results of a clinical trial, as well as guidelines for the reporting of drug development data to regulatory authorities. The guidelines include recommendations for the design and conduct of clinical trials, the collection and analysis of data, and the reporting of results. The guidelines are intended to ensure the quality and reproducibility of clinical trial results and to facilitate the evaluation of new treatments by regulatory authorities. The guidelines are based on scientific evidence and expert opinion and are subject to periodic review and update. The guidelines are available online at www.icmje.org.

10. The International Committee of Medical Journal Editors (ICMJE) is a group of medical journal editors who work together to develop and maintain guidelines for the conduct, reporting, editing, and publishing of clinical research. The ICMJE guidelines are widely used as a basis for the ethical and scientific standards of clinical research. The guidelines cover a wide range of topics, including the design and conduct of clinical trials, the collection and analysis of data, and the reporting of results. The guidelines are intended to ensure the quality and reproducibility of clinical trial results and to facilitate the evaluation of new treatments by regulatory authorities. The guidelines are available online at www.icmje.org.

11. The American Heart Association (AHA) is a national, non-profit organization that is dedicated to improving the lives of people around the world by preventing and treating heart disease and stroke. The AHA is the largest voluntary health organization dedicated to a purpose of futility: saving lives by preventing and treating heart disease and stroke. The AHA is devoted to advancing research regarding the prevention as well as treatment of heart disease and stroke. The AHA is also dedicated to disseminating information to the public in order to enhance the quality of life. The AHA is involved in a variety of activities, including funding research, providing education and training, and advocating for public policy that supports healthy living.

12. The World Health Organization (WHO) is a specialized agency of the United Nations that is responsible for international public health. The WHO is the lead organization for coordinating global health within the United Nations system. The WHO is responsible for providing leadership on global health matters, developing standards and guidelines for public health, and providing technical support and training for health professionals and organizations around the world. The WHO is also responsible for providing information and guidance on public health issues to governments and the public. The WHO is headquartered in Geneva, Switzerland.

13. The International Society for Clinical Biostatistics (ISCB) is a professional organization that is dedicated to the advancement of clinical biostatistics. The ISCB is a non-profit organization that is composed of researchers, clinicians, and other professionals who are interested in the application of statistical methods to clinical research. The ISCB is dedicated to the development and dissemination of knowledge in clinical biostatistics, as well as the promotion of ethical and professional standards in the conduct of clinical research.

14. The International Society for Pharmacoepidemiology (ISPE) is a professional organization that is dedicated to the advancement of pharmacoepidemiology. The ISPE is a non-profit organization that is composed of researchers, clinicians, and other professionals who are interested in the study of the relationship between drugs and human health. The ISPE is dedicated to the development and dissemination of knowledge in pharmacoepidemiology, as well as the promotion of ethical and professional standards in the conduct of pharmacoepidemiological research.

15. The International Society for Pharmacology (ISP) is a professional organization that is dedicated to the advancement of pharmacology. The ISP is a non-profit organization that is composed of researchers, clinicians, and other professionals who are interested in the study of the effects of drugs on living organisms. The ISP is dedicated to the development and dissemination of knowledge in pharmacology, as well as the promotion of ethical and professional standards in the conduct of pharmacological research.

16. The International Society for Pharmacology and Therapeutics (ISPT) is a professional organization that is dedicated to the advancement of pharmacology and therapeutics. The ISPT is a non-profit organization that is composed of researchers, clinicians, and other professionals who are interested in the study of the effects of drugs on living organisms, as well as the development of new drugs and therapies. The ISPT is dedicated to the development and dissemination of knowledge in pharmacology and therapeutics, as well as the promotion of ethical and professional standards in the conduct of pharmacological and therapeutic research.

17. The International Society for Pharmacology and Therapeutics (ISPT) is a professional organization that is dedicated to the advancement of pharmacology and therapeutics. The ISPT is a non-profit organization that is composed of researchers, clinicians, and other professionals who are interested in the study of the effects of drugs on living organisms, as well as the development of new drugs and therapies. The ISPT is dedicated to the development and dissemination of knowledge in pharmacology and therapeutics, as well as the promotion of ethical and professional standards in the conduct of pharmacological and therapeutic research.
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Role of CT Perfusion in Identifying the Core and the Potentially Salvageable Penumbra in Patients with Acute Non-Haemorrhagic Stroke - Experience at Tertiary Care Center

Arvind Borde¹*, Ajita Nawale², Rajarshi Aich³

Abstract

Objectives: To evaluate the role of CT Perfusion in identifying the core and the potentially salvageable penumbra in brain infarcts by observing perfusion maps (CBV, CBF and MTT). Also to identify patients who would benefit from reperfusion therapy and to evaluate the feasibility of identifying the penumbra on non-contrast CT vide comparison with perfusion maps.

Materials and Methods: A prospective study of 50 patients who presented with acute onset neurological deficit within 6 hours of symptom onset and in whom initial NCCT revealed no evidence of cerebral hemorrhage; evaluated with CT Perfusion was done at tertiary care center in 1 calender year 2014.

Observations: In our study, about 68 percent of patients presented within 6 hours of stroke had salvageable penumbra, were eligible for revascularization therapy. HU less than 25 on NECT significantly correlated with infract core but not with presence of Penumbra. Presence of penumbra cannot be predicted from NECT ASPECT and CBV ASPECT Score.

Results and Conclusion: CT Perfusions study being easily available, faster and cost effective modality to identify patients of acute ischemic strokes having salvagable penumbra for which further can be subjected to revascualrization therapy. It is strongly recommended that CT Perfusion should be made an integral part of acute non-haemorrhagic stroke management protocol, wherever the facility is available.

Introduction

Acute ischemic stroke being one of the major non communicable disease in India leading to death and disability. If patients within golden period are identified with salvageable brain tissue, can be treated with revascularization by means if IV thrombolysis or mechanical thrombectomy. CT Perfusions study being easily available, faster and cost effective modality to identify patients of acute ischemic strokes having salvageable penumbra.

Review of literature

Stroke is an acute onset neurological deficit characterized by motor and/or sensory loss caused due to acute vessel occlusion or haemorrhage in the brain parenchyma. Stroke is broadly classified into two categories Haemorrhagic and non-haemorrhagic (Ischaemic).

According to the World Health Organization, 15 million people suffer stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disabled. Developing countries like India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India. The poor are increasingly affected by stroke, because of both the changing population exposures to risk factors and, most tragically, not being able to afford the high cost for stroke care. According to the India stroke factsheet updated in 2012, the estimated age-adjusted prevalence rate for stroke ranges between 84/100,000 and 262/100,000 in rural and between 334/100,000 and 424/100,000 in urban areas.¹

The central goal of therapy in acute ischemic stroke is to preserve tissue in the ischemic penumbra. An infarct typically has a dense ischaemic core, which is irreversibly damaged and non-salvageable. In early stages, the core infarct is surrounded by a less ischaemic potentially salvageable penumbra if the blood supply is restored.² Tissue in this penumbra can be preserved by restoring blood flow to the compromised area and optimizing collateral flow. Recanalization strategies, including the administration of intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) and intra-arterial approaches, attempt to establish revascularization so that cells in the penumbra can be rescued before irreversible injury occurs. Restoring blood flow can mitigate the effects of ischemia only if performed quickly.

In addition to limiting the duration of ischemia, an alternative strategy is to limit the severity of ischeamic injury. Neuroprotective strategies are intended to preserve the penumbral tissues and to extend the time window for revascularization techniques. At the present time, however, no neuroprotective agents have been shown to impact clinical outcomes in ischemic stroke.

While stroke is essentially a clinical diagnosis, earlier the main role of neuroimaging in the setting of acute stroke was the differentiation of non-haemorrhagic stroke from haemorrhagic stroke, the management of which were drastically different in context of

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thrombolytic therapy. With advances in CT and MRI technologies, role of neuroimaging has been expanded in the clinical management of acute stroke to identifying stroke etiology and potentially salvageable penumbras earliest. Potentially salvageable penumbras is being more accurately identified on CT perfusion and MR perfusion studies.

Modalities of penumbral imaging of brain

Emergent brain imaging is essential for evaluation of acute ischemic stroke. Noncontrast computed tomography (CT) scanning is the most commonly used form of neuroimaging in the acute evaluation of patients with apparent acute stroke. The following neuroimaging techniques may also be used for penumbral assessment:

- CT perfusion scanning
- MRI perfusion scanning
- Diffusion weighted imaging; FLAIR-DWI mismatch; DWI-perfusion mismatch.

Unenhanced CT is widely available, can be performed quickly, and does not involve the administration of intravenous contrast material. Early-stage acute ischemia can shows features such as the hyperdense vessel sign, the insular ribbon sign, and obscuration of the lentiform nucleus.

CT perfusion having certain advantages over MRI perfusion in the form of being faster, with widespread availability, cost effective, being less sensitive to patient motion and no risk to the patient with implantable medical devices, such as cardiac pacemakers, ferromagnetic vascular clips, cochlear implants and nerve stimulators. During CT perfusion, a rapid intravenous infusion of contrast is administered and sections of the brain are repeatedly imaged. Based on the total amount and speed that blood flows to different vascular territories of the brain this technique can assist in identifying a stroke and potential areas of reversible and salvageable brain tissue in the ischemic penumbra.1

The cerebral blood flow (CBF) is equal to the cerebral blood volume (CBV) divided by the mean transit time (MTT). The MTT is the time difference between the arterial inflow and venous outflow.3-5 **MTT is the most sensitive measure used to evaluate for flow abnormalities.** It is prolonged in conditions such as hypotension along with occluded and stenotic blood vessels. The area of the brain undergoing infarction has both decreased CBF and CBV. Decreased total CBV is the most specific indicator for an area actually undergoing irreversible ischemia or infarct and is non-salvageable. Areas of the brain that are at risk for injury known as the ischemic penumbra show decreased CBF with normal to increased CBV; CBF-CBV mismatch. This potentially salvageable area of the brain must have an intact cerebral auto-regulation system to maintain homeostasis. Cerebral auto-regulation causes the dilation of the collateral blood vessels and increases the CBV to the areas of the brain that are compromised by decreased CBF.

CT perfusion imaging can identify the penumbra, and it has been used in case reports and studies to guide the treatment of patients in which there is an unknown time of stroke onset, awakening stroke or when the patient cannot communicate the time of onset due to aphasia. These patients may still benefit by intravenous, intra-arterial or mechanical reperfusion.

The software package that is used for CT perfusion analyses the images obtained and colour coded maps representing many levels of the brain are produced to help differentiate the potential cause of the flow abnormalities.

**Alberta stroke program early CT score (ASPECTS):** In a patient with acute onset ischemic stroke who presents within the golden period for thrombolysis (3 hours from symptom onset in case of intravenous thrombolysis and 6 hours from symptom onset in case of intra-arterial thrombolysis), the main issue in deciding management from the clinician’s perspective is whether attempted thrombolysis will have significant impact. The decision to thrombolysis depends on whether more or less than one third of the territory of the middle cerebral artery (MCA) was involved. If more than third of the territory is involved, the prognosis is poor. There is also a significant risk of haemorrhage in the infarct.6-10

The Alberta stroke program early CT score (ASPECTS) was developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes (<3 hours from symptom onset) on pre-treatment CT studies in patients with acute ischemic stroke of the anterior circulation.11 This CT score is simple and reliable and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment.

ASPECTS is determined from evaluation of two standardized regions of the MCA territory: the ganglionic and supra-ganglionic levels. Ganglionic level where the caudate, lentiform, internal capsule and insular ribbon each carrying one point. Also cerebral cortices (anterior, lateral and posterior) at ganglionic and supraganglionic levels each carrying one point. All cuts with basal ganglionic or supraganglionic structures visible are required to determine if an area is involved. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions. ASPECTS is range from 10 where normal CT scan to 0 indicating diffuse involvement throughout MCA territory.

Large numbers of studies have been done in imaging of penumbra by imaging. In various studies shown that while absolute numerical parameters of CT Perfusion maps vary according to individual variability, and reconstruction algorithm employed, qualitative perfusion maps are still a valuable tool to detect early ischemia and identify salvageable brain tissue by comparing with the contralateral hemisphere.

A prospective study of 50 patients who presented with acute onset neurological deficit within 6 hours of symptom onset and in whom initial NCCT revealed no evidence of cerebral hemorrhage; evaluated with CT Perfusion was done in our department in 1 calender year 2014. Institutional ethics committee clearance and approval was obtained and patients were selected via convenient consecutive sampling (non-probability sampling). Written informed consent was obtained from the subjects for inclusion of their images in the study, with the standard disclosures.

**Aims and Objectives**

- To evaluate the role of CT Perfusion in Identifying the core and the potentially salvageable penumbras.
in brain infarcts by observing perfusion maps (CBV, CBF and MTT).

- To identify patients who would benefit from reperfusion therapy.
- To evaluate the feasibility of identifying the penumbra on non-contrast CT vide comparison with perfusion maps.

**Inclusion Criteria**

- Patients presenting with acute onset neurological deficit within 6 hours of symptom onset.

**Exclusion Criteria**

Initial non-contrast CT Brain revealing intracranial haemorrhage; Patients not consenting for the study; Patients with deranged renal function (Serum creatinine >1.4 mg/dl); Pregnancy; Known h/o allergy to intravenous contrast material; Haemodynamically unstable patients and Paediatric patients.

**Study Protocol**

No specific pre-procedure preparations were employed. After placement of a wide bore i.v. cannula, patient was taken for CT scan. Initially, a non-contrast scan was taken covering the entire brain. The non-contrast scan served to rule out any evidence of parenchymal haemorrhage. Signs of an acute infarct like parenchymal hypodensity, hyperdense vessel sign, sulcal effacement, obscuration of lentiform nucleus and insular ribbon sign were also searched for. In patients having findings suggestive of acute infarct, the perfusion scan was planned covering the area of interest. In patients in whom the non-contrast scan was normal, perfusion scan was planned covering the ganglio-capsular region and corona radiata corresponding to the side of neurodeficit.

PHILIPS CT scanners have two protocols for performing CT Perfusion.

- **Non-Jog scans**: In which the table remains stationary. These are performed using infusion of 40–50 mL iv contrast, followed by 20–40 mL saline.
- **Jog scans**: In which the table moves back and forth between two positions. These are performed using infusion of 70 mL contrast, followed by 45 mL saline.

**Inclusion Criteria**

- Patients presenting with acute onset left hemiparesis showing no significant abnormality. (B and C) Perfusion maps at the level of basal ganglia showing altered perfusion in right ganglio-capsular region. The central part appearing blue-violet indicating reduced blood volume and reduced blood flow in CBV and CBF maps respectively is s/o core infarct. The peripheral part appearing blue-violet in CBF map but red in CBV map indicating reduced blood flow but preserved blood volume is s/o ischaemic penumbra. (D) The corresponding area appearing red-yellow in MTT map s/o increased mean transit time. These findings are s/o an acute infarct with ischemic penumbra in right ganglio-capsular region, which was not detectable in NCCT but picked up in CT Perfusion.

**Exclusion Criteria**

- Patients presenting with acute onset right hemiparesis showing no significant abnormality. (B and C) Perfusion maps at the level of basal ganglia showing altered perfusion in right ganglio-capsular region. The central part appearing blue-violet indicating reduced blood volume and reduced blood flow in CBV and CBF maps respectively is s/o core infarct. The peripheral part appearing blue-violet in CBF map but red in CBV map indicating reduced blood flow but preserved blood volume is s/o ischaemic penumbra. (D) The corresponding area appearing red-yellow in MTT map s/o increased mean transit time. These findings are s/o an acute infarct with ischemic penumbra in right ganglio-capsular region, which was not detectable in NCCT but picked up in CT Perfusion.

**Fig. 1**: Normal CBF, CBV and MTT maps at Gangliocapsular level

**Fig. 2**: (A) NCCT section at the level of basal ganglia in a patient presenting with acute onset left hemiparesis showing no significant abnormality. (B and C) Perfusion maps at the level of basal ganglia showing altered perfusion in right ganglio-capsular region. The central part appearing blue-violet indicating reduced blood volume and reduced blood flow in CBV and CBF maps respectively is s/o core infarct. The peripheral part appearing blue-violet in CBF map but red in CBV map indicating reduced blood flow but preserved blood volume is s/o ischaemic penumbra. (D) The corresponding area appearing red-yellow in MTT map s/o increased mean transit time. These findings are s/o an acute infarct with ischemic penumbra in right ganglio-capsular region, which was not detectable in NCCT but picked up in CT Perfusion.

**Fig. 3**: (A) NCCT section at brainstem level in a patient presenting with acute onset dizziness and vertigo showing ill-defined hypodensity (red arrow) in superior aspect of left cerebellar hemisphere. (B and C) The corresponding area appearing blue-violet-black in CBV and CBF maps indicating reduced blood volume as well as reduced blood flow. (D) The corresponding area appearing red in MTT map indicating increased mean transit time. The matched reduction of both CBV and CBF suggests that this area is irreversibly ischaemic s/o core infarct. There is no surrounding area where CBF is reduced but CBV is preserved s/o absence of significant penumbra.
In our study, the cerebral perfusion scans were performed using the Non-Jog Protocol using infusion of 50 ml of iv contrast @ 4 ml/sec followed by 40 ml saline @ 2.5ml/sec by using an automated dual power injector. The iv contrast medium used was non-ionic iso-osmolar iodinated contrast material (Iohexol, Omnipaque 300 mg I/ml; GE healthcare). As per the protocol in our institution, a 2 minutes delayed scan was performed covering the entire brain.

**Observations and Results**

Out of the study population of 50 patients presenting with clinical features of acute onset ischaemic stroke, 28 patients (56.0% of the cases) were male and 22 patients (44.0% of the cases) were female. The mean age of our study group was 66.02 years.

In the study population, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by Slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was Dizziness and imbalance, present in only 3 patients (6.0% of cases).

Majority of the patients (68.0% of the cases) presented within 2 – 4 hours of symptom onset, followed by 30.0% of the cases who presented within 5 – 6 hours of symptom onset while only 2% cases presented within 2 hours.

History of any previous episode of focal neurodeficit indicates increased risk of a second episode. In the study population, 64.0% of the patients had no history of previous similar episode while 32.0% had multiple (>1) episodes of focal neurodeficit.

A patient suffering an episode of acute neurodeficit may either recover completely within 24 hours of symptom onset (as seen in patients with TIA) or recover gradually over a prolonged period of time. This recovery is often partial. In the study population, 33.3% of the cases who suffered similar episode in the past had complete recovery with 24 hours, while 66.7% had gradual partial recovery.

Diabetes Mellitus and Hypertension are both considered independent risk factors for cerebrovascular ischemic episodes. In the study population, majority of the patients (46%) had neither of these two diseases followed by 12 patients (24%) who suffered from hypertension but not diabetes. 9 patients (18%) of the study population suffered from both diabetes and hypertension.

**Statistical Associations and Correlations between various parameters**

As per the above data, using Chi square test, there is a significant statistical association between HU on NECT and presence of Core Infarct (Tables 4, 6).

As per the above data, using Chi square test, there is no significant statistical association between HU on NECT and presence of Penumbra (Tables 3, 7).

As per the above data, using Chi square test, there is no significant statistical association between NECT ASPECT Score and presence of Penumbra (Table 8).

As per the above data, using Chi square test, there is no significant statistical association between CBV ASPECT Score and presence of Penumbra (Table 9).

As per the above data, using Student t test, there is no significant statistical association between NECT ASPECT Score and CBV ASPECT Score (Table 10).

As per the above analysis, 38.3% of the cases were suitable for Thrombolysis on the basis of NECT ASPECTS which was significantly more as compared to 38.3% of the cases on basis of CBV aspects.

**Discussion**

The results were correlated with various studies done on role of CT Perfusion in evaluation of patients with acute non-haemorrhagic stroke.

1. **Age Distribution**: Age is the single most important risk factor for stroke. For each successive 10 years after age 55, the stroke rate more than doubles in both men and women. In our study of 50 adults patients presenting with acute onset neurodeficit, the mean age of the study patients was 66.02 years and age group ranging from 40 to 85 years.

In a study done by A.R. Jain et al with a study group of 83 patients, the median age was 72 years. In a study done by J. Hopyan et al with a study group of 191 patients, the mean age was 67 years with a standard deviation of 16.

2. **Gender Distribution**: In our study of 50 adult patients, 28 patients (56%) were male while 22 patients (44%) were female. In the study done by A.R. Jain et al with a study group of 83 patients, 44.6% patients were female while 55.4% patients were male. In a study done by J. Hopyan et al with a study group of 191 patients, 45.1% were female while 54.9% were male.

3. **Profile of symptoms**: In our study, the most common presenting symptom was combined weakness of upper limb and lower limb, present in 39 patients (78.0% of cases), followed by Slurring of speech, which was present in 36 patients (72.0% of cases). The least common symptom was Dizziness and imbalance, present in only 3 patients (6.0% of cases).

In our study, the cerebral perfusion scans were performed using the Non-Jog Protocol @ 4 ml/sec followed by 40 ml saline @ 2.5 ml/sec by using an automated dual power injector. The iv contrast medium used was non-ionic iso-osmolar iodinated contrast material (Iohexol, Omnipaque 300 mg I/ml; GE healthcare). As per the protocol in our institution, a 2 minutes delayed scan was performed covering the entire brain.
patients (34.9% of cases) had previous history of stroke / TIA.

5. Pre-existing Systemic Diseases: Diabetes mellitus and hypertension are both considered independent risk factors for ischaemic stroke. Hypertension is the single most important modifiable risk factor for ischemic stroke. A summary of seven studies assigning a relative risk of 1 for borderline or mild hypertension determined the relative risk to be about 0.5 at a blood pressure of 136/84 mm Hg and about 0.35 at a blood pressure of 123/76 mm Hg.17 Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes with a relative risk of ischaemic stroke in persons with diabetes from 1.8 to 3.0.18

6. NECT findings in study population: In our study population, a total of 39 patients (78%) had findings related to acute ischemia while 11 patients (22%) had no CT detectable evidence of acute cerebral ischemia (Table 1). The sensitivity of standard noncontrast CT for brain ischemia increases after 24 hours. However,

Table 1: NECT findings in study population

<table>
<thead>
<tr>
<th>NECT findings</th>
<th>No. of cases (N = 50)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal hypodensity</td>
<td>37</td>
<td>74.0</td>
</tr>
<tr>
<td>Only hyperdense MCA, no parenchymal hypodensity</td>
<td>02</td>
<td>04.0</td>
</tr>
<tr>
<td>Normal</td>
<td>11</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Table 2: CT Perfusion Maps

<table>
<thead>
<tr>
<th>CT perfusion maps</th>
<th>No. of cases (N = 50)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core infarct + Penumbra</td>
<td>26</td>
<td>52.0</td>
</tr>
<tr>
<td>Only Core infarct</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>None</td>
<td>08</td>
<td>16.0</td>
</tr>
</tbody>
</table>

Table 3: Distribution of HU of the Penumbra

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean HU of the penumbra ($T \pm SD$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>26.56</td>
</tr>
<tr>
<td>SD</td>
<td>02.82</td>
</tr>
<tr>
<td>Range</td>
<td>22.00 – 33.00</td>
</tr>
<tr>
<td>Median</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 4: Distribution of HU of the Core Infarct

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean HU of the Core Infarct ($T \pm SD$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.26</td>
</tr>
<tr>
<td>SD</td>
<td>04.33</td>
</tr>
<tr>
<td>Range</td>
<td>12 – 29</td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 5: Suitability for Thrombolysis on the Basis of NECT and CBV Maps

<table>
<thead>
<tr>
<th>Methods</th>
<th>NECT ASPECTS (n=47)</th>
<th>CBV ASPECTS (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Suitable</td>
<td>31</td>
<td>66.0</td>
</tr>
<tr>
<td>Not suitable</td>
<td>16</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Table 6: [A] HU on NECT and Presence of Core Infarct

<table>
<thead>
<tr>
<th>HU on NECT</th>
<th>Core infarct</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 (N = 27)</td>
<td>37</td>
<td>100.0</td>
<td>-</td>
</tr>
<tr>
<td>≥ 25 (N = 13)</td>
<td>05</td>
<td>38.5</td>
<td>08</td>
</tr>
<tr>
<td>By Chi Square test; P = 0.001</td>
<td>Significant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: [B] HU on NECT and Presence of Penumbra

<table>
<thead>
<tr>
<th>HU on NECT</th>
<th>Penumbra</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 (N = 27)</td>
<td>05</td>
<td>83.3</td>
<td>01</td>
</tr>
<tr>
<td>≥ 25 (N = 13)</td>
<td>21</td>
<td>47.7</td>
<td>23</td>
</tr>
<tr>
<td>By Chi Square test; P = 0.101</td>
<td>Significant</td>
<td></td>
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</table>

Table 8: [C] NECT ASPECT Score and Presence of Penumbra

<table>
<thead>
<tr>
<th>NECT aspect score</th>
<th>Penumbra</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7 (N = 16)</td>
<td>07</td>
<td>43.7</td>
<td>09</td>
</tr>
<tr>
<td>≥ 7 (N = 31)</td>
<td>17</td>
<td>54.8</td>
<td>14</td>
</tr>
<tr>
<td>By Chi Square test; P = 0.471, Not Significant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
in a systematic review performed by Wardlaw et al in 2005 involving 15 studies where CT scans were performed within six hours of stroke onset, the prevalence of early CT signs of brain infarction was 61% (standard deviation +/- 21%).

7. Distribution of HU of the Penumbra and core infarct: To the best of our knowledge, there is no significant literature available pertaining to distribution of HU values of the penumbra and HU values of the Core Infarct (Tables 3, 4).

8. Suitability for Thrombolysis on the Basis of NECT and CBV Maps: According to standard ASPECTS criteria, a patient is considered suitable for thrombolysis if NECT ASPECT Score is ≥7 or CBV ASPECT Score is ≥8. Even in presence of identifiable penumbra, NECT ASPECT Score of <7 or CBV ASPECT Score of <8 is predictive of poor outcome after thrombolysis.

In our study, 47 patients presented with clinical or imaging features of anterior circulation ischemia, for which ASPECTS was applicable. In NECT, 31 patients (66%) had ASPECT Score of ≥7 while on CT Perfusion, 18 patients (38.3%) had ASPECT Score of ≥8 (Table 5).

Cerebral blood volume ASPECTs sensitivity, specificity, positive predictive value, and negative predictive value for clinical outcome were 60%, 100%, 100%, and 45%, respectively. Hence, only this 18 patients were considered suitable for thrombolysis.

3 patients presented with clinical or imaging features of posterior circulation ischemia, out of whom 2 had presence of identifiable penumbra. These 2 patients were considered suitable for thrombolysis. To the best of our knowledge, there is no significant literature available pertaining to predicting the outcome of thrombolysis in posterior circulation stroke according to extent of involvement.

**References**

An Observational Study on the Mortality Pattern of Type 1 Diabetic Patients in West Bengal, India: A 22 Years’ Follow Up Report of 212 Patients

Debasish Maji1*, Shibendu Ghosh2, Tapati Maji3, Ram Udayan Roy4, Soma Kundu5, Banani Ghosh6

Abstract

Background: Limited information is available on the total profile of type 1 diabetes mellitus (T1DM) patients in India as type 1 diabetes is not common in India. The present study has been undertaken therefore, in search of mortality pattern of the type 1 diabetics attending the diabetic clinic run by the Calcutta Diabetes and Endocrine Foundation at Kolkata which has a special diabetes care program for the type 1 diabetics.

Objectives:

• To obtain the mortality rate of type 1 diabetes in India and to compare it with overall Indian mortality.
• To identify the role of different complications of diabetes responsible for the death and thereby, getting a mortality pattern in type 1 diabetes.
• To take necessary action for prevention of the complication(s), mainly responsible for the death

Study Design and settings: Longitudinal Observational Study: A number of 264 type 1 diabetics attending our clinic were considered for the study. The patients registered in the clinic since April 1996 and had at least one or more follow up visits per year have been included in the study. Follow-up up to 31st March, 2019 have been determined as selection criteria. Out of 264, 212 patients satisfied the criteria and therefore have been included in the study.

Methods of Study: Age, sex, height, weight, educational qualifications, profession, annual family income and number of family members of each patient was recorded in the first visit. Age and year of detection of diabetes was also recorded. Fasting and Post Prandial plasma glucose level, insulin type and dose, daily dietary habit, presence of diabetic complications, i.e. Retinopathy Neupathy, Nephropathy, Coronary Artery Disease. Life Style and diabetic education status were assessed during first visit and also in successive visits. An average value for each of the above parameters was calculated for every patient and recorded to explain their individual status. Mortality data was collected from the patients expired during this period.

Results: 22 (10.38%) out of 212 patients were expired during the study period. 8 (36.36%) of them were males and 14 (63.64%) were females. The age of the expired patients at death varied from 5 to 73 years. 3 (13.64%) patients died within 20 years of age, 14 (63.64%) between 21-40 years, 2 (9.09%) between 41 - 60 years and 3 (13.63%) were above 60 years. Chronic Kidney Disease (CKD) was the cause of death for maximum number of patients (45.45%) followed by Diabetic Ketoacidosis (DKA, 18.18%), 3.63% died of Coronary Artery Disease, 9.09% of infections (pneumonia, encephalitis). Accidental and psycho-social reasons were present in 13.63%.

Conclusion: In this observational study, the total number of death observed was 22 out of 212 type 1 diabetic patients in this 22 years’ period. CKD is the leading cause of death in this cohort, followed by DKA, Infection, and Coronary Artery Disease. Infection and DKA was found in the poor socio economic group. Some patients died of accident and other psycho social problem in the family. A regular communication with the patients made a lot of positive influence in our patients.

Introduction

Limited information is available on the total profile of type 1 diabetes mellitus (T1DM) patients in India as type 1 diabetes is not common in India compared to western world. However, because of huge population, over 100,000 children are living with type 1 diabetes in India. Along with 10 other countries, India comprises the WHO’s South East Asia region, which has a prevalence of type 1 diabetes of 1, 11,500 in children.7 Several studies with standardized mortality ratios reveal that patients with type 1 diabetes have mortality rates that are 3–18 times higher than the general population. There is marked geographic variation in mortality, and further notable differences between males and females, compared to...
the general population. However, DCCT/EDIC shows higher mortality in conventional Treatment group only. Healthy diet plan, regular use of insulin in appropriate dose, routine physical activities and overall a proper monitoring of health status through regular check up of glycemic status and other parameters as lipid, renal, cardio vascular and neurological profile, eye check up, can prevent early development of diabetic complications as well as premature mortality. Interestingly this is not achieved for most of the type 1 diabetic patients. The Socio Economic Status (SES) of the patients also plays an important role on the preterm mortality in type 1 diabetes. The present study has been undertaken to make a complete survey on type 1 diabetic patients with special reference to their life expectancy and mortality in West Bengal, India.

### Objectives

1. To obtain the mortality rate of type 1 diabetes in India and to compare it with overall Indian mortality.

2. To identify the role of different complications of diabetes responsible for the death and thereby, getting a mortality pattern in type 1 diabetes.

3. To take necessary action for prevention of the particular complication(s), mainly responsible for the death

### Study Design

Longitudinal Observational Study.

### Selection of Subjects from those attending the clinic

The Diabetic Clinic run by Calcutta Diabetes and Endocrine Foundation (CDEF), Kolkata has a complete diabetes care providing team especially for the type 1 diabetic patients, consisting of 2 specialist doctors, 2 diabetes educators and 2 dietitians. Apart from those, Clinical Podiatrist, Pediatrician, Gynecologist & Obstetrician and Clinical Psychologists are also available on call. A senior Type 1 Diabetic patient who is the Secretary of CDEF, working as the co-ordinator since 1995. She keeps regular communication with the type 1 diabetic subjects and maintains regular records in the computer of all information received from the patients. One annual residential educational camp is organized by CDEF and 3 months’ interim open house group discussion program to maintain good relationship and communication with type 1 patients are arranged at the CDEF office. The death incidence and other data updated and regularly entered into the computer.

A number of 264 type 1 diabetics attending our clinic have been registered in the study. The patients registered in the clinic since April, 1996 and had at least one or more follow up visits per year have been considered for the study. Follow-up up to 31 March 2019 have been determined as selection criteria. Out of 264, 212 patients satisfied the criteria and therefore have been included in the study.

### Table 1: Recruitment of Type 1 Diabetic subjects

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 - 2000</td>
<td>47</td>
</tr>
<tr>
<td>2001 - 2005</td>
<td>55</td>
</tr>
<tr>
<td>2006 - 2010</td>
<td>54</td>
</tr>
<tr>
<td>2011 - 2015</td>
<td>65</td>
</tr>
<tr>
<td>2016 - 2019</td>
<td>43</td>
</tr>
</tbody>
</table>

### Table 2: Baseline data of the expired Patients (n = 22 out of 212)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of male Patients</td>
<td>08</td>
</tr>
<tr>
<td>Number of Female Patients</td>
<td>14</td>
</tr>
<tr>
<td>Maximum age of the Patient</td>
<td>73 Years</td>
</tr>
<tr>
<td>Minimum age of the Patient</td>
<td>04 Years</td>
</tr>
<tr>
<td>Mean HbA1c Level</td>
<td>8.2 ± 1.4</td>
</tr>
<tr>
<td>Overall Life Style Modification</td>
<td>Moderate</td>
</tr>
<tr>
<td>Overall Diabetic Education</td>
<td>Good</td>
</tr>
<tr>
<td>Overall Diet Control</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

### Fig. 1: Recruitment of Type1 Diabetics According to Time Period 1996-2019

### Fig. 2: Age at Reporting (N = 22)

### Fig. 3: Death occurred during the study period

### Fig. 4: Male and female percentage of death

### Fig. 5: Death within the time period
Table 3: Baseline information of type 1 diabetic patients expired in the period

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Initial Sex</th>
<th>Date of diagnosis</th>
<th>Age at diagnosis (Years)</th>
<th>Height (cm)</th>
<th>Weight (Kg)</th>
<th>Age at death (Years)</th>
<th>Year of death</th>
<th>Cause of death</th>
<th>Hypoglycemic Control Events</th>
<th>No. of Hospitalization</th>
<th>No. of Family Members</th>
<th>Annual Family Income Approx. (Rs)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>AD</td>
<td>M</td>
<td>1985</td>
<td>34</td>
<td>155</td>
<td>54</td>
<td>62</td>
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<td>Multiple Myeloma</td>
<td>3-4/week</td>
<td>Good</td>
<td>2</td>
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<tr>
<td>2</td>
<td>AB</td>
<td>M</td>
<td>1997</td>
<td>26</td>
<td>162</td>
<td>66</td>
<td>35</td>
<td>2006</td>
<td>CKD 1/day</td>
<td>1</td>
<td>Mod</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>PP</td>
<td>F</td>
<td>1990</td>
<td>15</td>
<td>150</td>
<td>46</td>
<td>33</td>
<td>2008</td>
<td>CKD 6-7/15 days</td>
<td>Poor</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>PK</td>
<td>M</td>
<td>2000</td>
<td>25</td>
<td>165</td>
<td>60</td>
<td>30</td>
<td>2005</td>
<td>Nil</td>
<td>Poor</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>NP</td>
<td>M</td>
<td>1995</td>
<td>40</td>
<td>165</td>
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<td>57</td>
<td>2012</td>
<td>Pneum. 3-4/week</td>
<td>Mod.</td>
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<td>4</td>
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<tr>
<td>6</td>
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<td>F</td>
<td>2001</td>
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<td>46</td>
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<tr>
<td>7</td>
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<td>M</td>
<td>2001</td>
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<td>140</td>
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<td>Drown Not reported</td>
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<tr>
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<td>30</td>
<td>2008</td>
<td>CKD 2-3 15 days</td>
<td>Poor</td>
<td>1</td>
<td>4</td>
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<tr>
<td>9</td>
<td>PM</td>
<td>F</td>
<td>1996</td>
<td>16</td>
<td>158</td>
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<td>30</td>
<td>2010</td>
<td>Enceph Frequent</td>
<td>Good</td>
<td>2</td>
<td>5</td>
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<tr>
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<td>KO</td>
<td>F</td>
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<td>15</td>
<td>150</td>
<td>49</td>
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<td>2011</td>
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<td>Poor</td>
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<td>3</td>
</tr>
<tr>
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<td>F</td>
<td>1996</td>
<td>16</td>
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<td>28</td>
<td>2008</td>
<td>CKD 6-8/week</td>
<td>Mod.</td>
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</tr>
<tr>
<td>12</td>
<td>IC</td>
<td>F</td>
<td>1983</td>
<td>27</td>
<td>168</td>
<td>66</td>
<td>58</td>
<td>2014</td>
<td>CAD Frequent</td>
<td>Mod.</td>
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<tr>
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<td>M</td>
<td>1996</td>
<td>12</td>
<td>170</td>
<td>70</td>
<td>29</td>
<td>2013</td>
<td>CKD 1-2/week</td>
<td>Poor</td>
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<td>5</td>
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<td>F</td>
<td>1998</td>
<td>4</td>
<td>136</td>
<td>30</td>
<td>5</td>
<td>1999</td>
<td>DKA 1/day</td>
<td>Poor</td>
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<td>3</td>
</tr>
<tr>
<td>15</td>
<td>RSG</td>
<td>F</td>
<td>1980</td>
<td>36</td>
<td>166</td>
<td>50</td>
<td>73</td>
<td>2017</td>
<td>CAD 4-5/15 days</td>
<td>Good</td>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>16</td>
<td>TKR</td>
<td>M</td>
<td>1988</td>
<td>37</td>
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<td>2017</td>
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<td>Good</td>
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<td>CKD 1-2/3 days</td>
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<td>4</td>
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<td>1996</td>
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<td>2015</td>
<td>CKD 2-3 15 days</td>
<td>Poor</td>
<td>3</td>
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</tr>
</tbody>
</table>

Table 4: Survival of patients in relation to their age at diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Mean Survival (Yrs) ± S D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Pubertal</td>
<td>12.71 ± 7.13</td>
</tr>
<tr>
<td>Teenage</td>
<td>16.57 ± 5.88</td>
</tr>
<tr>
<td>Above 19 yrs</td>
<td>20.50 ± 12.25</td>
</tr>
</tbody>
</table>

Methods of Study

Age, sex, height, weight, educational qualifications, profession, annual family income and number of family members of each patient was recorded in the first visit. Age and year of detection of diabetes was also recorded. The diagnosis of type 1 diabetes was made on the basis of clinical presentation, high blood sugar, positive ketone in urine, positive GAD antibody and insulin treatment for the survival. Intensive patient education on diabetes was given at the first and subsequent visits to the patient, as well to the family members. Fasting and post prandial plasma glucose level, insulin type and dose, daily dietary habit (in terms of total daily calorie intake and dietary composition), presence of diabetic complications, i.e. Retinopathy, Nephropathy, Cardiovascular, Life Style and diabetic education status were assessed during the first visit and also in successive visits. An average value for each of the above parameters was calculated for every patient and recorded to explain their individual status. Mortality data was collected from the regular telephonic communication by the Coordinator.

Statistical Analysis

Pie and Bar Diagrams are being used to explain the results. Tables and graphs are used whenever found necessary.

Results

The number of patients recruited every five years is shown in Figure 1. Around 40 – 65 patients were recruited in an average every five years. The data has numerically been described...
predominance was observed. 8 (36.36%) of the patients were males and 14 (63.64%) were females. A female predominance was observed.

**Lifestyle:** The term “Moderate” was being used to explain the overall Life Style modification. The patients who were doing proper diet control and regular physical exercise along with proper intake of daily insulin as suggested by the diabetic expert and diettian were in GOOD life style, those who did diet control and took proper medication but not doing physical exercise regularly, were placed in MODERATE group and those who violated any two of the three above were in POOR group.

**Education:** Those patients who attended the annual residential camp regularly and participated at least two interim sessions in one year were expected to get GOOD education, those who attended the camp regularly but did not participate more than one interim session in a year were placed in MODERATE educated group and those who neither participated in the camp, nor did attend the interim session regularly, were treated as POOR educated group.

**Diet Control:** Regarding diet control, the patients who followed the daily diet schedule strictly and never allowed anything in their daily diet without permission of the diettian, were in GOOD diet control group, those who sometimes took some non permissible foodstuffs (once in a week) with his own were in MODERATE control group and the rest who violated the diet control rule many times with his own will were in POOR control group.

N.B. The terms Good, Moderate and Poor were being arbitrarily used for clinical assessment purpose.

The control of diabetes for each patient was considered according to his/her Glycated Hemoglobin(HbA1c) level. Below 7.0% was treated as good control, 7 – 8.5% was moderate control and beyond 8.5% was poor control. It has been observed from the above table that the number of hospitalization was less (1 – 3) in general with only one exception (4). Possibly the continuous monitoring and communication improved the patients’ self education skill and therefore, less number of hospitalization was observed.

Baseline data of expired patients are shown in Table 2. Table 3 shows information of all patients who expired in this period.

The number of patients died every five years within the study period has been expressed in Figure 5. Maximum number of patients expired in between 2011 – 2015 (10 out of 22), followed by 2006 – 2010 (7 out of 22). Incidentally the patient recruitment was highest in 2011 – 2015 periods (65 out of 212) and the number of death and number of recruitment were almost similar in 1996 – 2000 (2 out of 47 recruited) and 2016 – 2019 (2 out of 43 recruited), but in 2001 – 2005, although the recruitment was second highest (53), the number of death was minimum (only one).

The age of the expired patients at death varied from 5 to 73 years. 3 (13.64%) patients died up to 20 years of age, 14 (63.64%) between 21-40 years, 2 (9.09%) between 41-60 years, and 3 (13.63%) patients above 60 years. The results expressed in percentage is shown in Figure 6.

Comparison between the mean age at diagnosis and survival in years. The patients divided in three groups: Pre pubertal; where the disease was diagnosed before or at 12 years, Teen agers, where the diagnosis was between 13-19 years and the third group where the age of diagnosis was above 19 years. The maximum survival was observed in the third group and the minimum was in the pre pubertal group. The result was numerically expressed in Table 4 and represented diagrammatically in Figure 7.

Chronic Kidney Disease (CKD) was the cause of death for maximum patients, 10 (45.45%) died of CKD followed by Diabetic Kato Acidosis (DKA) 4 (18.18%). 3 (13.63%) patients died of CAD (Coronary Artery Disease) and 2 (9.09%) patients were expired in infections (pneumonia, encephalitis).

Accidental, psycho-social and cancer were responsible for death in 3 (13.63%) patients which may not be directly related to diabetes. The different causes of death in Type1 diabetic subjects has been expressed diagrammatically in Figure 8.

**Discussion**

Significant improvement in life expectancy of type 1 diabetic patients have been observed due to advancement in management and care. Despite the fact, the mortality rates of those patients still remain higher than the general population. A finding confirmed by several studies with standardized mortality ratios reveal that patients with type 1 diabetes have mortality rates that are 3–18 times higher than would be expected in general population. In the present study, we observed 22 deaths out of 212 patients in 22 years which comes approximately at 5 deaths/1000/year, which is lower than the all cause mortality. Mortality rate of type 1 diabetic was about 05/1000/year which was lower than in general population. (7.3/1000/year in 2017) in India. This difference of mortality on the better side in this cohort of T1DM patients is not explainable. However, it could be due to proactive involvement of the Diabetic Care group of CDEF with the T1DM patients. In DCCT study, it was commented that more tight glycemic control might be the cause of frequent hypoglycemia which could be fatal in some cases, but on the reverse, loose control could give rise to the development of complications causing shortening of life. In the present study, neither of the patients died of hypoglycemic coma or any other condition related to hypoglycemia because the patients had repeated and intense training to diagnose and treat hypoglycemia.

There is marked geographic variation in mortality, and further notable differences between males and females, compared to the general population. Sex-specific differences in type 1 diabetes mortality were clearly observed in our study. Females with type 1 diabetes consistently have higher standardized mortality than their male counterparts supported by several other studies. Maximum number of deaths were between the age of 20 and 40 as maximum number of patients expired during the period.
were in this age group.

The Wisconsin Epidemiologic Study included 996 individuals with presumed type 1 diabetes (defined as age of diagnosis <30 years and on insulin therapy). In a 20-year follow-up report, 64% of deaths involved heart disease, and retinopathy and nephropathy status significantly predicted cardiovascular mortality. We found Chronic Kidney Disease (CKD) as the major cause of death in 45.45% patients, followed by Diabetic Ketoacidosis (DKA) in 18.18% cases. 22 years’ follow up study. The Cardio Vascular mortality was found in 13.63% cases. In this cohort elderly T1Dm patients are less in number and elderly T1DM (>40 yrs) patients are supposed to be more prone to have coronary artery disease.

DKA and infection as cause of death in this cohort is significantly higher compared to the western literature. It has been seen more common in the poor socio economic group of patients who lived in remote areas where the diabetic care was difficult to get. In this part of the world socio economic statuses plays a great role in the quality of diabetic care in T1 DM. Almost same comment was given in a different study where it was said that poor access to health care is responsible for poorer prognosis for some patients with T1 DM. Some observation has been noted in a German Study where it was found that, the Socio Economic Status (SES) effect on mortality persisted after adjusting for other risk factors.

In our study, 13.63% of death was due to accidental, suicidal or other reasons because of psycho social factors. More than 10% of death cannot be neglected considering the behavioral pattern of type 1 diabetic patients which somehow may be different from the general population, although the standardized mortality ratios for violent deaths were not significantly different from the general population for either sex, similar to type 1 diabetes findings in Europe. To minimize this aspect of problems, a regular group discussions are held at the clinic with a Consultant Clinical Psychologist where T1 DM patients with the family members are free to interact.

Role of glycemic control on the mortality of type 1 diabetics is not beyond debate. Some studies have implicated poor glycemic control in type 1 diabetes mortality while others have found no survival advantage for improved control. In our study, we found mean HbA1c level of the expired patients was 8.2% ± 1.4 which could not be considered as good glycemic status. However, the role of development of microangiopathy and secondary infections related to poor glycemic control leading to death in type 1 diabetics should not be over looked.

There were no clear patterns in the standardized mortality ratios estimated by age at onset. In our study, we found maximum (12 out of 18) patients expired between ages of 21-40 years but no such clear relationship between the age of onset and mortality. Although, it was found that the patients diagnosed at pre pubertal stage, showed less survival than those diagnosed at teen ages and above. It is interesting to note that the incidence, as well as mortality in T1 DM vary countrywide.

Conclusion

In this observational study, the death pattern of type 1 diabetics has been reported only. Diabetic Nephropathy leading to Chronic Kidney Disease is the leading cause of death in our cohort, followed by DKA and Infection which were found mostly in the poor socio economic group. Coronary Artery Disease was less in this cohort because there are less number of elderly patients in this cohort. Some patients died of accident and other psychosocial problem in the family which may not have direct relationship with the quality of diabetes care. A regular communication with the patients made a lot of positive effect in our patients. In spite of available infrastructure of management of type 1 diabetics, all efforts should be given to tight glycemic control, regular follow up at clinic, regular communication with patients and extensive education to all levels to maintain good health and reduce mortality in type 1 diabetic patients.

References

India’s Novel Immunomodulator

An Adjunct Therapy For Gram –ve Sepsis,

Sepsivac®

Save More Lives

A randomized trial of Mycobacterium w in severe sepsis

Intepraj Singh Senge, Drish Agarwal1, Aditiabh N. Agarwal1, Sushil K. Verma1
Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Study Design:
Randomized, double-blind, 2–parallel arm, comparative controlled prospective study in 50 severe sepsis patients (Mw arm: 25 pts | Control arm: 25 pts)

Study Outcomes

Significant Reduction in

Mechanical ventilator days (6 vs 9 days)  
Length of ICU stay (7 vs 12 days)

Length of hospital stay (10 vs 16 days)  
Delta SOFA score (0 vs 4)

Incidences of secondary nosocomial infection

Use of Immunomodulator Mw is beneficial in severe sepsis

Intradermal Administration Dosage

0.3 ml per day for 3 consecutive days  
(0.1 ml intradermal at 3 different sites)

Each kit contains:

- 1 vial
- 3 syringes
- 3 needles of 24 G (to draw medicine)
- 3 needles of 26 G (to inject medicine)
Importance of Imaging in Work up of Cardiovascular Diseases by Using Telemedicine in Rural India

Shridhar Dwivedi1*, Vinod Sharma2, Kalpeeta Roy3

Abstract

Background: Cardiovascular diseases have emerged as an epidemic in India. Telemedicine is a useful tool for sending ECG, x-ray and ultrasound images to telemedicine centre for diagnosis and management of cardiovascular diseases in rural areas as it overcomes the distance barrier.

Methods: National Heart Institute collaborated with Hospital Guide Foundation (HGF) Jewar, Greater Noida for conducting telemedicine sessions. Two hundred patients were analysed during time span of June 2018 to August 2019. Imaging tools like ECG, Chest X-ray and ultrasound were studied besides usual laboratory parameters.

Results: Important ECG abnormalities included LVH (10.9%), ischemia (10.1%), LBBB (2.4%), RBBB (3.9%), p-mitral (1.5%), hyperkalaemia (2.3%) besides normal ECGs (56.2%). Chest x-ray revealed features of COPD (8.3%), cardiomegaly (6.9%), hilar shadows (6.9%), bronchitis (2.7%) and prominent broncho-vascular markings (6.9%). Ultrasound abdomen showed hepatomegaly (23.2%), fatty liver (15.1%), gallstones (2%), bilateral renal stone / left or right renal stone (42.4%).

Conclusion: Telecardiology/ Teleradiology are important and useful imaging tools in the diagnosis and treatment of cardiovascular diseases in rural India.

Introduction

Cardiovascular diseases (CVD) constitute disorders of heart. Type 2 diabetes mellitus (T2DM) is also considered as a vascular disease. Development of information and communication technology has empowered telemedicine as a powerful tool for health care delivery. Patients living in remote areas are provided physical check-up and timely diagnosis with this innovation. The important imaging techniques which can be conveniently employed currently in telemedicine are: ECG, X-ray chest and ultrasound. Teleradiology and Telecardiology are the part of telemedicine which consist of transmitting of X ray, ultrasound and ECG. Out of three imaging modality ECG is the most reproducible investigation as far as telecardiology is concerned. Likewise, ultrasonography is very efficient and widely available technique for the detection of fatty liver which can be transmitted to expert through telemedicine. The other common imaging tool is chest X ray which may show cardiomegaly, signs of congestion and /or aortic calcification indicating aortic atherosclerosis. As part of our regular telemedicine program we noticed a high prevalence of cardiovascular diseases including diabetes and obesity. We therefore decided to study the ECG, ultrasonographic and x-ray profile of these cases and correlate with the final diagnosis.

Methods

The present study was conducted at the National Heart Institute, East of Kailash, New Delhi, in collaboration with Health Guide Foundation (HGF) in Jewar, Greater Noida. Most people in this area were from low socioeconomic strata. Telemedicine session was conducted at the National Heart Institute (NHI) on every Tuesday and Thursday between 12 and 1 pm. The telemedicine sessions were held biweekly over a period of 14 months (June 2018–August 2019). A total of 200 patients attended the tele sessions. The basic details like name, age, sex, occupation, socioeconomic history, tobacco habit, height, weight, blood pressure, and blood sugar estimation of all cases were done by NGO and details beamed to telemedicine room at the NHI. There is a real-time connection between the doctor at NHI and the patient along with the doctor at Jewar Health Centre. They were offered cardiovascular work up comprising ECG (128 cases), X-ray chest (72 cases), ultrasound abdomen (99 cases). These tests were carried out at Jewar itself coordinated by the NGO. A comprehensive diagnosis was made in second tele-session after reviewing lab workup and treatment advised.

Results

Common cardiovascular diseases observed in our study were diabetes (79.5%), hypertension (31%) and CAD (4.5%) in that order. As regards obesity 40.5% were overweight, 16.5% belonged to obese class I, 3.5% were obese class II, 2.5% - obese class III, 3.5% were underweight and 33.5% had normal BMI. It was also observed that out of 44 tobacco users 63.6% quit tobacco in follow up tele sessions.

Out of the 122 ECG done 10.9% showed LVH, 10.1% revealed ischemia, another 10.1% showed sinus tachycardia, 3.9% exhibited RBBB, 3.1% had evidence of old MI and evidence of hyperkalaemia was seen in 2.3% of cases (Table 1). LBBB and p-mitral was observed in two cases (1.5%). More than half (56.2%) patients had normal ECG.

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Chest x-ray revealed features of COPD (8.3%), cardiomegaly (6.9%), hilar shadows (6.9%) and prominent broncho-vascular markings (6.9%). 68% did not show any radiological abnormality in the chest (Table 2).

Ultrasound abdomen showed hepatomegaly (23.2%), fatty liver (15.1%), and gallstones (2%). Surprisingly 42.4% of patients had ultrasonographic evidence of either bilateral renal stone/ left or right renal stone. It was observed that 15 (15.1%) cases which showed fatty liver suggesting metabolic syndrome had high incidence of diabetes (80%), obesity (67%), and hypertension (40%) (Table 3).

**Discussion**

Cardiovascular diseases (CVD) constitute disorders of heart and blood vessels including hypertension, coronary artery disease, stroke, peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease and cardiomyopathy etc. In addition to these type 2 diabetes mellitus (T2DM) is also considered as a vascular disease. Further, cardiovascular diseases are major cause of death and disability among people with type 2 diabetes. Lack of early detection and care of diabetes results in severe complications, including heart attacks, strokes, renal failure, vision impairment. Today, with the rapid expansion of information & communication technology (ICT) and internet facilities throughout India telemedicine is destined to play a major role in health care particularly in rural areas where health facilities are not so easily available. Distance in terms of cost and distance acting as a deterrent to people consulting this technology helps us to overcome this factor. The important imaging techniques which can be conveniently employed in telemedicine are: ECG, X-ray chest and ultrasound which comes under popular telemedicine specialities like teleradiology and telecardiology. Besides there are more specialities like telepsychiatry, tele dermatology, teleophthalmology, tele nephrology, tele oncology, telepathology, telerelaboration, telesurgery, tele paediatric surgery, tele obstetrics and tele gynaecology, tele endocrinology, tele neurophysiology, telenursing, tele family medicine, tele somnology and telerobotic surgery. As considering telecardiology we can use communication technology the Bhabha Atomic Research Centre (BARC) had developed base technology for “handheld 12-channel Tele-ECG instrument a small hand held device that facilitates viewing the medical grade of a 12-lead ECG in real time on android smart phones. On a press of a button of a bottom, a noise-free, 3-page PDF report comprising a standard report, a rhythm report and a vector cardiogram in PDF format can
Dermatological Disorders in the Intensive Care Unit: A Descriptive Study at a Tertiary Care Centre

Ankita Srivastava1*, AD Mathur2, Sakshi Agarwal3

Abstract

Background: Dermatological disorders are common in patients being treated in intensive care units (ICU). However, they are often neglected in context of a critically ill patient. Very few studies focusing on these dermatoses have been undertaken.

Objectives: To determine the prevalence and spectrum of dermatological disorders in patients being treated in medical ICU of a tertiary care centre.

Methods: This was a descriptive study conducted over a period of one year. All the patients admitted in the medical ICU were examined for the presence of any preexisting or newly developed dermatological disorder. Dermatological disorders were initially classified into infective and non-infective disorders. Patients with dermatological findings were classified into two groups: those who survived and those who died; which were compared with each other with respect to age and sex distribution, length of ICU stay and dermatological findings.

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Results: Out of 776 cases admitted in ICU during the study period, dermatological disorders were observed in 164 (21.13%) cases. Life-threatening dermatological disorders were seen in 3.05% cases. Twenty nine (17.68%) patients with dermatological findings died. Amongst these cases, infectious dermatological disorders were significantly less common; while no significant difference was noticed in context of reactive dermatological disorders.

Conclusion: Dermatological disorders in ICU are common and have a wide spectrum. They often need treatment and may be indicative of underlying potentially fatal systemic illness. Besides, a subset of cutaneous lesions may develop in response to various medical interventions, immunosuppression and immobility. Knowledge of such dermatoses is thus, essential, both for the intensivist and dermatologist.

Introduction

Dermatological disorders in the intensive care unit (ICU) are often considered trivial. This is because most of the dermatological diseases are not life-threatening. However, there are certain dermatological diseases, which are severe enough to be treated in an ICU. Fortunately, the prevalence of such disorders is quite low, with a reported frequency of 0.42–0.47%. On the other hand, several dermatological findings are noted in critically ill patients being treated in ICUs; which may or may not be related to the primary illness. Sometimes, the cutaneous lesions might be an indicator of underlying systemic disease. Although most of the dermatological disorders are not life-threatening, they may impair patients’ quality of life. They can also occur as an adverse effect of medical intensive care due to the use of several drugs, interventions or inadequate skin care.

Dermatologists often find it difficult to diagnose the cutaneous lesions in such patients, partly due to difficulty in history taking and examination. Furthermore, while treating even the most common dermatoses in the ICU, one needs to be cautious about the comorbidities and possible drug interactions.

Very few studies across the globe have been conducted to investigate various dermatological disorders in patients requiring intensive care. Also, none of the standard dermatology textbooks have a chapter dedicated to these ‘ICU dermatoses.’ Therefore, we conducted this observational study to determine the prevalence and spectrum of dermatological disorders in patients being treated in medical intensive care unit at a tertiary care centre.

Material and Methods

This was a descriptive study, carried out at a tertiary care centre over a period of one year. The study was approved by the institutional ethics...
committee. All the patients admitted in the medical ICU as per the society of critical care medicine (SCCM) guidelines were screened within 24 hours of admission for the presence of any dermatological disorder and were followed up daily till discharge or death. The relevant details including age, sex, preexisting dermatological disorders and systemic illness were noted. Dermatological findings were recorded with respect to onset, duration, morphology, distribution and progression. The diagnosis was made clinically with relevant laboratory investigations as and when needed. Appropriate treatment for the dermatological disorder was instituted in collaboration with the treating physician and/or intensivist. The patients with dermatological findings were classified into two groups: those who survived and those who died.

These two groups were compared with each other with respect to age and sex distribution, length of ICU stay and dermatological findings.

Statistical analysis: The prevalence of dermatological disorders in the ICU was calculated as the proportion of patients who had cutaneous manifestations either at the time of admission or developed later during the course of treatment in the ICU.

Discrete categorical data is represented as n (%); continuous data as mean ± SD and range or median and interquartile range, as appropriate. For a comparison of the variables, the χ2 (chi square) test was used for categorical variables; and the Mann-Whitney U test was used for continuous variables. Differences between values were considered significant at p < 0.05. Analysis of data was carried out by using Statistical Package for the Social Sciences software, version 20 (IBM® SPSS Statistics).

Results

A total of 776 patients were admitted in the medical ICU over a period of one year (from January 2018 to December 2018). Out of these, 164 (21.13%) patients had dermatological disorders. These patients included 107 (65.24%) males and 57 (34.76%) females. Age ranged from 13 years to 85 years with average age of 49.96 ± 19.07 years. Age and sex distribution is shown in Table 1.

The average length of stay in ICU was 7.69 ± 6.38 days, ranging from 1 day

### Table 3: Various non-infective dermatological disorders noticed in the ICU

<table>
<thead>
<tr>
<th>Dermatological disorder</th>
<th>Total cases</th>
<th>Preexisting</th>
<th>Newly developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura</td>
<td>21</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>• Purpura fulminans</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>• Senile purpura</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>• Traumatic</td>
<td>11</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>• Due to thrombocytopenia</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Xerosis</td>
<td>19</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Post oedema exfoliation</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Pressure ulcer</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Psoriasis/seborrhoea</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Angular chelitis</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Miliaria</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Traumatic erosions on lips</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Acne vulgaris/acneiform eruption</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pigmentary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vitiligo</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>• Melasma</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>• Idiopathic guttate hypomelanosis</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>• Systemic sclerosis</td>
<td>2</td>
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<td>0</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>2</td>
<td>2</td>
<td>0</td>
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</table>

### Table 4: Classification of dermatological disorders in the ICU and associated mortality

<table>
<thead>
<tr>
<th>Type of dermatological disorder</th>
<th>Total no. of cases noticed</th>
<th>No. of patients who died</th>
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</thead>
<tbody>
<tr>
<td>Infective dermatological disorders</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>Previous dermatological disorders</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>Life-threatening dermatologic disorders</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Systemic dermatological disorders</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Reactive dermatological disorders</td>
<td>36</td>
<td>7</td>
</tr>
</tbody>
</table>

Some patients had more than one dermatological disorder

### Table 5: Comparison of patients (with dermatological disorders) who survived and those who died

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with dermatological disorders who survived (n = 135)</th>
<th>Patients with dermatological disorders who died (n = 29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>49.16 ± 19.04</td>
<td>53.69 ± 18.79</td>
<td>0.322</td>
</tr>
<tr>
<td>Sex (males, percentage)</td>
<td>86 (63.7%)</td>
<td>21 (72.4%)</td>
<td>0.371</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>7.55 ± 5.73</td>
<td>8.31 ± 8.78</td>
<td>0.555</td>
</tr>
<tr>
<td>Infective dermatoses</td>
<td>50 (37.04%)</td>
<td>3 (10.34%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Newly developed lesions</td>
<td>47 (34.81%)</td>
<td>12 (41.38%)</td>
<td>0.503</td>
</tr>
<tr>
<td>Systemic dermatological disorders</td>
<td>24 (17.78%)</td>
<td>12 (41.38%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Reactive dermatological disorders</td>
<td>29 (21.48%)</td>
<td>7 (24.14%)</td>
<td>0.753</td>
</tr>
</tbody>
</table>
to 43 days. Out of these 164 patients, 103 (62.88%) had preexisting dermatological disorders, while 44 (26.83%) cases developed new cutaneous lesions while being treated in the ICU. The remaining 17 (10.37%) patients had both—preexisting dermatoses, and they also developed new lesions during ICU stay. The average duration of ICU stay before onset of new cutaneous lesions was 6.08 ± 4.69 days, ranging from 1 day to 22 days. A total of 40 (24.39%) cases had more than one dermatological condition.

Spectrum of dermatological disorders in the ICU: A variety of dermatological disorders were noted in the study (Figure 1). We broadly classified these disorders into infective and non-infective. Final diagnosis could not be established in six (3.66%) cases due to death or leaving against medical advice. Five (3.05%) cases were admitted in the ICU for primary dermatological disorders. These included 3 cases of pemphigus vulgaris and one each of erythroderma and toxic epidermal necrolysis (TEN). In addition, two cases of herpes zoster were shifted from dermatology ward to ICU, due to development of systemic complications.

Infectious dermatological diseases were seen in 55 (33.54%) cases, further classified into bacterial, viral, fungal and parasitic. Of these cutaneous infections, majority (49, 81.81%) were preexisting, only 18.18% cases developed these manifestations after admission in ICU. Overall, fungal skin infections were the most common followed by viral infections. The details are shown in Table 2.

A total of 142 non-infectious dermatoses were noticed in 115 (70.12%) cases. Few cases had both infectious and non-infectious manifestations. The details are enumerated in Table 3. Most commonly encountered non-infective cutaneous manifestation was purpura followed by xerosis. We further classified these non-infective dermatoses according to classification proposed by Badia et al. (Table 4).

Treatment was initiated for all cases with infectious dermatoses, and 85 (59.86%) cases of non-infective dermatoses. The remaining cases were either part of systemic disease (eg. connective tissue disorders) or were benign dermatoses for which no immediate intervention was needed (eg skin tags, melasma). Out of these treated cases, however, we needed to modify the standard treatment in 31 (22.14%) cases, taking care of comorbidities and concurrent medications.

Out of these 164 patients, 29 (17.68%) died. It included 21 (72.41%) males and 8 (27.59%) females. The average age was 53.69 ± 18.79 years. The median ICU stay in these patients was 5 days (mean ICU stay: 8.31 ± 8.78 days). Only three (10.34%) cases suffered from infectious dermatoses, while 23 cases (79.31%) had non-infectious dermatoses. Final diagnosis could not be established in remaining three patients. In nine (31.03%) of these cases, cutaneous lesions were either part of fatal systemic illness, or contributed directly to death. These included two cases of systemic sclerosis and purpura fulminans, and one case each of pemphigus vulgaris, TEN, SLE, vasculitis and rhinocerebral mucormycosis. No statistically significant difference was found between age and sex-distribution of patients who died and those who survived (Table 5).

Discussion

Most of the dermatological disorders are not life-threatening. Hence, they are often ignored in a critically ill patient being treated in ICU. But, sometimes, the dermatological findings may aid the physician in establishing the diagnosis. That’s why skin is often regarded as a window to systemic disease. Also, the coexistent dermatological disorders may impair patient’s quality of life and need definite treatment also. In ICUs, as the patients are not able to take care of themselves, sometimes, cutaneous lesions may develop due to lack of adequate skin care and also as a result of various therapeutic interventions. Therefore, the medical team in the ICU must be aware of various dermatological disorders prevalent in ICU and pay adequate attention to them, in order to provide best possible care to the patient.

Adequate medical literature focusing on dermatological disorders in the ICU does not exist. However, based on available data, the prevalence of dermatological disorders in the ICU varies from 2.3% to 42.2%. Many of these studies have taken up only those patients for whom a dermatology consultation was requested, therefore, resulting in a false low prevalence. In the present study, the prevalence of dermatological disorders in the ICU was 21.13%. This is relatively higher, possibly because we screened all the patients in ICU and recorded all the dermatological findings whether they were associated with primary reason for ICU admission or not.

Owing to wide variety of dermatoses prevalent in the ICU, establishing a uniform system of classification is difficult. We initially classified the cutaneous findings into infectious and non-infectious dermatoses and then classified the non-infectious cases further as per classification proposed by Badia et al. It was noticed that non-infective dermatoses were more common than infective dermatoses. The most common of these was purpura followed by xerosis and/or asthenoloc dermatitis. Though both of these manifestations may not require immediate additional therapy, but they can point towards various causative factors. Both xerosis and purpura can occur simply as a part of senile skin changes. But at the same time, these can also occur as a result of internal disease, drugs and inadequate skin care and/or frequent cutaneous trauma. Sometimes, these can point towards fatal systemic illness (eg purpura fulminans) hence it is advisable to carefully analyse these manifestations.

As per classification proposed by Badia et al, preexisting non-infective dermatoses were seen in 62 cases, much higher than previous studies. This is because in previous studies many cutaneous findings such as skin tags, acne, melasma, pressure sores etc were not included; as they were not considered relevant in context of patient’s condition.

Life-threatening dermatological disorders were seen in five (3.05%) cases, a figure close to available literature. This group basically incorporates disorders that may result in acute skin failure, such as immunobullous disorders, TEN and erythroderma. Though, the prevalence of such disorders is low, but these are associated with high mortality due to complications including sepsis and multiorgan failure. These patients, therefore, require specialized care under collaboration of dermatologist.
and intensivist. Some researchers have also recommended the dermatology ICUs or specialized units dedicated for the treatment of these disorders.17,18

A total of 36 reactive dermatological disorders were recorded in the study. This category included disorders which developed after admission in ICU and are related to factors like inadvertent mucocutaneous trauma during therapeutic interventions, prolonged immobility, poor nutrition, immunosuppression etc. Common disorders in this group include thrombophlebitis, angular cheilitis, traumatic erosions on lips (while intubation) and purpura (at sites of injection/cannulation).

Systemic dermatological disorders form a large group amongst dermatoses prevalent in ICUs and included heterogenous entities including connective tissue disorders, vasculitis, purpura, and gangrene. The spectrum of skin manifestations of systemic disease is wide and these can be specific and nonspecific. This group is important to recognize because these manifestations often give clue towards the diagnosis and the disease can turn out to be fatal. In terms of mortality, this group accounted for 41.37% cases of deaths.

In our study, infectious dermatological disorders were observed in 33.54% cases, out of which fungal infections were most common followed by viral infections. This is consistent with previous studies.

We also tried to classify the cutaneous manifestations into pre-existing and newly developed lesions. It helped in recognizing a subset of dermatological findings that often occur either as a result of various interventions, inadequate nutrition, poor skin care, immobility and immunosuppression. It also included certain infective conditions such as herpes simplex reactivation and candidiasis. The drawback of this system is that a particular dermatological finding could be pre-existing in some patients and can develop later in others.

In the present study, we compared the patients who died and those who survived. No statistically significant difference was found between age and sex-distribution of both groups. Amongst patients who died, the proportion of patients with infectious dermatological disorders was significantly lower than those with non-infectious dermatological disorders. Only three cases had cutaneous infections—one each with rhinocerebral mucormycosis, herpes zoster and dermatomyositis. These patients had comorbidities such as diabetes mellitus, hypertension and chronic renal failure which contributed to death. No significant difference, however, was noticed in context of reactive dermatological disorders amongst both the groups. Available literature does not give adequate data about dermatoses in patients who died; hence it difficult to compare these results. We suggest further studies focusing on this aspect of ICU dermatoses which might be useful in prognosticating the patients.

Treatment for the dermatological disorder was initiated in all cases of infective dermatoses and approximately 60% cases of non-infective dermatoses. Certain cases, such as purpura due to thrombocytopenia, malar rash of SLE needed no additional treatment apart from treatment of primary illness, while definitive treatment of conditions such as skin tags, melasma, xanthelasma etc was deferred till patient improved, considering the benign nature of these diseases. However we would like to underscore that in several patients, the usual dermatological therapy needed to be modified. Some examples include reduced dose of antivirals in patients with chronic kidney disease, choosing appropriate antifungal, reduced need of antihistamines and delaying immunosuppressants till systemic infection improves. In the era with gradual shrinking of inpatient dermatology services,19 it is essential for dermatologists to be aware of these considerations while treating a patient having multiple health problems.

It may be quite difficult for the intensivist to diagnose and/or treat patients with dermatological disorders. While many of the cutaneous lesions are innocuous, some of them can prove to be fatal. There is also a subset of cutaneous lesions which develop in response to medical interventions, immunosuppression and immobility. Hence, it is essential that the intensivists timely examine and recognize such disorders with dermatology consultation whenever required. Jack et al20 provide handy guidelines, which could be adopted in the ICUs. Collaboration between dermatologist and intensivist is helpful in identifying these cutaneous manifestations to provide the best possible care to the patient.

References

Efficacy and Safety of Bioresorbable Vascular Scaffold (BVS) - Absorb in Acute Myocardial Infarction – A 45 Month Follow Up Study

Viveka Kumar¹, Vivek Kumar², Mitendra Singh Yadav², Sangeeta Dhir³*, Pradipta Nayak⁴

Abstract
Aim: Bioresorbable vascular scaffolds (BVS) over the years have emerged as a new treatment option in coronary revascularization. There is a limited data on the use of these novel devices in patients with acute myocardial infarction (AMI). The purpose of this study was to evaluate the safety feasibility and efficacy of BVS implantation in patients with AMI.

Methods and Results: 61 patients diagnosed for AMI underwent Absorb BVS device implantation. The mean age of the patients were 56.6 years with 86.89 % males. 34 patients has history of hypertension (HTN, 55.7%), 3 patients had history of myocardial infarction (MI,4.91 % ), 7 patients were diagnosed with unstable angina (UA,11%), 34 patients had anterior wall ST elevation myocardial infarction ( AWSTEMI,55.73%),13 with ST segment elevation myocardial infarction ( STEMI,21.31%), with Killips class 2 (39.34%), 6 patients had Non ST segment Elevation Myocardial Infarction (NSTEMI, 9.83%). Procedural success was achieved in 93% patients with thrombolysis in myocardial infarction flow (TIMI) 3. During the follow up period of minimum 44±16 months no peri-procedural MACE were reported. Incidence of TLF (22.95%), definite probable ScT (11.47%) and TLR was 8 %. Average duration of DAPT was 17.57 months and 8 days. Cardiac death occurred in 4 patients (6.5%) after discharge from the hospital.

Conclusions: The study results suggest that BVS implantation is feasible and safe in AMI. Specific device implantation technique is critical step towards success of BVS devices.

Introduction
Coronary Artery Disease (CAD) is the most common condition amongst heart ailments and is the leading cause of death. Interventional management of CAD involves balloon angioplasty, stent placement and coronary artery bypass surgery. Percutaneous transluminal coronary angioplasty (PTCA) using a balloon is a minimally invasive procedure used to open blocked coronary arteries to improve blood flow and allow blood to circulate to the heart muscle. Balloon angioplasty results in a dissection forming inside a diseased vessel, which can lead to an overgrowth of scar tissue, and in turn can result in restenosis of a previously treated section. Evolution of drug eluting stents have also reported risk of edge restenosis and late thrombosis. The development of biodegradable and bio absorbable stents or bio absorbable vascular scaffolds (BVS) present a promising future in cardiovascular medicine.¹ The long-term advantages of BVS include: possibility of using non-invasive follow-up imaging (such as multiple detector computed tomography, MDCT), restoration of vasomotion, and positive remodelling.² Clinical trials have shown the use of the BVS as a safe and feasible modality with acceptable short and mid-term clinical outcomes.³⁴⁻⁵ However, registries performed in more complex patients and lesions reported higher rates of early and late scaffold thrombosis.⁶⁻⁸

Studies on BVS in AMI are limited and there is a need for more data on the efficacy of BVS in the setting of PCI for AMI cases. The aim of our study was to evaluate the feasibility, efficacy and safety of bioresorbable vascular scaffold in patients presenting with acute myocardial infarction. To the best of our knowledge this study is the single longest follow up from India.

Methods
Study Center
This single center retrospective study was undertaken between June 2013 to April 2017. Study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics approval was obtained from the Institutional Ethical Committee. Based on the selection criteria, 84 patients were enrolled for percutaneous coronary intervention (PCI) and Absorb BVS (Abbott Vascular, Santa Clara, CA). The remaining 3 patients were treated with drug-eluting stent (DES). Prior written informed consent was obtained from all the patients for the study and the required follow-up.

Selection Criteria
Inclusion criteria: patients presenting with acute coronary syndrome (ACS) and acute myocardial infarction (AMI); presence of one significant coronary artery stenosis with no restrictions as to the number; severity or lesion location; target vessel reference diameter (2.3 mm- 3.7 mm) by visual estimate.
Exclusion criteria: Non ACS / MI condition; known intolerance to: acetylsalicylic acid, heparin, poly-L-lactide, everolimus contrast material; active bleeding; coagulopathy or patients on chronic anticoagulation therapy; poor compliance; cardiogenic shock; comorbidity with limited expected survival (<1 year); inaccessible vessel conditions: severe tortuosity, calcification or angulated coronary anatomy; fibrinolysis prior to PTCA.

Study Parameters

Demographic variables, angiographic findings, clinical outcome (hospital stay and subsequent follow up), lesion and procedural characteristics.

Study endpoints

The primary endpoint of the study was cumulative rate of major adverse cardiovascular events (MACE) including cardiac death, myocardial infarction (MI) and ischemia-driven target lesion revascularization (TLR) TLR was defined as the need for subsequent intervention of the target lesion due to the presence of a symptomatic > 50% diameter stenosis during follow-up. Cardiac deaths were defined as death resulting from an acute MI, heart failure and cardiac procedures. All deaths were deemed cardiac unless proven otherwise.10 The primary efficacy outcome of interest was target lesion failure.11 Secondary endpoints included cardiac death, all-cause death, MI, TLR, target vessel revascularization (TVR), stent thrombosis (ST), and very late stent thrombosis (VLST).19 Angiographic success was defined as successful scaffold deployment at the intended site with the residual stenosis of less than 30% (visual estimation), with thrombolysis in myocardial infarction (TIMI) flow grade 3. Procedure success was defined as angiographic success in the absence of in hospital major adverse cardiac events (MACE).

BVS implantation technique

Prior to implantation coronary angiograms were analysed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). PCI was performed using the radial or femoral approach using 6 or 7 French catheters. The recommended PSP technique was followed for device implantation in our study.13,14 This technique included: adequate lesion preparation (P), appropriate sizing (S) and post dilatation (P) with an objective to achieve final diameter stenosis of 10% with a +0.5 mm noncompliant balloon to high pressure (>16 atm).15 (Figures 1, 2) After the procedure all patients received dual antiplatelet therapy (DAPT) loading and maintenance dose i.e. Aspirin - Clopidogrel or Aspirin - Ticagrelor or Aspirin - Prasugrel for at least 12 months. In patients with complex lesions or an acute presentation, the use of ticagrelor or prasugrel as a substitute for clopidogrel was preferred (at least for the first 3 months).16 Prolonged DAPT prescription (>12 months) was encouraged, if well tolerated with no bleeding events in the patient.

Follow-up

Minimum follow up duration was 4 years. This was conducted through telephonic contact or live status examination for reporting of: adverse events, subsequent coronary interventions, use and changes in concomitant medications.

Statistical analysis

The data was recorded on an electronic format, tabulated and analyzed Statistical Package for Social Sciences version 20.0.1 (IBM SPSS Statistics for Windows, Version 20.0.1 Armonk, NY: IBM Corp) Continuous variables are presented as mean ± standard deviation and categorical variables are presented as counts and percentages.

Results

Study patients

Out of the 64 patients, BVS device was implanted in 61 patients. The mean age of the study population was 56.6 years, 86.89% were males. 55.74% subjects had hypertension with 4.91% reported history of MI. 7 patients were diagnosed with unstable angina (11%), 34 with AWSTEMI (55.73%), 13 with STEMI (21.31%) with Killips class 2 (39.34%) (Table 1).

Lesion and procedural characteristics

During percutaneous coronary intervention (PCI) with BVS implantation, femoral artery catheterization was done in 60.66% cases. A total of 78 vessels were treated: left anterior descending artery (n=40) 65.57%, right coronary artery (n=11) 18.03%, left circumflex artery (n=12) 19.67%. Out of treated lesions (34.4%) were type B2 or C according to ACC/AHA classification. Pre-dilation was performed in (80.32%), mostly with non-compliant balloons and preferring 1:1 balloon-vessel ratio. Total scaffold length and breadth per lesion and per patient were 3.49±2.10 cm and 23.24±5.99 cm. Out of the studied subjects, 42 (68.8%) BVS were post-dilated with noncompliant balloon utilizing high-pressure, progressive and prolonged inflations. Thrombus aspiration was done in 49 patients. Angiographic success was achieved with a TIMI score of 3 in 93% of the cases. TIMI score of 2 was achieved in 4% of the patients (Table 2).

Follow up
vessel and scaffold sizing. Aggressive
and ACS patients requires correct
use of bioresorbable scaffolds in AMI
minimum follow up of 4 years. The
bioresorbable scaffold in AMI with a
reported.
probable thrombotic events were
(59.9%), Prasugrel (20.9%) Ticagrelor
antiplatelet agent was: Clopidogrel
days. At discharge preferred second
of DAPT was 17.57 months and 8
was 8 % respectively. Average duration
Target-vessel myocardial infarction
death occurred in 4 patients (6.5%) (Table 3). Cardiac
Definite probable ScT occurred in 7
TLF occurred in 14 (22.95%) patients.
procedural MACE were reported.

Table 1: Baseline demographics, clinical
data and presentation at time of
hospitalization

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Age (Years)</td>
<td>Mean = 56.68 years</td>
<td>-</td>
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<tr>
<td>Gender ratio (% females: % males)</td>
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<td>Hypertension</td>
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<td>Clinical Presentation</td>
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<td>Non-ST Elevation MI</td>
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<td>AWSTEMI</td>
<td>34</td>
<td>55.73</td>
</tr>
<tr>
<td>STEMI</td>
<td>12</td>
<td>21.31</td>
</tr>
<tr>
<td>Killip Class at Admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>18.03</td>
</tr>
<tr>
<td>II</td>
<td>24</td>
<td>39.34</td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>29.51</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>13.11</td>
</tr>
</tbody>
</table>

| CAD= Coronary Artery Disease , CABC = Coronary Artery Bypass Grafting , MI=Myocardial Infarction , PCI=Percutaneous coronary artery intervention , NSTEMI=Non ST Elevation Myocardial Infarction , STEMI- ST Elevation Myocardial Infarction , AWSTEMI = Anterior Wall ST Elevation Myocardial Infarction , IWSTEMI = Inferior Wall ST Elevation Myocardial Infarction , LVEF= Left Ventricular Ejection Fraction |

The duration of clinical follow-up was minimum 44±16 months. No peri-procedural MACE were reported. TLF occurred in 14 (22.95%) patients. Definite probable ScT occurred in 7 patients (11.47%) (Table 3). Cardiac death occurred in 4 patients (6.5%) after discharge from the hospital. Target-vessel myocardial infarction and target-vessel revascularization was 8 % respectively. Average duration of DAPT was 17.57 months and 8 days. At discharge preferred second antiplatelet agent was: Clopidogrel (59.9%), Prasugrel (20.9%) Ticagrelor (19.2%). DAPT was not discontinued prematurely. 4 cases of definite and probable thrombotic events were reported.

Discussion

Our study reports efficacy of bioresorbable scaffold in AMI with a minimum follow up of 4 years. The use of bioresorbable scaffolds in AMI and ACS patients requires correct vessel and scaffold sizing. Aggressive

Table 2: Procedural and angiographic characteristics

<table>
<thead>
<tr>
<th>Procedural Findings</th>
<th>Number (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Catheterization access radial / femoral (%)</td>
<td>24 / 37 (39.34 / 60.66)</td>
</tr>
<tr>
<td>2. Profile of PCI</td>
<td>3</td>
</tr>
<tr>
<td>Single vessel coronary PCI (%)</td>
<td>48 (78.68)</td>
</tr>
<tr>
<td>Double vessel coronary PCI (%)</td>
<td>9 (14.75)</td>
</tr>
<tr>
<td>Triple vessel coronary PCI (%)</td>
<td>4 (6.55)</td>
</tr>
<tr>
<td>POBA (%)</td>
<td>0</td>
</tr>
<tr>
<td>4. Target Vessel</td>
<td>0</td>
</tr>
<tr>
<td>Left main coronary</td>
<td>0</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>40 (65.57)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>12 (19.67)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>11 (18.03)</td>
</tr>
<tr>
<td>5. Thrombus aspiration</td>
<td>30 (49.18)</td>
</tr>
<tr>
<td>6. TIMI flow grade after procedure</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 (1.63)</td>
</tr>
<tr>
<td>3</td>
<td>2 (3.91)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>37 (93.44)</td>
</tr>
<tr>
<td>7. Coronary Stenting</td>
<td>0</td>
</tr>
<tr>
<td>BMS</td>
<td>0</td>
</tr>
<tr>
<td>DES</td>
<td>3 (4.91)</td>
</tr>
<tr>
<td>POBA</td>
<td>0</td>
</tr>
<tr>
<td>BVS</td>
<td>61 (100)</td>
</tr>
<tr>
<td>8. Procedure Success</td>
<td>60 (98.36)</td>
</tr>
<tr>
<td>Successful PCI</td>
<td>60 (98.36)</td>
</tr>
<tr>
<td>Failed PCI</td>
<td>0</td>
</tr>
<tr>
<td>9. IABP</td>
<td>18 (29.50)</td>
</tr>
<tr>
<td>10. Use of intravasopressors during the procedure</td>
<td>25 (40.98)</td>
</tr>
<tr>
<td>11. AHA/ACC lesion classification</td>
<td>4</td>
</tr>
<tr>
<td>A</td>
<td>14 (22.95)</td>
</tr>
<tr>
<td>B1</td>
<td>16 (26.22)</td>
</tr>
<tr>
<td>B2</td>
<td>8 (13.11)</td>
</tr>
<tr>
<td>C</td>
<td>13 (21.31)</td>
</tr>
<tr>
<td>100 % Thrombotic occlusion</td>
<td>24 (39.34)</td>
</tr>
<tr>
<td>12. In Scaffold Visual Estimate (QCA analysis)</td>
<td>0</td>
</tr>
<tr>
<td>RVD</td>
<td>2.9±0.3 mm</td>
</tr>
<tr>
<td>MLD</td>
<td>3.0±0.4 mm</td>
</tr>
<tr>
<td>DS</td>
<td>0.3±0.1 mm</td>
</tr>
<tr>
<td>13. Lesion Length</td>
<td>22.41±22.4 mm</td>
</tr>
<tr>
<td>14. Pre-dilation</td>
<td>49 (80.32)</td>
</tr>
<tr>
<td>15. Post dilatation</td>
<td>42 (68.78)</td>
</tr>
<tr>
<td>16. Device Name - Absorb</td>
<td>61 (100)</td>
</tr>
<tr>
<td>17. Device length</td>
<td>3.49±2.10 cm</td>
</tr>
<tr>
<td>18. Device Breadth</td>
<td>3.24±5.99 cm</td>
</tr>
<tr>
<td>19. Imaging at Baseline (%)</td>
<td>0.25 (40.98)</td>
</tr>
<tr>
<td>OCT</td>
<td>20 (32.78)</td>
</tr>
</tbody>
</table>

POBA = plain old balloon angioplasty; BMS = bare metal stent; DES = drug eluting stent; BVS = bio absorbable vascular scaffold; IABP = intra-aortic balloon pump; IVUS = intravascular ultrasound; OCT= optical coherence tomography; RVD= mean reference vessel diameter; MLD= Mean Luminal Diameter ; DS= Diameter Stenosis; PCI = percutaneous intervention

lesion preparation increases the rate of successful device delivery and correct expansion, thus pre-dilatation is advisable. However such manoeuvres in ACS carry additional risk of plaque disruption, thrombus mobilization and distal embolism. Hence in highly thrombotic lesions, thrombus aspiration prior to balloon inflation seems mandatory with the patient. In our study thrombus aspiration was done in 49 % and pre-dilatation was performed in 80% of patients.

Vessel sizing is important prior to scaffold placement and optical coherence tomography (OCT) provides precise vessel and lesion measurements, optimal for sizing and positioning and also allows accurate assessment of scaffold apposition after completion of the procedure. In our study OCT and IVUS (intravascular ultrasound) was done in 32% and 42% patients respectively (Figures 3, 4).

Presence of thrombus increases the risk of late scaffold malposition. Post-dilatation, has been sought after step to correct scaffold malposition. Post dilatation was performed in 68% of the cases in our study which is in concurrence to the study that states post-dilatation should be performed with short non-compliant balloons. Scaffold thrombosis (ScT) post implantation might be related to a combination of incompletely embedded and non-absorbed scaffold struts, (predominant amongst the 1st generation scaffolds when implanted in small vessels) and late discontinuity or device dismantling of malapposed struts. The results of our study with a minimum 4 year follow up revealed: ScT was reported in 5 cases (8.1%). Very late stent/scaffold thrombosis was found in 2 cases (3.2%). Cardiac mortality in 4 cases (6.1%) (Table 3). Adopting standardized device implantation technique is key to minimise the incidence of adverse events.

Type of treated lesions (34.42%) were type B2 or C in our study which is lesser than the largest randomized trial (68.7%)20 and the largest real-world registry (53.5%).Our study reported highest number of 100 % thrombotic occlusion in 24(39.34%) patients. The duration of DAPT is potentially associated with the occurrence of late scaffold thrombosis. The AIDA trial investigators recommended continuation of DAPT for all BVS patients until 3 years post index PCI.This recommendation is supported by the results from the DAPT trial: treatment with metallic drug-eluting stents and DAPT beyond 1 year compared with aspirin alone was associated with a significantly reduced risk of stent thrombosis and cardiovascular events. Optimal DAPT duration for patients treated with BVS is unknown and might be challenging to determine given the variation in resorption time in every patient and lesion type. In a large meta-analysis, 92% of the cases of very
late ScT occurred in patients that were not on DAPT at the time of the event.\textsuperscript{15} Average duration of DAPT was 17.5/7 months and 8 days in our study. 60 % of the regular clinical follow up patients are still continuing the DAPT.

**Study limitations**

The main limitations of this study was the small sample size, single center and non-randomized nature. Patient and lesion characteristics could have led to possible biased outcomes. There is paucity in literature for the clear-cut guidelines for placement of BVS devices.

**Conclusions**

Despite high TLR rate as presented in our study of minimum 4 years follow up, we concluded that the implantation of bioresorbable vascular scaffold (BVS) is safe and feasible coronary revascularization alternative in ACS / AMI patient’s. Use of specific device implantation technique is crucial towards success of BVS devices. Advantages of BVS is well documented in terms of their superior ability to maintain the physiological vasomotion. Therefore, the BVS may become a very promising alternative to DES.

**Abbreviations**


**Table 3: Clinical Outcomes at minimum 4 years of follow up**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number (N)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiac Mortality</td>
<td>4</td>
<td>6.56</td>
</tr>
<tr>
<td>2. Target vessel MI</td>
<td>5</td>
<td>8.20</td>
</tr>
<tr>
<td>3. Target lesion revascularization</td>
<td>5</td>
<td>8.20</td>
</tr>
<tr>
<td>4. Target lesion failure</td>
<td>14</td>
<td>22.95</td>
</tr>
<tr>
<td>(Cardiac Mortality+ Target vessel MI+ Ischemia driven Target lesion revascularization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. All other cause mortality</td>
<td>3</td>
<td>4.91</td>
</tr>
<tr>
<td>6. Stent/scaffold thrombosis</td>
<td>5</td>
<td>8.19</td>
</tr>
<tr>
<td>7. Very late Stent/scaffold thrombosis</td>
<td>2</td>
<td>3.27</td>
</tr>
<tr>
<td>8. Primary safety outcomes (Stent/ scaffold thrombosis+ Very late Stent/scaffold thrombosis)</td>
<td>7</td>
<td>11.47</td>
</tr>
<tr>
<td>9. Ventricular arrhythmia</td>
<td>5</td>
<td>8.20</td>
</tr>
<tr>
<td>10. Major or clinically relevant bleeding</td>
<td>3</td>
<td>4.91</td>
</tr>
<tr>
<td>11. Acute renal failure</td>
<td>1</td>
<td>1.63</td>
</tr>
<tr>
<td>12. Stroke</td>
<td>1</td>
<td>1.63</td>
</tr>
</tbody>
</table>

**References**


16. Authors/Task Force m, S. Windeker, P Koh, et al. ESC/EACTS guidelines on myocardial revascularisation: the task force on myocardial revascularisation of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35:2541–2569.


Electronic Gadget Screen-time, Perceived Sleep Quality & Quantity and Academic Performance in Medical Students

Koushik Yeluri1, Kiran HS2*, Basavana Gowdappa H3, Subhash Chandra BJ4

Abstract

Background: Exposure to blue light has been found to affect sleep. Reduced sleep has been found to affect academic performance. However, electronic gadget screen time, sleep quality and quantity and academic performance in undergraduate medical students has not been explored so far. The primary objective of this study was to explore Electronic Gadget Screen time, sleep quality, and sleep quantity and academic performance in Medical students.

Methods: The study was done in JSS Medical College, Mysuru. 400 students from under graduate course were selected through clustered random sampling. Data of electronic gadget usage was collected using a pre-tested proforma. Data of sleep quality, quantity was collected using Pittsburg Sleep Quality Index. Data of academic performance was collected from the marks sheet provided by the college authorities.

Results: Average screen time overall was 5.13 hours per day. On the whole, total Screen time does not have a direct relationship with sleep quantity or quality or academic performance. Rather than the total screen time, bed time gadget use seems to have a more significant relationship with academic performance. A non-significant relationship has been identified between screen time and quality of sleep with a p value= 0.2. Higher academic performance correlated with better sleep quality and better global PSQI scores.

Conclusion: Bed time screen exposure plays a significant role in determining sleep quality, quantity and in turn academic performance.

Introduction

Sleep is a basic necessity for survival. While we sleep, important physiological events take place in the body. The importance of sleep is more pronounced in college students. Memory recall and ability to maintain concentration are much improved when an individual is rested. Prolonged sleep deprivation will affect mood, energy level and ability to focus, concentrate and learn, which directly affects academic performance. Decreased sleep quality has been correlated with having worse academic outcomes and poorer sleep quality.1

Electronic gadgets like laptops, Tablets, PCs, TVs have become an integral part of our modern lives and our work flows. However, these devices emit a spectrum of light. Among the whole spectrum, blue light is the one we are interested in and it has numerous sources. Daylight from the sun is the chief source followed by artificial sources in the form of LED lights, gadget screens. Blue light was found to impact the secretion of melatonin (N-acetyl-5-methoxytryptamine) in the Suprachiasmatic Nucleus.2 Suprachiasmatic nucleus, which keeps signaling throughout the day, influences the pineal gland such that the levels of melatonin keep fluctuating throughout the day.3 Thus production and secretion of melatonin occurs with a clear diurnal pattern. The peaking of melatonin secretion was found to be highest at night.4

Once produced, melatonin circulates through the CSF and Blood stream looking for receptors in target organs like brain, retina, cardiovascular system, liver and gallbladder, colon, skin, kidney.5

This relationship provides information to the body that adjusts peripheral organs to the light-dark cycle. However, as we increase our screen times and hence the exposure to artificial light from the screens exposure to mobile screens delay the onset of sleep and cause sleep displacement.6

Studies looking into the concept of sleep displacement as a 2 step process have also been undertaken where the process has been classified into bedtime, shuteye time.7 However, studies looking into Under Graduate medical students (UG MBBS students) with respect to the above concepts are scanty.

Hence, we carried out this study to assess the effects of screen time on sleep and academic performance in UG medical students. The primary objective was to explore Electronic Gadget Screen-time, sleep quality, sleep quantity in medical students and their association if any.

Subjects and Methods

Institutional Ethics Committee clearance was obtained.

It was a prospective observational study done at JSS Medical College, a premier medical institution attached to JSSAHER in the heritage city of Mysuru, Karnataka state in South India.

The study was carried out over...
are using older android models, were time in iOS and iPad OS”). Those who settings (can be searched as “digital built into their smartphone and tablet identify their “screen on time” that is. Students were demonstrated how to use the app - Digitox: Digital Wellbeing – Screen time.

Data with respect to sleep quality, quantity was collected using Pittsburgh Sleep Quality Index (PSQI). A significant adverse relationship was noted (Figure 2).

Results

The overall reliability coefficient alpha (Cronbach’s alpha) for PSQI was 0.744 which is satisfactory. Total number of participants were 400. However, only 398 were analyzed as there were 2 drop outs from third year who did not return their filled proforma. Hence, 398 proformas were analyzed. Out of the 398 filled proformas, 207 were female and 191 were male. 100 participants were from first year, 98 from second year, 100 from third year, and 100 from final year. 52 subjects from first year were male and 48 were female. 55 subjects from second year were male and 45 were female. 45 subjects from third year were male and 55 were female. 39 subjects from final year were male and 61 were female.

The average screen time recorded overall for all the subjects was 5.13 hours per day. No significant difference was observed between average screen time of male and female subjects. Most commonly used gadget was smart phone. On the whole, total Screen time does not have a direct relationship with sleep quality or quantity or academic performance (Figure 1).

A significant portion of the subjects had the habit of using gadgets before sleep (68.5%). Rather than the total screen time, bed time gadget usage seemed to have a more significant relationship with academic performance. Bed time gadget use had a significant adverse relationship with sleep quality and quantity (Table 1). Perceived quality of sleep and bedtime use of gadget had significant association in the participants who perceived their sleep quality as “Fairly good” and “Fairly Bad” groups whereas in the group with “Very good” sleep quality a reverse relationship was noted. An overall p value <0.0001 was noted (Figure 2).

Bed time gadget use was found to have a significant adverse impact on the time taken to fall asleep (sleep latency). Bed time gadget use had a significant adverse relationship with academic performance of the students (Table 2).

A significant adverse relationship was noted between total screen time and the...
time taken to fall asleep (sleep latency). Sleep latency also carries a significant adverse relationship with academic performance. Increasing global PSQI score had an adverse relationship with academic performance. This proves the importance of sleep with respect to academic performance.

Both total screen time and bed time usage of gadgets was found to influence sleep latency. Bed time usage of gadgets has an impact on the quantity and quality of sleep. Sleep latency and Quality of sleep affects academic performance. Though direct correlation is not evident in the analysis, we can infer that both total screen time and bed time usage of gadgets have a negative impact on sleep latency, sleep quantity and sleep quality which in turn may have a negative impact on academic performance.

Discussion

The objective of this study was to explore electronic gadgets’ screen time and its association with sleep quality, quantity and academic performance in undergraduate medical students. A total of 398 students were part of the study and they were spread across 4 different years during the MBBS course.

Screen time: The average screen time recorded overall for all the subjects was 5.13 hours per day. Average screen time for male subjects was 5.17 hours/day and for female subjects it was 5.09 hours/day. This was significantly higher when compared to the screen time of 2 hours as reported by a similar study done in December, 2017 in Tamil Nadu.1 The first-year medical students had the highest screen time 5.6hrs/day. However, there was no particular trend that was noted among different batches. Most commonly used gadget was the smartphone (100%), followed by laptops (78.7%) and tablets at (42.3%).

Sleep quality: 82 subjects had reported to have very good sleep quality, 219 subjects reported their sleep quality as fairly good, 97 subjects as fairly bad. However according to PSQI grading based on Global PSQI scores, 88.5% of the subjects were found to have poor sleep quality (PSQI >5) and 11.5% had good sleep quality (PSQI <5). This represents a higher fraction of people with poor sleep quality when compared to previous literature.1

Bed time gadget use: More than 2/3rd of the subjects were found to use a gadget within 30 minutes of bed time. This accounts to 273 (68.5%) subjects out of the total 398. There was no significant variation between each year with respect to bed time gadget usage. The highest usage at bed time was seen among 4th years where as lowest was seen in second years.

Screen time and sleep quantity: With respect to screen time and sleep quantity, a negative correlation was noted between total screen time and sleep quantity (Pearson correlation= -0.065). The correlation between the parameters though was not significant (p=0.194). The results from our findings are in contrast to other studies which have found a direct significant correlation between overall screen time and the quantity of sleep.1 Similar findings were noted in American pediatric population where they found a modest impact of screen time on sleep quantity.11 However, once the subjects were grouped according to their duration of screen time, there was a moderately significant relationship between duration of sleep and screen time. Except subjects with >7 hours of sleep, others had an inverse relationship between screen time and duration of sleep with a p value=0.03.

Screen time and academic performance: Screen time did not significantly correlate as a whole with academic performance. This is also in contrast to older studies where it was identified that screen time had directly and negatively correlated with academic performance of the subjects.1,12,13 It had an insignificant correlation with an overall p value=0.325 in our study. We anticipated a positive correlation with academic performance at higher screen times. However, it was not found in our study. This pattern is probably due to the fact that quoted studies being carried out 3 years prior to our study and the increasing prevalence of eBooks which need either a mobile phone, tablet or a laptop to read. This might be an indication of changing trend in the way students read their books and changes in the way gadgets play a role in a student’s life. Interestingly Male subjects had a significant positive correlation between academic performance and screen on time. We were able to identify one study where it was concluded that total screen time has either minimal or no effect on sleep time; however, this study was performed in pediatric population.14

Screen time and quality of sleep: Increasing screen time showed a negative correlation with quality of sleep. The same continued to be true after doing a sub-analysis into various academic years except in final year students, where poorer sleep quality was independent of screen time. However, the correlation in our study was not statistically significant with a p-value=0.2.

Screen time and time taken to fall asleep: Total screen time had a significant correlation with the time taken to fall asleep. The average screen time for subjects needing >30 minutes to fall asleep was 5.58 hours, whereas, those needing <15 minutes was 4.98 hours.

Bed time gadget use and sleep quality: Bed time gadget use was found to be positively correlating with the duration of sleep and the perceived quality of sleep irrespective of gender or the year in MBBS. The overall correlation was highly significant with a p-value=0.0001 for both the quantity and perceived quality of sleep. Similar results have been noted in previous studies where correlation has been noted between the usage of electronic gadgets within 30 minutes, within 1 hour, and the number and types of gadgets used. In pediatric studies, watching TV at bedtime accounted for 30min less sleep.15 This phenomenon is probably secondary to melatonin suppression in response to the blue light from the gadget screens.

Bed time gadget use and time taken to fall asleep: In our study, that time taken to fall asleep was higher in

<table>
<thead>
<tr>
<th>Use of gadget before bed</th>
<th>Time taken to fall asleep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;=15 min</td>
</tr>
<tr>
<td>Not used within 30 min of going to bed</td>
<td>Count</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>103</td>
</tr>
<tr>
<td>Used within 30 min of going to bed</td>
<td>3</td>
</tr>
</tbody>
</table>
subjects who used gadgets at bed time and it carried a significant correlation \( p=0.002 \). The same significant correlation carried forward when analyzed by gender and academic year. This solidifies the previous findings from other studies that bedtime gadget usage is significantly associated with poorer sleep quality and quantity. The probable cause for delay of sleep might be suppression of melatonin secretion, displacement of the sleep by gadget use, psychological arousal resulting from usage of the gadgets. The maximum suppression of melatonin is found to be occurring at shorter wavelengths that correlates with blue light specifically.  \(^{16,17}\) 

**Bed time gadget usage and sleep quantity:** Usage of gadgets at bed time have been found to have a significant impact on duration of sleep with a significant correlation \( p<0.0001 \). Though there were numerous studies in pediatric population measuring bed time gadget usage and sleep quality and quantity, very few studies have been carried out in the adult population. \(^{11,15}\) Here we have found a significant correlation that gadget usage 30 minutes before going to bed has a very significant impact on sleep duration. Even after being sub analyzed by the gender, bed time gadget use continued to have a significant impact on the duration of sleep with those using any form of gadgets within 30min of sleep having lesser sleep duration as compared to those who did not use a gadget. The possible reason being, secondary to a delay in falling asleep, there might be an overall decrease in sleep duration. Generally, the waking up time in most of the individuals is fixed and less likely to be changing due to fixed life style like the need to attend classes in the morning. Hence, going to bed on time becomes even more important. In our study, time taken to fall asleep (sleep latency) was influenced by both total screen time and bed time usage of gadgets, Bed time usage of gadgets had an impact on the quantity and quality of sleep, Sleep latency and Quality of sleep affected academic performance. Though direct correlation is not evident in the analysis, we can infer that both total screen time and bedtime usage have a negative impact on sleep latency, sleep quantity and sleep quality which in turn may have a negative impact on academic performance.

**Strengths and limitations**

This study is one of the few studies undertaken in India and the first from this part of the country that looks at gadget use, sleep quality and quantity, and academic performance in UG Medical students. It included a large sample size and looked at multiple variables like sleep quality and quantity, bed time gadget usage, total screen times and the correlations they had among each other. However, the study was based on self-reporting by the subjects which always carries a bias. Further studies involving higher number of students with a larger sample size and higher number of variables like subjects’ physical activity, BMI scores is desirable. Other variables like accident proneness, substance abuse, sleeping during the classes and performance during practical, anxiety were not included in the study which is also one of the limitations of this study.

**Conclusion**

On the whole, total Screen time does not have a direct relationship with sleep quantity or quality or academic performance. However, total screen time has a negative correlation with academic performance and also on sleep quality in males only. Rather than the total screen time, bed time gadget usage seems to have a more significant relationship with the sleep quality, quantity and academic performance. A significant proportion of the subjects had the habit of using an electronic gadget before sleep (68.5%). Total screen time had a significant negative correlation with the time taken to fall asleep (sleep latency). Bed time gadget use had a significant negative correlation with sleep quality, quantity. Bed time gadget use was found to have a significant negative impact on sleep latency. Bed time gadget use had a significant negative correlation with academic performance. Sleep latency has a significant negative correlation with academic performance. Increasing global PSQI score negatively correlated with academic performance. This study highlights the impact of gadget use and importance of sleep for academic performance.

**References**

Evaluation of Expected Ventilatory Response to Metabolic Acidosis in Severely Ill Patients

Marco Marano¹, Deepak Jain²*, HK Aggarwal³, Francesco Izzo⁴

Abstract

Introduction: Winters’ formula (pCO₂=1.5*HCO₃+8) is used worldwide to predict the ventilatory response to metabolic acidosis, namely to predict the pCO₂ value complying with reduction of serum bicarbonate concentration (HCO₃⁻). This equation was obtained half a century ago in mostly pediatric subjects. Subsequently different and inconsistent rules have been suggested. The study was done to verify the reliability of Winters’ formula in severely ill patients with respect of other modern and commonly used formulas.

Methods: We applied Winters’ formula and some other formulas to a dataset of arterial gas analysis from 29 severely ill malaria patients (about half of them requiring ICU or hemodialysis). The expected pCO₂ value was computed by each formula and the root mean square error (RMSE) was measured. Beyond predicting the expected pCO₂ value, expected range of values was also computed (as expected value ± each own error) and agreement with the best fit equation (± its error) was assessed.

Results: In this dataset featured by metabolic acidosis of moderate degree (mean pH 7.2, mean HCO₃⁻: 15.3 mmol/l) a strong positive linear relationship between pCO₂ and HCO₃⁻ was found (R squared =0.97). The best fit linear equation was in form of pCO₂ = 1.28*HCO₃⁻+11.55. Winters’ formula exhibits the lowest RMSE (1 mmHg) and shows the better agreement (Cohen’s kappa=0.7) with the best fit equation.

Conclusions: Winters’ formula can still profitably used to compute the expected pCO₂ value and in turn to infer mixed (metabolic plus respiratory) acid-base disorders in severely ill patients.

Introduction

Metabolic acidosis is commonly encountered acid-base disturbance in clinical settings. The hallmark is decreased serum bicarbonate concentration (HCO₃⁻) and low pH. As compensatory tool, triggered by low pH and sensed by central chemoreceptors, alveolar ventilation increases and arterial partial pressure of carbon dioxide (pCO₂) decreases, thus alleviating pH derangement. The degree of ventilatory response to metabolic acidosis, namely the amount of pCO₂ reduction was assessed 50 years ago by Winters and coworkers in critically ill patients.¹ They provided the basic formula to compute the expected value of pCO₂ complying with the decreased HCO₃⁻. Although obtained in mostly pediatric subjects and a long time ago, their equation is still relevant worldwide.² However, other researchers suggested different and inconsistent rule-of-thumb serviceable in less severe acidosis.³⁻⁶ Moreover Winters’ formula has been recently associated with high error-in-prediction in cases of metabolic acidosis of small degree.⁶⁻⁷ As recent evidence on performance of Winters’ rule is lacking, we tried to gain further insights on this issue by interrogating gas analysis dataset from patients with severe malaria. It is well known that etiology of the acidosis does not affect the magnitude of the ventilatory response, but degree of severity does, so we looked for patients virtually experiencing moderate to severe metabolic derangement.

Materials and Methods

We retrospectively analyzed data of patients presenting to a tertiary healthcare center Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India fulfilling the modified WHO criteria of severe malaria.⁸ These patients had their blood gas analysis assessment at time of in-hospital admission. Patients older than 18 years with uncomplicated metabolic acidosis were screened from data sheet/records. Inclusion criteria were pH<7.38; HCO₃⁻ < 22 mmol/l and pCO₂ < 38 mmHg according to well-acknowledged rule.² Moreover we selected only patients with arterial oxygen saturation >90% especially to exclude lung failure. Finally, arterial blood gas analysis from 29 severely ill adult patients were analyzed. In this dataset, the relationship between pCO₂ and HCO₃⁻ was evaluated by the best fit equation method and the inaccuracy of the predicted value of pCO₂ in respect of the one actually measured was computed as root mean square error (RMSE). Furthermore, the R squared coefficient of correlation (between pCO₂ and HCO₃⁻) was obtained. Afterwards, some rules found in the literature to compute the pCO₂ value fitting the HCO₃⁻ reduction in metabolic acidosis, were applied and RMSEs pertaining to each formula were computed.

We have tested Winters’ formula that reads pCO₂=1.5*HCO₃⁻+8,¹ the very simple formula (2,6,7) (pCO₂= HCO₃⁻ +15);²,⁶⁷ Fulop’s rule stating that the expected pCO₂ value is equal to the 2-digit numbers to the right of the
pCO\textsubscript{2} value, that is a single number, was requested. The latter rule is written as pCO\textsubscript{2}=(pH-7)*100. Finally, we assessed the common practical rule according to which, the reduction of pCO\textsubscript{2} equals to 1.2 times the reduction of HCO\textsubscript{3}; here, if 24 mmol/l and 40 mmHg are regarded as normal values of HCO\textsubscript{3} and pCO\textsubscript{2} respectively, the expected pCO\textsubscript{2} should be 40 - 1.2*(24 - HCO\textsubscript{3}) and in turn pCO\textsubscript{2} = 1.2*HCO\textsubscript{3}+11.2.\textsuperscript{4,5}

Beside the efforts to have the best equation to compute the expected pCO\textsubscript{2} value, that is a single number, our purpose was also to obtain a pair of values to be regarded as upper and lower limit of the normal ventilatory response to the decreased HCO\textsubscript{3}. In other words, we also looked for the range of pCO\textsubscript{2} values going together with compensatory ventilation rate change. For each formula this range was empirically computed as expected pCO\textsubscript{2} value ± 1 RMSE. Values outside this range were regarded as result of a superimposing respiratory disorder, namely belonging to instances of mixed (metabolic plus respiratory) acid-base disorders. Finally, we assessed Cohen’s kappa agreement between different formulas to label data points as belonging to simple or mixed disorders.

Being the retrospective nature of this study the ethical approval has not been requested.

**Results**

Blood gas analysis data from 29 critically ill patients with severe malaria (mean age 34.7±17.7 years, 17 male) were included in this study. One of these patients died, seven were managed in ICU and 13 needed hemodialysis. As per inclusion criteria, all patients showed metabolic acidosis. Overall, this was in moderate range of severity, the mean HCO\textsubscript{3} was 15.3 mmol/l (SD: 3.2 mmol/l; range: 7.9-20.4 mmol/l). The pH ranged from 7.02 to 7.36 (mean: 7.2; SD: 0.09) and the pCO\textsubscript{2} always below the normal limit (mean: 31.2 mmHg, SD: 4.2 mmHg, ranging from: 21 to 37 mmHg).

The best fit linear equation linking pCO\textsubscript{2} and HCO\textsubscript{3} was found in the form of pCO\textsubscript{2} = 1,28*HCO\textsubscript{3}+11.5 (Figure 1).

![best fit linear equation](image)

**Discussion**

Winters’ formula has been used over half a century to predict the fall of pCO\textsubscript{2} intended to minimize the pH derangement during metabolic acidosis. However, over the years other simple rules have been proposed and validated for this purpose. Remarkably, it has not been emphasized enough that other formulas, can correctly predict the ventilation response along the full range of severity of metabolic acidosis and have no linear equation, like Winters’ formula. This is because of the gradual and progressive, namely nonlinear, engagement of compensatory mechanisms. Bushinsky and coworkers showed that the relationship between pCO\textsubscript{2} and HCO\textsubscript{3} is curvilinear.\textsuperscript{3} This notwithstanding they were able to report three linear approximations,
each valid to predict the ventilatory response to definite reductions of HCO₃⁻: the more severe the metabolic acidosis and the higher the slope of the linear equation. Accordingly, the key point in investigating the ventilatory response to metabolic acidosis is the amount of HCO₃⁻ reduction or, in other words, the degree of severity of acidosis, whatever is the cause of acidosis.

Study population in Winters’ group was featured by metabolic acidosis of severe degree: mean HCO₃⁻ was close to 10 mmol/l and all values were below 16 mmol/l. In a recent study of metabolic acidosis with HCO₃⁻ close to 10 mmol/l, the magnitude of ventilatory response was similar. But one cannot assume that Winters’ formula works well in patients with less severe acidosis or, in other words, it cannot be regarded as always and anywhere valid rule, as is currently considered.

In most of dialysis patients investigated in the recent decades, the degree of severity of acidosis was mild with HCO₃⁻ closer to 20 mmol/l rather than to 10 mmol/l. In this population, rules other than Winters’ formula are more effective: the common practical rule - a linear equation with slope of 1.2 - runs better and the very simple formula, having slope equal to 1, works just as well.

In general population, authoritative literature states that the secondary ventilation response to metabolic acidosis has to be computed by means of the common practical rule and by using a generous limit of ± 5 mmHg of CO₂, which is a suggestion from the clinical practice and has not been experimentally validated.

As an original line of research, Fulop investigated the chance of computing the expected pCO₂ value from the pH number. In a large series of patients with HCO₃⁻ slightly over 10 mmol/l, his two digit rule was able to correctly predict pCO₂ only in the half of instances, although he also resorted to the wide range of ± 5 mmHg. Indeed, efficacy of this rule is poor. Overall, many different and inconsistent rules exist and it is unclear which rule should be used. In addition, suitability of Winters’ formula surprisingly seems to be undermined.

With purpose to gain further insight in this field, we selected severely ill patients with Malaria aiming to mirror Winters’ analysis. In these patients parasitized erythrocytes pack the microcirculation and impair oxygen delivery. Anaerobic glycolysis leads to lactic acidosis with multi-organ involvement. Renal tubular injury and kidney failure further contribute to metabolic acidosis whose severity strongly affects the morbidity and mortality rates. However, despite the adverse clinical outcomes featuring our population, the degree of acidosis was not as severe as in Winters’ population and had moderate to severe acidosis.

In these patients, the best fit linear equation looks like to the common practical rule, virtually sharing the same slope (Table 2), but equations’ similarity doesn’t allow to select the best formula and errors pertaining to different formulas must be checked. Thus, Winters’ formula - associated with the lowest error (Table 1) - turned out to be the best formula to rule out superimposed respiratory disorders in the patients with not so severe acidosis also.

As a further point of investigation, we also looked for the lower and the higher limit of compensation, at which mixed disorders occur. Winters’ and coworkers estimated these as 2 standard errors (SE) above and below the expected pCO₂ value (in that case SE=1.11 mmHg) leading to 4.4 mmHg range. Supporters of the common practical rule empirically defined such limits as ±5 mmHg leading to a wider range of 10 mmHg. More recently, one of this study’s author, reported a 6.7 mmHg range associated with both the common practical rule and the very simple formula by using 2 RMSEs, instead of empirical numbers.

In the present investigation many efforts have been made to build a dataset of pure, uncomplicated, metabolic acidosis, indeed pCO₂ and HCO₃⁻ were strongly related with R squared approaching the unit. The RMSE associated with Winters’ formula was exactly 1 mmHg, which, besides being an useful clinical threshold, corresponds to a very low error. By using two RMSEs upon and below the expected pCO₂ value, the range pertaining to uncomplicated metabolic acidosis amounted to 4 mmHg, the narrowest ever found.

We also assessed the agreement between different formulas (± each own RMSE) to rule out respiratory acid-base disorders. As shown in Table 2, Winters’ formula was featured by the highest agreement with the best fit equation.

In conclusion, although obtained a long time ago, Winters’ formula still profitably allows to predict both the expected pCO₂ value and the range of pCO₂ values pertaining to uncomplicated metabolic acidosis. Hence, this formula seems suitable to rule out respiratory acid-base disorders superimposing metabolic acidosis.

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Evaluation of Vascular Health of E-Beta Thalassemia Patients: Effect of Iron Overload

Dibyendu De1*, Uttam Kumar Nath2, Prantar Chakrabarti3

Abstract
Hb E-β thalassemia is the most common form of hemoglobinopathy in Southeast Asia and eastern India. Iron overload resulting from blood transfusion and increased intestinal iron absorption promotes the formation of reactive oxygen species (ROS), leading to oxidative stress, organ dysfunction, and tissue damage. Of these, cardiovascular complications are the leading cause of mortality. Impaired endothelial function is a biomarker of vascular health in patients with cardiovascular risks. Therefore, assessment of endothelial function is a useful prognostic tool. In the present study, 60 E-β thalassemia patients and 60 healthy, age, sex matched control subjects were taken. The mean hemoglobin and ferritin of thalassemic patients were 7.43gm/dl and 1032 mcg/dl respectively. The vascular health was compared by measuring flow-mediated vasodilation (FMD), arterial elastic parameters, and carotid intima-medial thickness (CIMT). There was lower FMD (7.49%) and higher CIMT (0.46mm) in thalassemic group than control (10.52 % and 0.36mm respectively) (p value< 0.05). Also arterial stiffness is elevated and arterial distensibility is lower in thalassemic patients than control. Among the thalassemic patients FMD or CIMT did not correlate with serum ferritin value. So, the E-β thalassemia patients had poor vascular health and are at a higher risk of developing atherosclerosis and cardio-vascular complication than normal population. The vascular dysfunction does not correlate with serum ferritin value, so regular monitoring with Doppler study is required for early diagnosis of subclinical atherosclerosis in this group of patients. However the effects of chelation therapy, Hydroxyurea, or other targeted therapies needs to be validated by further study.

Introduction
Thalassemia is a most common genetic disorder of haemoglobin, first described by Cooley and Lee1 in 1925, in which there is quantitative deficiency of one or more globin chain. In India, about 10 % population is either affected or carrier of thalassemia, the commonest form in Eastern India being E-β thalassemia. A large population study in Eastern India showed prevalence of β (beta) thalassemia trait 4.60%, Hb E trait 3.02% and Eβ thalassemia as 1.16%.2

Accumulation of iron, resulting from blood transfusion and increased intestinal iron absorption in Thalassemia, promotes the formation of reactive oxygen species (ROS), which leads to oxidative stress, organ dysfunction, and tissue damage.3 Of these, cardiovascular complications are the leading cause of mortality. Hyper-coagulaibility, thrombo-embolic complications and early and subclinical arterial atherosclerosis have now become major cause of morbidity in these patients. Impaired endothelial function is an important biomarker for these changes in patients with cardiovascular risks.4 Therefore, assessment of endothelial function is a useful prognostic tool.

Effective ways to diagnose hidden subclinical atherosclerosis, and early vasomotor dysfunction and determining its risk factor may help in reducing the emergence of vascular complications in thalassemic patients. Identification of such target for therapy along-with comprehensive thalassemic care with optimal transfusion and good chelation therapy may help in further prolongation of morbidity free life for thalassemic patients.

Aim and Objectives
In this study, we aimed to determine the presence of vasomotor dysfunction and subclinical atherosclerosis in patients of E β thalassemia in eastern Indian population. We also studied the relationship of serum ferritin and other parameters with vasomotor dysfunction.

Materials and Method
This is a Hospital based prospective, observational and analytical study. 60 E- β thalassemia patients, who attended the Thalassemia Clinic of Department of Hematology, were included in the study and baseline parameters and iron status were measured. 60 healthy non hypertensive, non diabetic, non smoker, age sex matched control subjects were also taken. The exclusion criteria were age ≥ 55 year for male and ≥ 65 year for female, patients having overt heart failure (Left Ventricular Ejection fraction < 55%), presence of congenital heart disease, hypertension(SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg), overt Diabetes (FBS ≥ 126 mg/dl or PPBS ≥ 200 mg/dl), severe pulmonary hypertension (Pulmonary Arterial Systolic Pressure ≥ 55mm Hg), active infection, active neoplasm, patient on any vaso active, antihypertensive drugs, any history of smoking.

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Flow Mediated Vasodilatation (FMV)

Flow Mediated Vasodilatation (FMV) was assessed on the brachial artery by ultrasonography. Any drug known to affect endothelial function, including nitrates, hypolipidaemic drugs, and aspirin was withdrawn ≥ 1 week before examination. The measurements were performed in supine position on the right arm after 10-20 minutes resting in a quite room. The brachial artery was scanned longitudinally just above the antecubital crease using a 10 MHz transducer probe in hp Agilent machine (Netherlands), by experienced sonographer in the department of radiology. The diameter of the brachial artery was measured at the time of systolic flow of blood observed by Doppler, on the interface between the media and adventitia of the anterior and posterior wall. Hyperaemia was induced by inflation of a pneumatic cuff [Blood Pressure measuring instrument sphygmanometer was used] at 230-250 mm of Hg for four minutes on the most proximal portion of the upper arm. The arterial diameter measurement was repeated 45-60 seconds after sudden deflation of the cuff. The average of the three measurements of basilar (before occlusion by pneumatic cuff) and post-hyperaemia (after occlusion by pneumatic cuff) diameter was used for the analysis. FMV was expressed as the relative increase in brachial artery diameter during hyperaemia, and defined as - [(post-hyperaemia diameter - basilar diameter) / basilar diameter] x 100.

It is expressed as percentage value.

Carotid Intima Medial Thickness (CIMT)

For measurement of Carotid Intima Medial Thickness (CIMT), ultra sound imaging of both common carotid arteries up to their bifurcation, the carotid bulb, as well as proximal 10 mm of internal carotid artery of both sides was done. Presence of any intimal plaques is searched. Plaque was defined as a focal structure encroaching into the arterial lumen at least 0.5mm or 50% of the surrounding IMT. Sites with intimal plaques are avoided during measurement of CIMT. The distance between the boundaries of lumen-intima and media-adventitia interfaces at the far wall of the common carotid arteries were measured. Mean values of CIMT of three sites of a particular side are taken for calculation of CIMT of that side. Mean values of CIMT of both sides is calculated.

Arterial Elastic Properties

For measurement of arterial elastic properties, arterial diameters were obtained by two dimensional-guided M-mode tracing in Common Carotid Arteries. Diameters were measured as the distance between the trailing edge of the anterior arterial wall and the leading edge of the posterior arterial wall. The systolic diameter (As) was measured at the time of maximum diameter whereas the diastolic diameter (Ad) was measured at time of minimum diameter. Both diameters were indexed to body surface area. Five consecutive cycles were measured and averaged.

Blood pressure was measured simultaneously at the brachial artery using the same mercury sphygmanomanometer in all cases. Pulse pressure (PP) was calculated as systolic minus Diastolic blood pressure. (PP=SBP-DBP)

Subsequently, the following indexes of aortic elastic properties were calculated:

\[\text{i. Arterial Strain (AS)} = \frac{100 \times (A_s - A_d)}{A_d}\%\]
\[\text{ii. Arterial Distensibility (AD) = } 2 \times \frac{(A_s - A_d)}{PP} \times A_d \times 10^4\]
\[\text{iii. Arterial Stiffness Index (ASI) = } \ln(\text{SBP/DBP})\]
\[\frac{(A_s - A_d)}{A_d}\]

Analysis of Data

Data are presented as Mean ± Standard Deviation for continuously distributed variables, and in absolute numbers and percentages for the discrete variables. Independent sample Student’s t-test was performed to compare parametric variables. The nonparametric variables were compared using chi-square test. P value < 0.05 considered statistically significant.

The subgroup analysis was done among the patients of E-beta Thalassemia. The patients were divided into two groups of low and high iron load, using cut off values of serum ferritin as 1000 ng/ml. The other subgroup analysis was done according to splenectomy status and according to the transfusion requirement i.e. regular transfusion group (requiring > 4 unit PRBC per year), vs occasional transfusion group (requiring ≤ 4 unit PRBC per year). The data were stored and analyzed statistically using Microsoft® Excel 2002 and SPSS ver. 19.0.

Results

The mean age of the E-beta thalassemia patients was 22.87 years, and 56% of them were male. The mean age of diagnosis was 8 years and average requirement of transfusion was 8 units PRBC per year. About 31.67% patients underwent splenectomy for increased transfusion requirement and mean age of splenectomy. About 50% patients were receiving iron chelation, and 80% patients were on Hydroxyurea therapy as HB-F inducer.

The clinical, laboratory, iron status and vascular function parameters of E-β thalassemia patients and control group are shown in Table 1. The E-β thalassemia patients were having higher prevalence of endothelial dysfunction as evidenced by decreased flow mediated vasodilatation (FMD), [7.92% vs 10.53%, p value<0.05]. The derived parameters of arterial elastic properties, such as arterial strain, arterial distensibility were also decreased while arterial stiffness index was increased in the E-β thalassemia patients. The study also showed a higher prevalence of subclinical atherosclerosis in the same cohort, measured in terms of increased carotid intima medial thickness [0.5mm in E-β thalassemia patients compared to 0.36mm in healthy volunteer, p value<0.05]. The serum ferritin values were predictively lower in control group than in E-β thalassemia patients (138.18 ng/ml vs 1032.5 ng/ml).

However, when E-β thalassemia patients were analysed by dividing them into different ferritin level subgroups, the FMD or CIMT values were not significantly different between those groups. Also Arterial Strain, Distensibility or Stiffness Index did not show any significant differences among the different groups of iron overload (Table 2).

When the splenectomised patients were compared with non splenectomised one, the FMD was lower, and CIMT was higher in splenectomised patients, signifying poor vascular health for splenectomised thalassemics. Also Arterial Strain and Distensibility were lower and Stiffness Index was higher in splenectomised patients. But these
Changes did not assume statistical significance (p value > 0.05) (Figure 1).

Comparing the vasomotor functions of E-β thalassemia patients, between those who were on regular transfusion (requiring > 4 unit PRBC per year) with those who required occasional transfusion (requiring ≤ 4 unit PRBC per year), revealed that the patients on occasional transfusion were having poor vascular health (lower FMD, and increased IMT) though only differences in substrates inpatients with high and low serum ferritin

### Discussion

Impaired FMD and increased IMT reflect early functional and structural abnormalities of vascular endothelium leading to atherosclerosis and are thus accepted as surrogate indicators of an increased cardiovascular risk.\(^4, 5\)

In 1981, Sullivan\(^6\) first proposed that iron load was one of the risk factors for early atherosclerosis. Also studies in hereditary hemochromatosis showed that impaired endothelial function and increased IMT are associated with iron overload, with subsequent induction of oxidative stress.\(^7\) The existence of arterial dysfunction in homozygous β-thalassemia has previously been reported by different authors (Cheung et al, 2002; Aggeli et al, 2005; Ulger et al, 2006; Gedikli et al, 2007).\(^8-14\) Similar studies in patients of E-β thalassemia are scanty. Our study corroborates with the previous study findings of impaired endothelial function and early subclinical atherosclerosis in patients of thalassemia.

Decreased nitric oxide bioavailability causes endothelial dysfunction. In patients of hypertension it has been suggested to be due to oxidant-mediated inactivation of endothelial nitric oxide bioactivity generated by NAD(P)H oxidases, xanthine oxidase, and nitric oxide synthase.\(^15, 16\) whereas in hemolytic disorders, release of cell-free hemoglobin into the plasma suggested to cause rapid nitric oxide scavenging and contribute to endothelial dysfunction.\(^17\)

The importance of the findings lies in the pathogenesis of cardiac failure in thalassemia. Overt cardiovascular and liver damage is usually apparent when thalassemia patients are in the third decade of life.\(^19\) Although CHF is the main cause of death; thromboembolic episodes, stroke, and myocardial infarction are also common in E-β thalassemia. Apart from myocardial iron deposition,\(^19\) myocarditis\(^20\) and immune profile,\(^21\) arterial dysfunction also contributes to the pathogenesis of cardiac failure. Endothelial dysfunction is, at least, partly reversible with appropriate treatment. Hence, early detection has important diagnostic and prognostic value.\(^21\)

The present study did not show any difference in endothelial function among E-β thalassemia patients with iron overload status. The literature shows mixed result regarding the same. Few studies\(^10, 22\) disclosed positive correlation between carotid IMT and serum ferritin in patients with β thalassemia; while other studies did not show the same.\(^8, 23, 24\) The enhanced inflammatory process, along with secretion of cytokines and TNF-α by inflammatory cells in presence of ineffective erythroipoisis in patients
of E-β thalassemia is more important than direct iron toxicity. Aphi

The study also had few confounding factors, like Hydroxyurea therapy as Hb-F inducer, which also has rheological effect. Hydroxyurea enhances NO and cGMP production through PKA-mediated stimulation of eNOS in endothelial cells, thereby can improve endothelial function. Also, chelation therapies, given to all thalassemic patients, are not uniform. Few patients, with very high ferritin value, were receiving double chelation. Cheung et al observed deferasirox can improve arterial function in thalassemia major. Because of small number of total patients in the present study, further sub-group analysis of these effects could not be done.

This study also revealed that splenectomy had a detrimental effect regarding vascular health, though no statistical significance could be drawn. It is well established in various previous studies, that Splenectomy increases thrombotic risk, and pulmonary hypertension in E-β thalassemia, but no previous studies have specifically looked for endothelial dysfunction in these group of patients. With splenectomy, not only nucleated RBC with altered membrane properties, but also the increased platelets microparticles are associated with increased inflammatory process leading to endothelial dysfunction.

The present study also showed that patients with regular transfusion had better endothelial functions. These patients had suppressed erythropoietic activity and lesser degrees of ineffective erythropoiesis, leading to less number of circulating monocytes and sticky RBCs. Therefore severity of endothelial dysfunction was also less.

Conclusion

Thus the study attempts to provide an insight into the vascular health of E-β thalassemia patients. The E beta thalassemics have increased endothelial dysfunction as well as subclinical atherosclerotic changes. Regular transfusion decreases the risk, whereas splenectomy increases the risk of endothelial dysfunction. However to identify the effects of chelation therapy, Hydroxyurea, or other targeted therapy, further study with large double blinded, properly randomized study design with follow up study is required.

References

RESULTS OF THE ELECTION OF THE ASSOCIATION OF PHYSICIANS OF INDIA, PHYSICIANS RESEARCH FOUNDATION AND INDIAN COLLEGE OF PHYSICIANS

The election results of the Office Bearers and Members of the Governing Body of the Association of Physicians of India, Elected Board Members of Physicians Research Foundation and Officer Bearers and Members of the Faculty Council of Indian College of Physicians 2022 – 2024.

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Association of Sarcopenia with Health Related Quality of Life in Cirrhotics

Neehar Shanavas¹, Krishnadas Devadas², Nibin Nahaz¹, Jijo Varghese¹*, Rathan Cyriac¹, David Mathew¹

Abstract

Background & Objectives: Sarcopenia is one of the most common complication associated with mortality in cirrhotic patients. However, the lack of an objective and reliable method to quantify muscle mass has limited the general incorporation of sarcopenia into cirrhosis prognostic scores. In this article, we highlight cross-sectional imaging-based estimation of skeletal muscle mass for diagnosing sarcopenia in cirrhotic patients and its effect on health related quality of life.

Methods: After getting ethical clearance and informed consent, all patients with cirrhosis were taken and assessed for sarcopenia using thigh muscle based index. The average feather index was used in conjunction with BMI in determining the probability of sarcopenia. The CLDQ was used to assess the health related quality of life. The chi-square and Pearson’s coefficient were used for analyzing correlation between sarcopenia and other variables.

Results & Discussion: In our study, out of the 288 patients, sarcopenia was present in 132 patients (45.83%). Sarcopenia was present in 18.2% in CHILD A, 42.4% in CHILD B and 90.5% in CHILD C cirrhotics. Sarcopenia was highest in autoimmune hepatitis related cirrhosis (80%), followed by NASH (61.9%), followed by ethanol (42.4%), followed by HCV (28.5%) and HBV (16.6%). Sarcopenia had a moderate negative correlation with health related Quality of life as assessed by CLDQ particularly in relation with systemic symptoms and activity.

Conclusion: The factors like high MELD, CHILD C cirrhosis, NASH as etiology, were associated with higher prevalence of sarcopenia. NASH related cirrhosis have high prevalence of sarcopenia even in CHILD A patients. The patients with sarcopenia were having a low overall quality of life as per CLDQ, especially in specific aspects related to systemic symptoms and activity.

Introduction

CHILD and MELD scores are the most widely used prognostic factors for cirrhosis. Apart from mortality, cirrhosis also significantly affects the quality of life. Malnourishment is one serious complication of cirrhosis which affect the functional status of patients. One indicator of malnourishment is sarcopenia. The role of sarcopenia in predicting mortality is also well established.

Despite the importance of HRQoL in patients with cirrhosis, studies in this aspect is largely lacking. The measures of Health related Quality of life are two self-administered questionnaires: the Medical Outcomes Study Short Form 36 (SF-36) and the Chronic Liver Disease Questionnaire (CLDQ), a validated liver disease specific questionnaire. CLDQ is a liver disease-specific HRQOL questionnaire that consists of 29 items divided into six domains.

Sarcopenia is generally defined as a reduction in muscle mass to a value two standard deviations below that of healthy young adult mean.

EWGSOP consensus definition for sarcopenia is:

- Low muscle mass, (e.g. >2 standard deviations below that mean measured in young adults [aged 18–39 years in the 3rd NHANES population] of the same sex and ethnic background).

And either:

- Low gait speed (e.g. a walking speed below 0.8 m/s in the 4-m walking test)
- Low muscular strength (e.g. grip strength: <30 kg in males, <20 kg in females)

Severe sarcopenia requires all three conditions.

The study ‘Clinical relevance of sarcopenia in patients with cirrhosis’ by AldoJMontanoLoza concluded that Sarcopenia affects the quality of life, survival and the development of the complications in cirrhosis. Inclusion of sarcopenia into prognostic scores is limited by lack of dependable methods to quantify muscle wasting. CT scan or MRI are the gold standard tools to quantify sarcopenia.

Cross-sectional imaging can expose patients to high levels of ionizing radiation. A study by Tandon P et al developed a model for predicting sarcopenia based on Thigh muscle thickness and BMI. When compared to measures of nutritional assessment like SGA, MAMC, MAC, hand-grip strength, BMI, and serum albumin, thigh muscle ultrasound (average feather index) had the strongest association with sarcopenia in patients with cirrhosis, when cross-sectional imaging was used as the gold standard. The average feather index was associated with a significantly less inter-observer variability than a corresponding compression assessment.

A systematic review and meta-analysis by GaeunKim et al suggested that sarcopenia is an important prognostic factor, independent of MELD and CTP scores. MELD score remains strongly associated with...
AIDS, stage 4, 5 CKD, severe COPD, cardiac failure with Ejection fraction less than 40 % and neuromuscular disorders were excluded. Nutritional assessment was done with anthropometric measurements including height, weight, BMI, mid arm circumference(MAC), mid arm muscle circumference(MAMC), mid arm muscle area(MAMA), hand grip (HG) with jamar dynamometer.

Sarcopenia was diagnosed using a combination of BMI and the novel measure of thigh muscle thickness, a model to identify sarcopenia based on sex specific nomograms developed by Tandon et al.13 The right thigh muscle thickness was measured using the ultrasound machine (Mindray). Measurement points were marked at ⅓ and ⅔ of the total distance from the top of the patella to the iliac crest. Two readings were obtained from each point: (i) a compression reading taken by pressing the probe downwards until no further compression of the muscles was possible; and, (ii) a featherweight reading was obtained when the probe was held without pressure on the two points. Measurements at both points were corrected and averaged for stature (divided by square of height) to obtain an average compression index and an average feather index. Sex specific normograms is there for detection of sarcopenia. It contains points for Average feather index and BMI. When the points for BMI and average feather index are added together, it gives points and an estimated probability of sarcopenia. Patients whose probability of sarcopenia was more than 80% was detected to be having sarcopenia.

Every patient wasasked to fill CLDQ for quality of life assessment. CLDQ consists of 29 items grouped into 6 domains, which has been validated for liver disease by Ferrer et al.14,15

The six domains included abdominal symptoms (items 1, 5, 17), fatigue (items 2, 4, 8, 11, 13), activity (items 3, 6, 21, 23, 27), systemic symptoms (items 3, 6, 21, 23, 27), emotional function (items 10, 12, 15, 16, 19, 20, 24, 26) and worry (items 18, 22, 25, 28, 29). A Likert scale response format was used for all items ranging from 1 (most impairment) to 7 (least impairment). Scoring of the questionnaire was done by dividing each domain score by the number of items per domain.16 Overall CLDQ score was obtained by adding scores for each item in the domain and dividing it by the total number of items (n=29). The CLDQ score was classed as low (<4) or high (4–6).

**Statistical Analysis**

All the data was analysed by SPSS version 25.0 software (SPSS, inc, chicago, IL, USA).The correlation between Sarcopenia and qualitative variables were analysed by chi-square correlation. The correlation between Sarcopenia and quantitative variables were analysed by Pearson’s correlation.

**Results**

310 patients were taken up for the study out of which 22 patients were excluded due to incomplete data and 288 patients outcome were taken up for the analysis. There were 60 females and 228 males.104 (36.1%) patients had alcoholic liver disease, 48 patients (16.7%) HBV, 28 (9.7%) patients HCV, 84 patients (29.2%) NASH, 20 patients (6.9%) Autoimmune hepatitis and 4 patients (1.4%) were having Wilson’s disease. 88(30.6%) had Child A cirrhosis 116 (40.3%) Child B cirrhosis and 84 (29.2%) Child C cirrhosis. Patients were equally distributed among all CHILD classes.

Out of the 288 patients included, sarcopenia was present in 132 (45.83%). 108(47.3%) of the 228 male patients and 24 (40%)of the 60 female patients had sarcopenia. 80% (16 patients out of 20) of AIH disease related cirrhosis had sarcopenia. Prevalence of sarcopenia was higher in NASH related cirrhosis, 61.9% (52 patients out of 84) and ethanol related cirrhosis, 42.4% (44 patients out of 104) when compared to HCV related cirrhosis, 28.5 % (8 patients out of 28) and HBV 16.6 % (8 patients out of 48). In Wilson’s disease related cirrhosis 100% of patients were having sarcopenia. But there were only 4 patients in the Wilson’s disease arm.

Among various CHILD classes, 90.5% (76 out of the 88 patients) CHILD C cirrhotic patients had sarcopenia whereas 34.5% (40 out of the 112 patients) of CHILD B cirrhotos and 18.2% (16 out of the 88 patients) of CHILD A cirrhotic patients were sarcopenic. Among CHILD A, 14 out of this 16 CHILD A cirrhosis had NASH related cirrhosis. NASH related cirrhosis were more likely to be sarcopenicat a earlier stage of cirrhosis. Higher MELD patients (MELD >15)
Table 2: Distribution of sarcopenia in study population

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Frequency</th>
<th>Percentage (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>108</td>
<td>47.3</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>AIH</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>Ethanol</td>
<td>44</td>
<td>42.4</td>
</tr>
<tr>
<td>HBV</td>
<td>8</td>
<td>16.6</td>
</tr>
<tr>
<td>HCV</td>
<td>8</td>
<td>28.5</td>
</tr>
<tr>
<td>NASH</td>
<td>52</td>
<td>61.9</td>
</tr>
<tr>
<td>Wilson</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Underweight</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Preobese</td>
<td>20</td>
<td>27.7</td>
</tr>
<tr>
<td>Obese</td>
<td>80</td>
<td>51.2</td>
</tr>
<tr>
<td>Child A</td>
<td>16</td>
<td>18.2</td>
</tr>
<tr>
<td>B</td>
<td>40</td>
<td>35.7</td>
</tr>
<tr>
<td>C</td>
<td>76</td>
<td>90.5</td>
</tr>
<tr>
<td>MELD &gt;15</td>
<td>92</td>
<td>63.8</td>
</tr>
<tr>
<td>=15</td>
<td>40</td>
<td>27.7</td>
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Table 3: Prevalence of sarcopenia in various etiologies and distribution according to CHILD status

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
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<tbody>
<tr>
<td>Sarcopenia</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AIH</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Alcohol</td>
<td>19</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>HBV</td>
<td>28</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>HCV</td>
<td>7</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>NASH</td>
<td>15</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Wilson</td>
<td>0</td>
<td>0</td>
<td>0</td>
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Table 4: Correlation Between sarcopenia and various determinants by pearson's coefficient

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Pearson's Coefficient</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age</td>
<td>0.042</td>
<td>0.474</td>
</tr>
<tr>
<td>CLDQ Abdominal symptoms</td>
<td>0.195</td>
<td>0.342</td>
</tr>
<tr>
<td>CLDQ Systemic symptoms</td>
<td>-0.272</td>
<td>0.026</td>
</tr>
<tr>
<td>CLDQ Fatigue</td>
<td>-0.064</td>
<td>0.009</td>
</tr>
<tr>
<td>CLDQ Activity</td>
<td>-0.258</td>
<td>0.002</td>
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<tr>
<td>CLDQ Worry</td>
<td>0.139</td>
<td>0.218</td>
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<tr>
<td>CLDQ Emotion</td>
<td>-0.067</td>
<td>0.255</td>
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<tr>
<td>CLDQ Overall</td>
<td>-0.129</td>
<td>0.028</td>
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<tr>
<td>MAMA</td>
<td>-0.45</td>
<td>0.004</td>
</tr>
<tr>
<td>Hand grip dominant</td>
<td>-0.638</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>0.115</td>
<td>0.052</td>
</tr>
<tr>
<td>MELD</td>
<td>0.573</td>
<td>0.023</td>
</tr>
<tr>
<td>MELD Na</td>
<td>0.505</td>
<td>0.023</td>
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Table 5: Correlation between sarcopenia and various determinants by Chi square analysis

<table>
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<tr>
<th>Determinant</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Child A</td>
<td>9.02</td>
<td>0.035</td>
</tr>
<tr>
<td>B</td>
<td>10.080</td>
<td>0.002</td>
</tr>
<tr>
<td>C</td>
<td>95.199</td>
<td>0.001</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.815</td>
<td>0.391</td>
</tr>
<tr>
<td>NASH</td>
<td>12.338</td>
<td>0.001</td>
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</table>

In our study other measures of Sarcopenia like MAMA was found to have strong negative correlation with sarcopenia (pearsoncoefficient of -0.45, p value of 0.004). Dominant hand grip also had a strong negative correlation (pearsoncoefficient of -0.638, p value of 0.003). It was found that BMI had a weak positive correlation with sarcopenia (pearsoncoefficient of 0.115 with a p value of 0.052), MELD has a positive correlation (pearsoncoefficient of 0.573 with a p value of 0.023) and MELD Na has a positive correlation (pearsoncoefficient of 0.505 with a p value of 0.023).

The Health related quality of life was analysed using the CLDQ. The overall quality of life by overall CLDQ score had a negative weak correlation (r=-0.129) which was statistically significant, suggesting that patients with sarcopenia were having a low overall quality of life. Among the various domains of the CLDQ, score related to Systemic symptoms (r=-0.272 p value of), and activity (r=0.258) were having a significant moderate negative correlation with sarcopenia. Whereas scores related to fatigue, Abdominal symptoms, Emotion and Worry did not have a significant correlation.

The correlation between sarcopenia and CHILD class was analysed. The prevalence of sarcopenia in CHILD A was 18.2% and CHILD B was 34.5% and CHILD C was 18.2 %. When analysed by chi-square test, Increasing CHILD status was a significant risk factor for developing sarcopenia.

Among the various etiologies analysed, prevalence of sarcopenia in NASH related Cirrhosis was 61.9%. When analysed by chi-square test, NASH, was an independent risk factor. However alcohol was not a significant risk factor for development of sarcopenia even though 40% had sarcopenia.

Discussion

In a systematic review and meta-analysis, Gauem Kim et al screened around 312 studies and 20 studies were included for the analysis and found out that 48.1% patients were having sarcopenia and among males it was 61.6% and among females it was 36%. In our study sarcopenia was present in 33 patients (45.8%), with 47.3 % males and 40 % females having sarcopenia. In our study,100% of Patients with wilson disease cirrhosis was (4 patients), followed by autoimmune hepatitis (80%), followed by NAFLD (61.9%), followed by ethanol (42.4%), followed by HCV (28.5%) and HBV (16.6%). All the Wilson disease patients and most patients with Autoimmune hepatitis had CHILD C cirrhosis. This and the small number of patients may be the reason for such high prevalence for sarcopenia. HBV and HCV patients had a lower prevalence. This could be due to the fact that patients may have taken or are on treatment. Among the common etiologies, NASH was an independent risk factor for sarcopenia. In the study” Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis” Koo BK et al found that the prevalence of sarcopenia in subjects without NAFLD, with non-alcoholic fatty liver (NAFL), and with NASH were 8.7%, 17.9%, and 35.0%, respectively (p<0.001). In our study 14 out of total 16 CHILD A patients with sarcopenia had NASH related cirrhosis. The early development of sarcopenia among NAFLD patients may be linked to sarcopenic obesity. Study on Sarcopenia in patients with advanced liver disease by Ponziani FR et al found out that sarcopenia was found in 70% of advanced cirrhosis. We found that 90.5% of CHILD C cirrhotic patients had sarcopenia. In CHILD B cirrhotic patients 35.5% were having sarcopenia. The CHILD A cirrhotic patients were having the least sarcopenia of 18.2%. Increase in CHILD status is associated with a greater loss in muscle mass. CHILD score is also a determinant of Quality of life as it encompasses encephalopathy and ascites. The correlation between CHILD and Sarcopenia further emphasize the significance of sarcopenia as a marker of Health related quality of life. MELD(r=0.573) and MELD Na(r=0.505) scores also correlated strongly with Sarcopenia. The correlation with MELD thus signifies the role of sarcopenia as a prognostic indicator for mortality. A recent study showed that modification of MELD score by adding objective measure of sarcopenia like Total psoas area is associated with a modest improvement in the prediction of mortality in patients with cirrhosis.

Previous studies has used MELD sarcopenia with total psoas muscle...
area for prognosticating the need for liver transplantation. We had used sarcopenia measured by Average feather index and BMI according to Tandon P et al model, since it is easy to perform, reproducible and does not have any radiation hazard.

CLDQ is a liver disease-specific HRQoL questionnaire that consists of 29 items divided into six domains: 1) abdominal symptoms, 2) activity, 3) emotional function, 4) fatigue, 5) systemic symptoms, and 6) worry. Summary scores for each domain range from 1 denoting most impairment to 7 denoting least impairment. An overall score ranging from 1 to 7 may denoting least impairment. An overall CLDQ overall was having a weak negative correlation(r=-0.129) with sarcopenia. But, among the various domains of the CLDQ score related to Systemic symptoms than QoL as a whole.

The overall quality of life by CLDQ overall was having a weak negative correlation(r=-0.129) with sarcopenia. But, among the various domains of the CLDQ score related to Systemic symptoms (r=-0.272), and activity(r=-0.258) were having a moderate negative correlation with sarcopenia and was statistically significant. Whereas scores related to fatigue, Abdominal symptoms, Emotion and Worry were not correlated well negatively or had a very weak positive correlation. Thus the presence of sarcopenia has got effect on specific aspects on health related quality of life like those related to activity and systemic symptoms than QoL as a whole.

**Conclusion**

In conclusion it is found that sarcopenia is very common among cirrhotic patients and it significantly impairs their overall health related quality of life. The health related Quality of life particularly related to the systemic symptoms and activity were more affected by the presence of sarcopenia. Patients with NASH related cirrhosis had a higher prevalence of sarcopenia than alcoholic cirrhosis. NASH related cirrhosis patients were having sarcopenia even at an earlier stage of cirrhosis.

Thigh muscle ultrasound could be used for measuring sarcopenia as it is a low cost, easily available, reliable and reproducible measure of muscle mass that can be completed at the bedside or in a clinic setting and can be repeated without concern of radiation exposure. While there is still much to be defined, quantification of skeletal muscle mass sheds light on the prognostic role of sarcopenia and it may help for further development of prognostic models incorporating sarcopenia. Large prospective studies are required to validate the prognostic implication of sarcopenia in addition to conventional prognostic system.

**References**

### KEY PARAMETERS of Combination

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<th>Parameter</th>
<th>Allegra-M (Fexofenadine + Montelukast)</th>
<th>Levocetirizine + Montelukast</th>
<th>Bilastine + Montelukast</th>
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<td>Bioequivalence published data¹⁴</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Synergistic effect¹³,⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>HTH efficacy data in Indian patients⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>HTH efficacy (TNSS)⁴</td>
<td>92.5%</td>
<td>85.6%</td>
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<tr>
<td>HTH safety data (Sedation)⁴</td>
<td>9.6%</td>
<td>23.2%</td>
<td>No HTH data</td>
</tr>
</tbody>
</table>

References:
1. Walekar A, Chodankar D, Nazir M, Trivedi C: Assessment of Bioequivalence of Fexofenadine and Montelukast Fixed Dose Combination Tablet Versus Separate Formulations of the Individual Components at the Same Dose Levels. Indian journal of pharmaceutical sciences, 2016, 78(5), 651-656
2. This dissolution study compares Allegra-M, Allegra, Singular and one Fexofenadine + Montelukast fixed dose combination available as a monolayered tablet in India. Data on File, 2012 (b)
3. Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivitis and mild-to-moderate asthma. The SKY study, 2019

Hypertension in Young Adults in India: Perspectives and Therapeutic Options amongst Clinician’s in a Cross Sectional Observational Study

Uday Jadhav1*, Mangesh Tiwaskar2, Aziz Khan3, BC Kalmath4, JPS Sawhney5, MP Tripathy7, PK Hazra8, PK Sahoo9, SN Routray10, Sharad Chandra11, Thomas Alexander12, VK Chopra13

Abstract

Background: The prevalence of hypertension in the young adult population is rising in India. Increased arterial stiffness due to RAAS activation and increased sympathetic overactivity due to stress have been implicated as primary factors for the same. This study was aimed to understand the Indian clinician’s perspective on approach to management of hypertension in young adults.

Methods: A cross sectional observational survey using a structured questionnaire was conducted online with 2287 clinicians (cardiologists, diabetologists, consultant physicians and family physicians).

Results: The prevalence of hypertension was 10-30% as per opinion of 64.8% clinicians. The top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity. Around 57.4% respondents opined that both increased heart rate and systolic blood pressure were markers of sympathetic overactivity. More than 60% respondents across specialities preferred ARBs to treat hypertension in young adults. Amongst the ARBs, telmisartan was the preferred ARB by >80% respondents. Metoprolol was the preferred beta blocker by almost 64% respondents. The objective of selection of beta-blocker by majority of clinicians due to sympathetic overactivity. Telmisartan and Metoprolol single pill combination achieved the BP goal in 40-60% of patients as reported by 41.3% of the physicians. The combination therapy was well tolerated in young hypertensive patients.

Conclusions: Initiation of an early and appropriate antihypertensive treatment in young population may lower the burden of cardiovascular disease in this population. ARBs and beta-blockers were the preferred class of anti-hypertensive drugs in the cohort of young hypertensive patients.

Introduction

Hypertension among young people is common, affecting 1 in 8 adults aged between 20 and 40 years.1 This number is expected to escalate with lifestyle behaviours and lowering of hypertension diagnostic thresholds to SBP/DBP of 130/80 mm Hg. Young adults with hypertension before the age of 40 years are at a high risk of developing cardiovascular events.2 Results of the analyses conducted in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study indicated that stage 2 hypertension before age 40 years was associated with a significantly higher risk of all-cause mortality.3 The prevalence of hypertension in India has been reported to be as high as 25% to 42%.4,5 Hypertension in the south east Asian region, India accounts for more than two-third of mortality.4 Cardiovascular disease is observed to occur at a younger age in Indians resulting in impaired health and productivity. The prevalence of hypertension was high even among young age individuals as observed in the hypertension epidemiological study conducted in India.7 The European hypertension guidelines have identified the South Asian population across ages to be the highest risk category and is considered to be most vulnerable to the consequences of increased blood pressure (BP).8 Hypertension escalates the risk of premature death and reduces work productivity. While hypertension is considered to be a silent disease, loss of work days can accrue with the onset of complications associated with hypertension such as ischemic heart disease.

None of the guidelines address the cohort of young hypertensives, a growing concern in India. Given the high burden of risk factors for hypertension in the cohort of young individuals, India must focus on increasing awareness of hypertension and advocating healthy BP levels for its citizens through early and effective intervention with lifestyle modification and drugs. Fortuitously, there are plenty of opportunities for intervention in the long road leading to cardiovascular disease (CVD). Indians stand to benefit immensely if early and appropriate intervention is instituted to control blood pressure in young people.
adults. In the absence of guidelines and good-quality studies, Indian clinicians will have to lead the war against hypertension in young adults based on their clinical experience. The current study is based on the experience of Indian clinicians to lead the way for effective management of hypertension in young adults in India.

The ACD algorithm has been proposed by various guidelines for the treatment of hypertension. The first line options being Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) when ACEIs are not tolerated, Calcium channel blockers (CCBs) and diuretics such as thiazide diuretics.9,10

One of the classes of drugs not accorded due respect is the beta-blockers. In fact, beta-blockers has the potential to have a special place in the management of hypertension in young adults in India because sympathetic over-activity is one of the factors implicated in the development of hypertension. The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines and Indian hypertension guidelines recommend that that beta-blockers be used when there is a specific indication for their use (e.g. angina, post-myocardial infarction, heart failure with reduced ejection fraction [HFrEF], or when heart rate control is required).9,10

Method

A cross-sectional observational survey using a structured questionnaire for hypertension in young was conducted online. The respondents included doctors like cardiologists, diabetologists, consultant physicians, and family physicians across the five zones of India (North, South, East, West, and Central). The survey questionnaire was developed by a panel of experts treating hypertension. The 14 item questionnaire were all forced-choice, with multiple-choice response options. The survey was quite straight forward and ensured a uniform mode of reporting. Study participants were interacted after receiving data whether they faced any other difficulty or bias.

The questionnaire included important aspects related to hypertension in young adults namely: prevalence of hypertension in young observed in real world setting, rating of key risk factors contributing to hypertension in young, parameters for deciding sympathetic overactivity (increased heart rate, increased systolic blood pressure), preferred class of antihypertensive drugs including preferred drug in the class and preferred beta-blocker used to treat hypertension in the young against the backdrop of sympathetic overactivity, understand whether sympathetic overactivity was the reason to choose a beta-blocker in the regimen of antihypertensives, the reason for use of beta-blockers in spite of them not being mentioned in any current guidelines, real world insights upon telmisartan/metoprolol single pill combination therapy.

Data were collected using the pre-designed questionnaire by trained medical personnel. The questionnaire did not contain any questions that revealed the identity of the patients treated by the physicians. The subgroup analysis of the responses was conducted based on the specialty of the respondents (cardiologists, diabetologists, consultant physicians and family physicians), years of experience of the respondents (less than or equal to 5 years, 6-10 years, 11-15 years, 16-20 years and more than 20 years) and zonal differences in prevalence and treatment approaches. Descriptive statistics, namely chi-square test was then run to test the associations among knowledge, awareness and practice among the respondents across India.

Results

Two thousand two hundred eighty seven doctors participated in the survey. Prevalence of more than 30% was reported by 14.6% clinicians, 20-30% by 28.6% clinicians, 10-20% by 36.2% clinicians, 5-10% by 18.4% clinicians and less than 5% by 2% clinicians.

Prevalence of hypertension in young adults of more than 20% was reported by 46.8%, 44.1% and 43.1% of cardiologists, diabetologists and consultant physicians respectively, while less than 10% was reported by 38% of family physicians.

The zonal analysis of the prevalence of hypertension indicated that the 10-20% prevalence of hypertension was highest in the east zone (43.2%) while prevalence of 20-30% was reported to be 44.1% in the central zone. The prevalence of hypertension in young adults of 10-30% was reported in the range of 63-66% by clinicians irrespective of years of experience (Table 1).

The top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity. The other risk factors were high salt intake, increased alcohol intake, sedentary lifestyle, and lack of adequate sleep (less than 7 hours) (Figure 1). Survey participant doctors

| Table 1: Prevalence of hypertension in young adults |
|---|---|---|---|---|---|
| **Overall Prevalence (n= 2287)** | < 5% | 5-10% | 10 – 20% | 20 – 30% | >30% |
| Speciality | | | | | |
| Cardiologists (n= 469) | 1.9 | 13.9 | 37.3 | 30.1 | 16.8 |
| Diabetologists (n=281) | 1.8 | 13.9 | 40.2* | 24.9 | 19.2 |
| Consultant physicians (n=1458) | 1.8 | 20.0 | 35.1* | 29.4 | 13.7 |
| Family physicians (n=79) | 7.6 | 30.4* | 35.4 * | 19.0 | 7.6 |
| Zone | | | | | |
| North(n = 455) | 3.1 | 31.4 | 30.6 | 21.5 | 13.4 |
| South (n = 758) | 2.1 | 16.5 | 38 | 28.0 | 15.4 |
| Central(n = 177) | 1.7 | 15.2 | 19.2 | 44.1* | 19.8 |
| East(n = 368) | 1.1 | 10.3 | 43.2* | 32.9 | 12.5 |
| West(n = 529) | 1.7 | 16.5 | 39.3* | 27.6 | 14.9 |
| Experience | | | | | |
| ≤ 5 years(n = 229) | 3.1 | 18.8 | 37.5* | 26.6 | 14.0 |
| 6 -10 years(n = 473) | 2.8 | 16.9 | 33.4 | 30.2 | 16.7 |
| 11-15 years(n = 424) | 2.2 | 19.1 | 37 | 27.8 | 13.9 |
| 16 -20 years(n = 365) | 1.4 | 17.3 | 37.8* | 27.9 | 15.6 |
| >20 years (n = 796) | 1.8 | 19.0 | 36.3 | 29.0 | 13.9 |

* P = 0.001 intra group comparison.
in the East Zone rated mental stress, obesity and extra salt in diet as top three risk factors followed by smoking. Parameters of sympathetic overactivity in young hypertensive patients were considered as only increased systolic blood pressure, only increased heart rate and both increased heart rate and increased systolic blood pressure by 15.1%, 24.2% and 57.4% of respondents respectively. A similar opinion was chronicled across specialties (Figure 2).

ARBs (61.6%) were considered the most appropriate class of drugs to treat hypertension in young patients (Figure 3). Beta-blockers were preferred by 15.8% respondents, followed by calcium channel blockers, diuretics and ACEI by 10.4%, 7.6% and 4.6% respondents respectively. Family physicians preferred diuretics as second choice after ARBs. 65.7% cardiologists preferred ARBs, while 61.2%, 61%, and 49.4% were the preference for ARBs chronicled with diabetologists, consultant physicians, and family physicians respectively. The highest preference for ARBs was reported in the east zone (72%) while the central zone, west zone, north zone and south zone registered a preference for ARBs ranging from 56.5% to 62.4% (Table 2).

Among the ARBs, telmisartan was preferred by almost 86% of respondents, while olmesartan, losartan and azilsartan were preferred by 6.5%, 2.5% and 0.7% clinicians respectively. About 4.3% of respondents showed no preference for specific ARB (Table 2). Telmisartan was the unanimous choice amongst the class of ARBs by cardiologists (89.3%), diabetologists (88.6%), consultant physicians (84.6%), and family physicians (82.3%). 93.8% clinicians in the east zone preferred telmisartan. A similar preference for telmisartan was reflected in the subgroup analysis of the choice of ARBs based on the experience of the clinicians participating in the survey.

About 62.9% of respondents were strong proponents of beta-blocker in young hypertensive patients. Of these, 68.7% cardiologists, 59% diabetologists, 61.9% consultant physicians and 62% family physicians preferred beta blockers in young hypertensive patients.

74.5% of clinicians across India selected beta-blockers as a part of the antihypertensive regimen in young hypertensive adults based on the rationale of sympathetic overactivity. In the class of beta-blockers, metoprolol (63.1%) was the preferred beta-blocker for the management of hypertension in the young (Table 3).

Combination therapy of telmisartan and metoprolol was preferred by 15.5%, 40.9%, 43.6% clinicians in young hypertension, uncontrolled hypertension, both young and uncontrolled hypertension patients respectively.

SBP reduction of 10-20 mmHg was observed in patients after the use of telmisartan/metoprolol single pill combination by 63.6% of the study investigators, while 20.1% of the
investigators observed > 20 mmHg SBP reduction. 41.3% of the respondents reported that 40-60% of patients achieved the goal BP with telmisartan/metoprolol single pill combination, while about 30.2% of respondents observed that 60-80% of patients achieved the goal BP (Figure 4).

Telmisartan/metoprolol single pill combination was well tolerated in young hypertensive patients according to the 79.4% of the study physicians. 83.3% of cardiologists agreed that combination therapy was well tolerated in young hypertensive patients which were significantly more as compared to observations made by other respondents.

**Discussion**

The high burden of risk factors for hypertension has resulted in an increasing prevalence of hypertension in the young adult population of India. The current all India survey brings forth the practice of Indian physicians treating hypertension in young Indians. Hypertension has been reported in 12.1% of young adults in the cross-sectional, nationally representative, population-based study by Geldsetzer P, et al. In the current study the prevalence of hypertension...
in young adults was observed in up to 30% and corroborate the earlier reported prevalence statistics. 

In the current survey, the top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity across India. In young adults in India, the substantial consumption of soft drinks has resulted in increased obesity and cardio-metabolic risk factors. Inappropriate nutrition affects different anthropometric parameters and has a tremendous impact on the blood pressure levels even during young age either directly or indirectly. Higher intakes of fat, saturated fat, a predilection for salty, fried, oily, sweet, and fast food and higher sedentary activity levels and lower sleep duration have been implicated in the development of obesity in young Indians. Prevalence of smoking in India has been reported to be as high as 28%. Even stress is a common feature amongst the young adult population.

Evaluating the underlying pathogenic features will help choose the appropriate treatment options for hypertension in young adults. In hypertension, the structure and function of the arterial wall are postulated to be altered at an early stage resulting in increased arterial stiffness. Increased arterial stiffness is an important risk marker of CVD. An abnormal collagen overproduction and diminished quantities of normal elastin contribute to vascular stiffness. Local renin-angiotensin-aldosterone system (RAAS) activation contributes to the development of arterial stiffness. The reduced arterial compliance may be one mechanism whereby the increased activity of the RAAS produces adverse vascular effects. This results in increased ventricular afterload and decreased coronary perfusion pressure leading to left ventricular hypertrophy (LVH) and subendocardial ischemia. Hence the approach to the management of hypertension in the young adults must not only aim at lowering the blood pressure, but must also aim to prevent progression or reverse the process of arterial stiffness and thus reduce the risk of CVD. ARBs and ACEI have been demonstrated to decrease arterial stiffness. The appropriate treatment of hypertension in young can result in reduced morbidity and mortality. The current evidence corroborates the choice of ARBs for the management of hypertension in young adults by 61.1% clinicians involved in the survey.

In the current survey, 86% of respondents reported telmisartan to be the preferred ARB. Telmisartan displays unique pharmacologic properties, such as the highest affinity for the AT1 receptors, longer half-life than any other ARB resulting in sustained reductions of blood pressure. Telmisartan regresses left ventricular hypertrophy, reduces arterial stiffness, and confers renoprotection. Telmisartan may also reduce vascular inflammatory change. Additionally, telmisartan modulates peroxisome proliferator-activated receptor γ (PPARγ), and thus modulates insulin resistance, diabetes, and metabolic syndrome. PPARγ activation enhances the production of adiponectin resulting in anti-inflammatory, anti-oxidative, and anti-proliferative effects exerted on the vascular walls, thus lowering the risks for atherosclerosis and cardiovascular disease. This current evidence of the unique features of telmisartan corroborates the choice of telmisartan as the preferred ARB by Indian physicians.

Telmisartan is the first ARB to demonstrate cardiovascular (CV) prevention in patients at high CV risk. The ONTARGET trial demonstrated that telmisartan effectively reduced CV morbidity (including myocardial infarction and stroke) and mortality in a wide range of patients at increased CV risk. In the TRANSCEND study, the reductions in risk for CV death, myocardial infarction, and stroke were 35%, 14%, and 19%, respectively.

In addition to providing 24-hour blood pressure control, clinical studies in patients with diabetes show that telmisartan improves renal endothelial function, prevents progression from microalbuminuria to macroalbuminuria, slows the decline in glomerular filtration rate and reduces proteinuria in overt nephropathy. Telmisartan offers a superior reduction in proteinuria as compared to losartan.

A considerable body of evidence relates sympathetic overactivity with high sodium intake, obesity, and hyperinsulinemia of obesity and mental stress. Smoking too is associated with an increase in plasma catecholamines related to adrenergic stimulation. The sympathetic neural function plays an important role in blood pressure regulation, and overactivity of sympathetic nerves may play an important role in the development of hypertension, LVH, and related cardiovascular disorders. Sympathetic vasoconstriction decreases glucose uptake in skeletal muscle and leads to insulin resistance and compensatory hyperinsulinemia. In the early stages of hypertension, particularly in young patients, there is marked adrenergic overdrive leading to the development of essential hypertension.

The prevalence of sympathetic overactivity in newly diagnosed hypertensive patients in India has been reported to be about 62.42%. Six out of ten newly diagnosed hypertensive patients in India have sympathetic overactivity. Chronically raised sympathetic nerve activity, independent of blood pressure, is a powerful predictor of myocardial infarction. The beta-1 blockade is effective in regressing and stabilizing coronary atheromatous plaque is effective in reducing the adverse effects of the raised sympathetic activity.

In our survey, the reported prevalence of sympathetic overactivity was reported to be about 74.5%. Hence, 62.9% respondents said that they were strong proponents of beta blocker in hypertension patients. 63.1% respondents preferred metoprolol as the beta blocker for their young patients with hypertension.

Metoprolol is a cardioselective beta-1-adrenergic receptor inhibitor. Metoprolol in adult competitively blocks beta-1 receptors with minimal or no effects on beta-2 receptors. Metoprolol significantly lowers the heart rate. The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial specifically showed a benefit of metoprolol over diuretics regarding sudden cardiac death as well as myocardial infarction.

Combination therapy has been proven to improve blood pressure control and more patients reach target blood pressure faster. A dose-escalation approach using monotherapy reduces coronary events by 29% and cerebrovascular events by 40%, while combining two antihypertensive agents with a different mechanism of action reduces coronary events by...
40% and cerebrovascular events by 54%. Hence the use of combination therapy offers greater target organ protection than increasing the dose of monotherapy. Cardiologists have been observed to prefer beta-blockers as initial antihypertensive drugs in the real-world setting in other countries and metoprolol is amongst the most commonly prescribed drug.

In the current all India survey, the preference for telmisartan and metoprolol in their respective classes paves the way for the use of combination therapy in young adults with hypertension in India. The use of combination therapy will depend on the grade of hypertension of the individual patient.

**Limitation**

This survey included urban, semi-urban areas and it does not reflect practice in rural India. Besides, the use of the purposive sampling technique may represent a confounding element. The survey only reflects clinician perception and does not reflect actual patient data. Real world studies and prospective trials in young patient’s hypertension will throw more light on the practice trend.

The perception and choice of class of drug for treating young patients with hypertension is based on the respondent’s individual opinion. Considering the uniformity of opinion amongst the specialty of varying experience in patient care, this perception can encourage further prospective studies. To overcome this limitation, it will be more prudent to collect the blood samples of young subjects with hypertension and analyze it for various biochemical parameters such as cytokines, anti-oxidants, NO, catecholamine and acetylcholine. This will lead to a better understanding of the pathobiology of hypertension in the young and correlate these findings to the response shown by the study population to various class of drugs used.

**Conclusion**

The data accrued from evaluation of practice pattern followed by clinicians across India for the management of hypertension in young adults will help institute an early and appropriate antihypertensive treatment in this population and may perhaps lower the burden of cardiovascular disease in this population in coming years. Amongst the current classes of drugs, ARBs and beta –blockers have been preferred by the clinicians who participated in the survey. Combination of telmisartan and metoprolol as a prototype of the respective anti-hypertensive class was preferred in the survey. ARBs are preferable and in the survey majority of Indian physicians seem to prefer telmisartan.

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Risk Stratification for Asymptomatic Coronary Artery Disease in patients with Type II Diabetes Mellitus

Lekha Adik Pathak1*, Ronak V Ruparelia2, Krishna K Bhadiadra3

Abstract
There is strong correlation between coronary artery disease (CAD) and Type II Diabetes Mellitus (T2DM). This can be attributed to early atherosclerosis in diabetic subset as compared to non-diabetic population. However, owing to neuropathy and other metabolic milieu, which exists in patients with diabetes mellitus, many patients present late to the health care for atherosclerosis and its complications. CAD being one of the commonest complication of atherosclerosis process, it comprises a huge number of patients suffering from T2DM. And many such patients are asymptomatic for longer period of time. Here in this review we will discuss about importance of various risk factors and their roles in detecting subclinical atherosclerosis and silent ischemia in asymptomatic patients with diabetes. We will also discuss about various imaging modalities and their role in asymptomatic CAD patients with T2DM.

Introduction
Diabetes mellitus (DM) is a chronic metabolic disorder defined by presence of hyperglycemia and/or insulin resistance. DM can be classified as type 1 diabetes mellitus or type 2 diabetes mellitus based on baseline pathology. The 2016 Global World Health Organization (WHO) report of Diabetes estimated a worldwide adult diabetes prevalence in 422 millions of individuals in 2014, rising from 4.7% in 1980 to 8.5% in 2014.1 As per International Diabetes Federation, rates of diabetes are increasing worldwide. And the estimated number of people living with diabetes will reach the number of 642 million by 2040.2

Diabetes Mellitus and Coronary Artery Disease
Multiple risk factors are found to be associated with DM that leads to development of coronary artery disease (CAD). These risk factors are dyslipidemia, hyperglycemia, hypertension, kidney failure and overweight. Owing to these risk factors, diabetics are prone to have various vascular complications ranging from microvascular (renal, retinal and neuropathic) to macrovascular (coronary artery and cerebral arteries).3 Apart from classical risk factors for CAD, several other factors like increased oxidative stress, increased coagulability, low grade inflammation, endothelial dysfunction and autonomic neuropathy are often present in patients with DM and contribute directly to development of CAD.

The risk of CAD increases two to four fold in diabetics as compared to non-diabetics.4 Diabetics have accelerated atherothrombosis as well as early onset of atherosclerosis.5 6 The atherosclerosis related to DM is more diffuse, more extensive, more complex and rapidly progressive as compared to non-diabetics. As a result, coronary angiogram in a diabetic is more often complex multivessel CAD.

Pathophysiology
Long standing hyperglycemia induces inflammation in the vessel wall, promoting atherothrombosis and abnormal vascular findings (e.g. earlier onset, higher degree, and more disseminated and aggressive) are much more common in diabetics compared with individuals without diabetes.7 Impaired fibrinolytic system balance and abnormalities of platelet structure and function results in a persistent prothrombotic milieu.8 Various adverse effects induced by hyperglycemia are as follows:

- A. Metabolic factors: Endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids and increased systemic inflammation.
- B. Vascular anatomic characters: More frequent diffuse disease, higher prevalence of extensive CAD, left main disease and multivessel disease. The narrow calibre vessels are associated with impaired collateral development.
- C. Adverse prothrombotic milieu and high atherosclerotic burden: Diabetics have a higher atherosclerotic burden and plaques, which are high risk and vulnerable to rupture.9 Proteofibrinolytic system and platelet biology are also unfavourably altered in diabetes.

The degree of pathophysiological changes varies from person to person amongst diabetics. Hence the clinical presentation varies from asymptomatic to stable angina and acute coronary syndrome (ACS) which includes unstable angina, STEMI and non-STEMI.10

Diabetes Mellitus: A CAD Risk Equivalent ??

Diabetics have 2 to 4 times increased risk of cardiovascular morbidity and mortality11 than non-diabetics. The NCEP (National Cholesterol Education Program) as well as guidelines from Europe considered T2DM as CAD equivalent, and considered it as the highest risk category.12 13 This recommendation was based upon
the observation that patients with “T2DM without a prior MI (Myocardial Infarction)” were at the same risk for MI (20 and 19 percent, respectively) and coronary mortality (15 versus 16 percent) as compared to patients “without DM with prior MI”.

Recent studies indicate that CAD risk in T2DM is not universally similar amongst various diabetic subsets. A meta-analysis of 13 epidemiological studies observed that the CAD risk in T2DM patients without prior CAD was 43% lower than individuals without diabetes with a prior MI. In a large population-based cohort, the CAD risk was much lower among T2DM without CAD than in non-diabetic patients with prior CAD (HR 1.70 vs. 2.80). In another meta-analysis, cardiovascular risk was evaluated through coronary artery calcium score (CAC) at baseline. The study revealed a 28.5% prevalence of diabetic patients with zero CAC scores, indicating a similar 5-year survival rate as in patients without diabetes.

So a significant part of patients amongst diabetics exists in lower CAD risk category, especially men less than 35 years of age, women less than 45 years of age and patients with diabetes duration of less than 10 years without other risk factors. While in the presence of traditional risk factors or evidence of subclinical coronary disease (e.g. high coronary calcium score), the coronary risk is much increased and patients may be classified at a higher risk category.

This is in contrast to older studies considering all diabetics as a “CAD risk equivalent”. Currently, 2016 ACC/AHA guidelines, 2013 ADA standard of diabetes care and the 2016 European Society of Cardiology (ESC) no longer consider diabetes a a coronary risk equivalent.

The ACC/AHA guidelines recommends stratification for patients with diabetes into 2 risk categories. Diabetics younger than 40 years with shorter duration of diabetes are defined as lower risk category. This categorization allows recognition of those who might benefit more from intensive cardiovascular interventions, intensive statin or aspirin prevention, while avoiding overtreatment in lower risk cases. It also allow the clinician to decide whether to intensify risk reduction actions through specific newer drugs for glucose control such as SGLT-2 inhibitors or GLP-1 agonists, which recently have shown additional cardiovascular protector effect.

How to identify Asymptomatic Diabetic patients at high risk for CAD

Silent myocardial ischemia is defined as the presence of objective evidence of myocardial ischemia in the absence of chest discomfort or another anginal equivalent symptom. The goal of risk stratification is to protect the patient from subsequent serious coronary events. The available screening tests can be divided into invasive (coronary angiography) and non-invasive tests. Non-invasive tests are preferred over invasive tests owing to its simplicity and cost effectiveness. Various non-invasive tests are described in Table 1.

Screening for CAD should be distinguished from the risk stratification. Both are performed in asymptomatic persons, and both aim to improve outcomes with interventions, if indicated. However, screening identifies existing disease, while risk stratification determines the likelihood of a person suffering from any future event of CAD. In the largest study conducted to date (Detection of Ischemia in Asymptomatic Diabetics (DIAD study)), 1123 T2DM patients without CAD symptoms at baseline were randomized to receive an adenosine rMPI, compared to no screening. After a mean follow-up of 4.8 years, there was

### Table 1: Screening methods for detecting asymptomatic coronary artery disease in patients with diabetes

<table>
<thead>
<tr>
<th>Screening methods</th>
<th>Detection of prevalent CHD</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Low sensitivity and specificity</td>
<td>Widely available, very low cost</td>
<td></td>
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<tr>
<td>Moderate sensitivity</td>
<td>Relatively low cost, widely available</td>
<td></td>
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<tr>
<td>Moderate to high cost</td>
<td>Widely available</td>
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<tr>
<td>High sensitivity for myocardial viability studies</td>
<td>Better image quality because of higher spatial resolution, less scattered, and fewer attenuation artifacts.</td>
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no significant difference in the primary endpoint (cardiac death or nonfatal MI) between the screening and no-screening groups. Similarly, DYNAMIT (Do You Need to Assess Myocardial Ischemia in Type-2 diabetes), a smaller study of 631 asymptomatic patients with T2DM and at least two other CAD risk factors randomized patients to either screening with rMPI (with symptom-limited bicycle exercise or dipyridamole SPECT) or no screening. The prevalence of silent myocardial ischaemia was found to be 21.5%, similar to the DIAD study. After a mean follow-up of 3.5 years, there was no significant difference in the composite primary endpoint (death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring emergency intervention) between the screening and the non-screening group.

Sensitivity and Specificity of a test are the core requirements while considering any test for risk stratification. In addition, whether the information gained from the study lead to additional testing and/or a significant difference in the composite primary endpoint (death from all causes, nonfatal MI, nonfatal stroke, or heart failure requiring emergency intervention) between the screening and the no-screening group.

Various approaches for Risk stratification of CAD in Diabetics

1. Age: It is the strongest non-modifiable risk factor for CAD. A large population based retrospective cohort study26 defined the relation between age and various risk categories for CAD in diabetics. Transition from low to moderate risk category occurred at 35 and 45 years while the transition to high risk category occurred at 48 and 54 years for men and women respectively.

2. Gender: In general population, the incidence of new MI is higher in men than in women.27 While in patients with diabetes, the men to women ratio is much narrower. And when considering the mortality rate from coronary causes, women with diabetes are at a higher risk than men. A meta-analysis27 observed that the relative risk for fatal CAD was greater among women in patients with and without diabetes. This was probably due to a less favourable cardiovascular risk profile in women linked to hypertension and hyperlipidemia. The presumed reduced likelihood of women receiving the standard treatment for acute coronary syndrome and cardiovascular prevention is also important.

3. Family History: The Women’s health study28 studied postmenopausal women with diabetes without CAD. The study observed that the incidence of CAD in those with at least 1 first degree relative with CAD was 50% higher while it was 79% higher in those with 2 or more affected first degree relatives. In the MESA study29 positive family history considered an independent risk factor and performed better than ankle brachial index, c reactive protein and flow mediated dilation. The ACC/AHA 2013 guidelines30 recommend to consider family history of premature CAD as a major risk factor defined as male <55 years and female <65 years in any first degree relative.

4. Smoking: It is one of the most important reversible risk factor for CAD. Active smoking is associated with the highest risk of total mortality and cardiovascular events, while smoking cessation reduces both mortality and cardiovascular events in diabetics. The incidence of acute MI increases six-fold in women and three-fold in men who smoke at least 20 cigarettes per day.31 Active smoking was associated with more than 50% increase in mortality and CV events.

5. Hypertension: Hypertension is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) and microvascular complications. A recent meta-analysis32 observed that for each 10-mmHg lowering in SBP there was a significant lowering in risk for mortality, cardiovascular events, coronary artery disease and stroke.

6. Long duration and early onset of diabetes: Patients with diabetes duration longer than 10 years are considered at increased risk.16 Diagnosis of diabetes at an early age is an additional risk independently of diabetes duration. In a large cross-sectional survey,33 using data from the China National HbA1c Surveillance System (CNHSS), observed higher risk in the group with earlier onset of T2DM.

7. Obstructive sleep apnea (OSA): OSA is associated with an increased incidence of fatal MI.34,35 Diabetics are at high risk of OSA and should be questioned for symptoms, which may warrant further investigation and treatment.

8. History of other atherosclerotic vascular diseases: Clinical history (transient ischemic attack, mesenteric ischemia, or claudication) and physical examination (for bruits and peripheral pulses) is important to determine the presence of vascular diseases. Atherosclerotic diseases involving lower extremity, cerebral, renal or mesenteric arteries identifies a patient with diabetes who is at increased risk for CAD.35 A diminished ankle-brachial index is a sensitive indicator.
of increased risk for future CVD events. In patients with claudication or asymptomatic peripheral arterial disease, 90% of deaths are attributable to CAD.

B. Laboratory work up

1. Blood lipids: Dyslipidemia is associated with cardiovascular morbidity and mortality. MERFIT study, in pre-statin era showed that the absolute adjusted risk of CAD death, stratified by cholesterol level was several times higher in diabetics than in non-diabetics. The Cholesterol Treatment Trialists’ (CTT) Collaborators meta-analysis observed that reducing LDL-c by 1 mmol/l with a statin reduces the CAD relative risk, a linear phenomenon that is likely to occur similarly at any level of baseline LDL-c, at least through a limit down to LDL-c 50 mg/dL. Thus, cholesterol is strong and independent risk factor for CAD mortality, which is potentiated by diabetes.

2. Low glomerular filtration rate and microalbuminuria: Both independently increase the cardiovascular risk in healthy as well as T2DM patients. HOPE study observed that, after 4.5 years of follow up, the relative risk for the primary end point (MI, stroke or CV death) in T2DM was 1.97 as compared to 1.61 in non-DM. For every 0.4 mg/mmol of increase in albumin-to-creatinine ratio, the adjusted hazard ratio of major CV events increased by 5.9%.

3. Severe hypoglycaemia: Severe hypoglycaemia (defined as hypoglycemic episode requiring hormone therapy) is approximately twice the risk of cardiovascular disease in T2DM. In the Hong Kong Diabetes Registry study, patients with severe hypoglycaemia showed increased incidence of mortality compared with those without SH, respectively: (32.8 vs. 11.2%). A possible mechanism is the acute induction of pro-inflammatory and pro-atherosclerotic mediators. In an experiment hypoglycaemia in healthy T1DM patients acutely increased circulating levels of PAI-1, VEGF, vascular adhesion molecules (VCAM, ICAM, E-selectin), IL-6, and markers of platelet activation (P-selectin).

4. High sensitivity CRP: Ridkar et al observed that hs-CRP was strongly related to the incidence of cardiovascular events, even after adjustments for age, smoking status, diabetes, categorical levels of blood pressure and the use of hormone therapy. Although the data regarding CRP in diabetic patients is controversial, a retrospective study, Diabetes Heart Study indicated that CRP may predict mortality in T2DM, but at a higher value than AHA CRP threshold of >3mg/l.

Based on above clinical parameters and laboratory work up, patient may be subjected to various imaging or non-invasive testing mentioned below.

C. Role of Imaging / non-invasive testing

1. Electrocardiogram: An abnormal ECG in diabetic patient usually trigger evaluation for underlying CAD. The abnormal ECG finding may ranges from abnormal Q-waves, deep T-wave inversions or bundle branch block to silent myocardial infarction. Testing in these patients should probably not be considered “screening,” but rather evaluation of an objective abnormality for clinical reasons. However, nonspecific ST-T wave changes also are a strong predictor of inducible ischemia in asymptomatic diabetic patients.

2. Echocardiography: The prevalence of asymptomatic LV dysfunction (LVEF < 50%) is 6% in men and 0.8% in women in general population and is twice as common in diabetics. Timely intervention to rule out ischemic etiology can reduce mortality to great extent.

Pharmacological stress echocardiography is another modality useful for risk stratification in asymptomatic diabetics with good diagnostic accuracy. Pharmacological agents being used for stress ECHO are either coronary vasodilators (dipyridamole or adenosine) or positive inotropics (dobutamine). The former increases differences in coronary flow reserve between normal and diseased vessel, whereas the latter mimics the effect of exercise on myocardial contraction. A positive dobutamine or dipyridamole stress echocardiography is predictive of mortality, in both diabetic and nondiabetic individuals. However, pharmacological stress ECHO loses 2 important sets of information, namely the exercise capacity of the patient and the precise workload threshold for the development of symptoms, such as angina. Bigi et al evaluated the prognostic value of pharmacological stress ECHO in diabetic patients suspected of CAD and demonstrated that the post stress wall motion score was the sole independent prognostic indicator.

More recently exercise ECHO is being used for the evaluation of asymptomatic CAD. During exercise ECHO patient undergoes ECHO evaluation pre and immediate post exercise.

3. Exercise Stress Testing: Stress testing provides physiological evidence of clinically significant coronary artery disease. It gives indirect evidence of reduced coronary flow reserve. The yield of stress testing in asymptomatic T2DM patients can be improved by proper patient selection based on pre-test clinical risk factors mentioned above.

There are many drawbacks of exercise stress testing like lack of exercise capacity secondary to underlying peripheral vascular disease (PVD), pulmonary, neurological, or orthopedic conditions. Other sets of patients are those who fail to achieve target heart rate on trade mill. Still others may have pre-existing abnormalities in the resting ECG, like bundle branch blocks, that obscure accurate reporting. Most of these concerns apply to the diabetic patient, who is inherently at whose exercise potential is often limited by obesity, deconditioning, PVD, or sensory or motor neuropathy.

4. Nuclear Imaging: Stress testing combined with radionuclide myocardial perfusion imaging is more sensitive and specific than exercise stress testing alone. In DIAD study the prevalence of perfusion defect or LV function abnormality was found to be 22% amongst diabetics. Stress nuclear test uses radionucleotides such as thallium and Tc-99m-sestamibi to perform myocardial perfusion imaging.

MPI-SPECT has the ability to provide operator independent measurement of myocardial perfusion and function in 3 dimensions. The visualization of regions of under perfused myocardium not only increases diagnostic accuracy, it also provides more precise information regarding LV shape and function. It also allows more precise assessment of the amount and specific location of myocardium at risk as well as the area of scar. Patient’s symptoms and the
extent of ischaemia, scar and decrease of ejection fraction will guide the treatment strategy. If more than 10% of the myocardium is ischaemic, it is very likely that patients will benefit from revascularisation.

One study done by two investigators from well-known laboratories in nuclear cardiology suggested that the stress ECHO and stress nuclear imaging have equal sensitivity but the stress ECHO is slightly more specific. A recent meta-analysis almost confirmed this findings, but the reanalysis suggested no major differences.

5. Positron Emission tomography Scan: The non-invasive assessment of coronary flow reserve (CFR = stress divided by rest myocardial blood flow) using PET is a powerful tool that integrates the effects of focal stenosis, diffuse disease, and coronary microvascular function and has been shown that impaired CFR (below the median) was associated with an adjusted 3.2- and 4.9-fold increase in the rate of cardiac death for diabetic and nondiabetic persons, respectively (P = 0.0004).

6. Coronary artery calcium score (Figure 1): Calcium is a common component of atherosclerotic plaques and is not present in the normal, “healthy” vessel wall. Atherosclerotic plaque proceeds through progressive stages where instability and rupture can be followed by calcification, providing stability to an unstable lesion. Agatston score is the most widely used calcium score. Simplified calcium scores of 0, 1 to 100, 101 to 400, and greater than 400 represent no, mild, moderate, and severe coronary calcification, respectively. Calcium score provides superior discrimination and risk stratification compared with the aforementioned other risk markers.

In diabetics, higher extent of coronary artery calcium was found compared with non-diabetic patients, with a great heterogeneity. The MESA Study observed higher event rate with high CAC score in patients with T2DM. In one series, of 155 asymptomatic diabetics, 72% had positive CAC scores and 48% had a CAC score >102. In PREDICT STUDY CAC was a highly significant independent predictor of events (p < 0.001). A doubling in CAC was associated with a 32% increase in risk of events. There was a progressive increase in hazard ratio according with the CAC score level, comparing to CAC <10. In a large study the increase in mortality was proportional to increases in CAC.

Negative results were observed in a subsequent large study examining the benefit of screening for CAD in diabetics without prior CAD (FACTOR-64 trial). FACTOR-64 trial observed that after a mean follow-up of 4 years, there was no significant difference in the primary endpoint (composite of all-cause mortality, nonfatal MI, or unstable angina) following screening with CCTA.

The long-term predictive value of CAC score for all-cause mortality in asymptomatic diabetics was recently addressed in a 15-year cohort study. The cumulative mortality rate over 15 years according to baseline CAC score was greater in T2DM than in non-diabetic individuals. Interestingly, a CAC zero conferred a similar mortality rate between T2DM and non-DM patients for the first 5 years. After 5 years, however, the risk of mortality increased significantly for diabetic patients even in the presence of a baseline CAC = 0.

Zero calcium is also consistent with the absence of noncalcified plaques and relevant coronary stenosis in more than 87% and 99% of patients, respectively. Absent coronary calcium therefore has an excellent negative predictive value for CAD and is a very important cornerstone of CAD risk stratification, either as a standalone result or in combination with functional testing.

7. CT Coronary Angiography: CT angiography is highly accurate for diagnosing CAD and predicting patient outcome based on the presence, extent and severity of CAD. In the SCOT HEART trial, CTA was significantly better than exercise treadmill testing. Also patients undergoing CTA had better outcomes than those assessed by ETT alone.

Although CTA has a potential advantage for detecting the entire spectrum of atherosclerotic plaque in asymptomatic diabetic patients, there are no data to suggest that it would perform better than a much simpler CAC. This is based on numerous studies in low-to-intermediate-risk patients with suspected CAD, wherein < 1.0% of patients had significant stenosis on CTA if the CACS was 0. At this juncture, routine CTA is not considered an appropriate test in asymptomatic patients.

8. Carotid intima-media thickness and carotid plaque: Carotid wall intima-media thickness (CIMT) is the distance from the lumen-intima interface to the media-adventitia interface of the artery wall, determined by a carotid artery ultrasound. It is a surrogate marker for new acute myocardial infarction and stroke in individuals above 65 years old, when maximal IMT is above 1.11 mm, both in common and in internal carotid arteries. Interestingly, CIMT seems to perform better in obese than in lean T2DM patients.

A carotid plaque, defined as the thickness of the intima, is a simple and highly reproducible method to quantify atherosclerosis. In asymptomatic patients with T2DM, the sum of the maximum plaque thickness above 1.1 mm from both sides of the carotid wall, increases the predictive value for detecting coronary stenosis greater than 50% (obstructive CAD).

Although promising, CIMT and carotid plaque detection are currently not recommended for routine use for risk assessment.

9. Non-alcoholic fatty liver disease: Non-alcoholic fatty liver disease is an independent predictor of CAD among patients with T2DM. The Valpolicella Heart Diabetes Study showed independent association of NAFLD with new CAD event after adjusting multiple confounding variables.

D. Assessment through risk score calculators:

Currently there are at least 45 risk calculators which are exclusive for patients with diabetes. Risk calculators enables the clinician to estimate an individual patient’s risk of developing CAD.

The UKPDS risk engine was originally designed by the Oxford University and may be the most popular global risk calculator for patients with diabetes. Components include age, duration of diabetes, gender, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, ethnicity and atrial fibrillation.

Conclusion

Asymptomatic CAD is common in
patients with T2DM. T2DM increases risk of CAD by 2 to 4 fold, but cannot be considered a risk equivalent due to the high heterogeneity. Risk stratification is necessary to individualize treatment. Almost 30% of diabetics have a 5-year CHD risk similar to general population, however, lifetime risk seems to be invariably high in almost all diabetics. Age above 40 years, diabetes diagnosis of more than 10 years, the presence of a first degree family history with premature CHD, male gender, high blood pressure, LDL above 100 mg/dl, low renal function, microalbuminuria, presence of non-alcoholic fatty liver disease, obstructive sleep apnea and specially chronic hyperglycemia and severe hypoglycemia are conditions that increase cardiovascular risk. Coronary artery calcium score, hs-CRP and CIMT can be useful tools.

For now, risk stratification in the patient with diabetes should include the traditional risk factors with or without risk calculators. Emerging risk factors are still awaiting confirmatory studies. For being useful in clinical practice a risk factor must be strongly associated with the outcome. They must have a favourable cost-effectiveness profile.

Although the yield of MPI in asymptomatic diabetics is excellent, it is unlikely to be cost-effective if used routinely to screen all asymptomatic diabetic patients. At present, evaluation of the calcium score may be beneficial in asymptomatic CAD patients with T2DM. Coronary CT angiography is also an excellent tool to exclude CAD, having a negative predictive value of 97 – 99%.

The current guidelines leave a lot of room as to which test to choose for non-invasive CAD risk stratification. The selection of the particular modality is, in part, led by the pre-test probability of CAD and local availability, expertise and preference. However, whenever possible, an imaging-based test should be used.

A novel strategy provides excellent discrimination of a low-risk population (no CAC), a moderate-risk population with evidence of non-obstructive CAD (with CAC and normal MPI), which warrants aggressive risk factor management, and a high-risk population with obstructive CAD (with moderate-severe CAC and abnormal MPI), which may benefit from invasive angiography and revascularization. Initial studies utilizing this strategy have revealed promising results, but the clinical and cost-effectiveness of such approaches need to be evaluated in future prospective trials.

Our Approach

3 basic questions which we need to answer

1. Which patients with diabetes are at increased risk for adverse cardiovascular outcomes?
   - The primary aim of risk stratification is to identify patients with high cardiac risk whose outcome might be improved with aggressive risk factor modification, medical management or revascularization of coronaries (Figure 2).
   - In day to day practice, risk stratification starts with the assessment of the pre-test probability, means the possibility of that person having CAD. Calculation of pre-test probability in asymptomatic patient is generally based on patient’s age, gender, family history, history of habits, evidence of other atherosclerotic vascular disease, renal disease, abnormal resting ECG or ECHO. Based on this patient is subclassified into low, intermediate or high pre-test probability of CAD. The numerical value of risk can be derived by use of various risk calculators.
     - However, clinical factors that confer risk for adverse cardiac events does not always predict which patient will have abnormal screening test. And more so, negative screening test does not rule out possibility of cardiac events.
     - Patients with a low probability of disease (<15%) does not require to undergo any further testing. However, in specific cases patients may benefit from further risk factor modification. Patients with an intermediate probability (15–85%) of CAD should undergo further non-invasive testing (e.g. Exercise Stress Test, Pharmacological / Exercise Stress ECHO or CT Calcium Scoring). In patients with a high probability of disease (>85%), non-invasive testing does not add much with respect to CAD diagnosis but may help to provide a better idea of the individual patient’s risk. Patients with a high pre-test probability of CAD therefore may directly undergo invasive coronary angiography, also with the possibility of treatment in the same procedure.

2. What are the implications of an
early diagnosis of coronary ischemia or atherosclerosis?

- Diabetics are at high risk for CAD, and aggressive treatment of risk factors is recommended in T2DM with asymptomatic CAD. The role of coronary imaging / non-invasive testing like MPI here is not to document the presence of coronary atherosclerosis but to identify those with more extensive disease. Diabetics with more extensive disease gets benefited by further testing and aggressive management.

- The available data suggest that patients with diabetes involving 10% or more of the left ventricle have a better outcome after myocardial revascularization compared with the results of medical therapy alone. Retrospective studies have shown similar results in patients with diabetes.

3. What tests, or sequence of tests, should be considered? With what frequencies should testing be done?

- At this point of time, the best non-invasive test for diabetic patients being evaluated for CAD remains unclear. Until further information is available, the choice of test should be based on local availability and expertise, cost considerations, as well as certain clinical concerns, such as the precise purpose for the test and unique patient-specific characteristics.

References


Contrast Induced Acute Kidney Injury (CI-AKI) – Myths and Realities

Kulwant Singh¹, Vinant Bhargava², Jyoti E Brar³, Mrinal Bhargava⁴, Raka Kaushal⁵, Dinesh Khullar⁶

Abstract
Contrast Induced Acute Kidney Injury (CI-AKI) is one of the most common causes of acute kidney injury in hospitalized patients. These days, contrast agents are widely being used in both cardiology and radiology procedures. Old age, history of diabetes, heart failure, proteinuria and low blood pressure are some important risk factors in the pathogenesis of CI-AKI.

Apart from risk stratification and the use of low and iso-osmolar contrast agents, intravenous fluid hydration with crystalloids is the only recommended strategy for the prevention of CI-AKI. Agents like N-acetylcysteine (NAC), atrial natriuretic peptide, ascorbic acid, theophylline, and fenoldopam have failed to show any proven beneficial role in the prevention of CI-AKI. Though hemodialysis is still being perceived by many clinicians as the modality for contrast removal but prophylactic hemodialysis is now not recommended for the prevention of CI-AKI.

Introduction
Contrast Induced Nephropathy (CIN) or Contrast Induced Acute Kidney Injury (CI-AKI) – as it is now referred to, is a common and preventable cause of acute kidney injury in hospitalized patients who get exposed to iodinated contrast agents. This leads to a considerable increase in the morbidity, mortality and length of the hospital stay. Preventive approaches involving risk stratification of patients before exposure to contrast agents, use of the lowest dose of iso-osmolar contrast agents and hydration are the cornerstones in reducing the risk of CI-AKI.

Previously lots of emphasis has been laid on the use of N-acetyl cysteine (NAC) in the prevention of CI-AKI. Is it a myth or reality? Nephrologists quite often get referrals for performing dialysis to negate the effect of contrast agents, particularly post-cardiac interventions but also after many other radiological procedures in which iodinated contrast media are used. Is prophylactic hemodialysis an option to prevent contrast-induced nephropathy or is prophylactic hemodialysis indicated at all? This review will address our contemporary knowledge regarding CI-AKI – definitions and risk factors and will also try to clarify controversies of various preventive approaches including but not limited to the role of prophylactic hemodialysis. Definition and Relevance Of CI-AKI

CI-AKI or CIN is defined as an absolute increase in serum creatinine of ≥0.5 mg/dl or as a relative increase of ≥25% from the baseline within 48-72 hours of contrast exposure.¹ CI-AKI has been described as the third most common cause of AKI in hospitalized patients after decreased renal perfusion (prerenal) and nephrotoxic medication(s). It constitutes about 11% of AKI cases.² CI-AKI is usually transient, with serum creatinine levels peaking at 2–3 days after administration of contrast medium and returning to baseline within 7–10 days.

Multiple communities in nephrology and radiology are now adopting broader terminology – contrast associated acute kidney injury (CA-AKI) or post contrast AKI that refers to any AKI occurring after administration of iodinated contrast agent and that may or may not be causally related to contrast agent.³,⁴ The term CI-AKI should particularly be reserved for AKI that can be causally linked to contrast agent administration. Thus, the term CA-AKI includes both CI-AKI as well as other coincidental etiologies like hypovolemia, cardiac dysfunction and infection which can also cause renal dysfunction.

Role of Biomarkers in the Diagnosis of CI-AKI
Apart from serum creatinine, serum cystatin C can also be used for the early identification of patients with CI-AKI. In a study using cystatin C as an early marker, a cut-off increase in cystatin C concentration of ≥ 10% at 24 hours after contrast-media exposure was detected in 87 patients (21.2%) with a negative predictive value of 100 %.³ As seen in other cases of AKI, it appears that in patients with pre-existing renal dysfunction, cystatin C may be a useful marker for the early diagnosis of CI-AKI.

Many recent studies have shown the potential role of biomarkers in predicting CI-AKI.⁵⁻⁷ Increased urinary levels of kidney injury molecule -1 (KIM-1), IL-18, N-acetyl-β-d-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) can predict CI-AKI much before the rise of serum creatinine.⁶ Once these investigations become cheaper and have a shorter turnaround time (TAT), they will definitely play a vital role in the diagnosis and prognosis of CI-AKI.

Incidence of CI-AKI
It has been shown that in patients with normal renal function, even in the presence of diabetes, the risk of
Table 1: Differentiation of Contrast Agents

<table>
<thead>
<tr>
<th>Osmolality (mOsm/kgH2O)</th>
<th>High-osmolar (1500-2100)</th>
<th>Low-osmolar (500-900)</th>
<th>Iso-osmolar (290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic</td>
<td>Ionic</td>
<td>Non-ionic</td>
<td>Non-ionic</td>
</tr>
<tr>
<td>Monomer</td>
<td>Diatrizoate (Gastrograffin)</td>
<td>Ioxaglate (Hexabrix)</td>
<td>Iodixanol</td>
</tr>
<tr>
<td>Dimer</td>
<td>Iohexol (Omnipaque)</td>
<td>Iopamidol</td>
<td>(Visipaque)</td>
</tr>
</tbody>
</table>

Table 2: Mehran Risk Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
<th>SUM</th>
<th>Class of risk (Total score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (systolic blood pressure &lt;80 mm Hg) for at least 1 hour requiring inotropic support</td>
<td>5</td>
<td>5</td>
<td>Low (≤5)</td>
</tr>
<tr>
<td>IABP</td>
<td>5</td>
<td>5</td>
<td>Low (≤5)</td>
</tr>
<tr>
<td>CHF (NYHA Class III/IV)</td>
<td>5</td>
<td>5</td>
<td>Medium (6-10)</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>4</td>
<td>4</td>
<td>Medium (6-10)</td>
</tr>
<tr>
<td>Anemia (hematocrit &lt;39% in men and &lt;36% in women)</td>
<td>3</td>
<td>3</td>
<td>Medium (6-10)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>3</td>
<td>Medium (6-10)</td>
</tr>
<tr>
<td>Contrast media volume 1 for each 100 ml</td>
<td>1</td>
<td>2</td>
<td>Very High (≥16)</td>
</tr>
<tr>
<td>eGFR ≤ 20 ml/min/1.73m²</td>
<td>6</td>
<td>6</td>
<td>Very High (≥16)</td>
</tr>
<tr>
<td>eGFR &gt; 20-40 ml/min/1.73m²</td>
<td>4</td>
<td>4</td>
<td>Very High (≥16)</td>
</tr>
<tr>
<td>eGFR &gt; 40-60 ml/min/1.73m²</td>
<td>2</td>
<td>2</td>
<td>Very High (≥16)</td>
</tr>
</tbody>
</table>

IABP = Intra-aortic balloon pump; CHF = Congestive heart failure; NYHA = New York heart association; eGFR = estimated glomerular filtration rate.

CI-AKI is as low as 1–2%. However, the incidence may be as high as 25% in patients with pre-existing renal impairment or in presence of certain risk factors such as the combination of pre-existing renal failure and diabetes, congestive heart failure (CHF), advanced age, and concurrent administration of nephrotoxic drugs.

Types of contrast agents

The term CI-AKI is generally employed in relation to the use of iodinated contrast media used for computed tomography (CT) scan. Various contrast agents being used are differentiated based on their osmolality (Table 1). The contrast media with high osmolality have higher nephrotoxicity as compared to low and iso-osmolar contrast agents. CI-AKI generally occurs after iodinated contrast agents, although gadolinium (Gd) based contrast agents used in MRI scans can also cause renal dysfunction apart from nephrogenic systemic fibrosis.

Pathogenesis of CI-AKI

The pathophysiology of CI-AKI is multifactorial. Intrarenal vasoconstriction, generation of reactive oxygen species, and direct tubular damage are the predominant factors that lead to CI-AKI. Contrast agents increase the release of adenosine, endothelin, and free radical species which induce vasoconstriction coupled with impaired nitric oxide and prostaglandin-induced vasodilatation. These mechanisms cause ischemia in the deeper portion of the outer medulla, an area with high oxygen requirement and remote from the vasa recta supplying the renal medulla with blood. Contrast agents retained in kidneys have direct toxic effects on renal tubular cells causing vacuolization, altered mitochondrial function and apoptosis (Figure 1).

Assessment of Risk Factors

In the current scenario, radiological evaluations which require contrast media are generally performed in the elderly population, many of whom already have CKD and diabetes—the principal risk factors for CI-AKI. It is, thus, of utmost importance to screen patients at risk for CI-AKI before the procedure.

A CI-AKI Consensus Working Panel has shown that the risk of CI-AKI becomes clinically important when the baseline Serum creatinine concentration is ≥1.3 mg/dl in men and ≥1.0 mg/dl in women, equivalent to an eGFR ≤ 60 ml/min per 1.73 m². Apart from pre-existing kidney disease, other major risk factors for developing CI-AKI include diabetes, congestive heart failure (CHF), advanced age, volume depletion and large volume or high osmolality of the contrast agent. Diabetes acts as a risk multiplier for CI-AKI. Concomitant use of nephrotoxic medication like Non-Steroidal Anti-Inflammatory drugs (NSAIDs), aminoglycosides, amphotericin B, high doses of loop diuretics, and antiviral drugs like acyclovir are additional risk factors.

Most risk factors for CI-AKI can be detected by a thorough history-taking and examination, and the risk rises exponentially with the number of risk factors present. Validated risk-prediction models can also help us to predict the risk of CI-AKI. A risk score for prediction of CI-AKI after the percutaneous coronary intervention has been reported by Mehran et al (Table 2). A risk score of <6 (Low), 6 to 10 (Medium), 11 to 16 (High), and >16 (Very High) indicates a risk for CI-AKI of 7.5%, 14%, 26%, and 57%, respectively.

Preventive Strategies

Prevention is always better than cure and this certainly holds true for CI-AKI as well. An alternative and safer modality of imaging that doesn’t involve use of the contrast agent like MRI is preferable. In high-risk cases,
we should use a minimal quantity of contrast volume and preferably use iso-osmolar or low-osmolar contrast agents. Other nephrotoxic drugs like NSAIDS, aminoglycosides or high dose loop diuretics should be discontinued.

Role of Fluid Hydration

Extracellular fluid expansion with intravenous crystalloids, either isotonic sodium chloride or sodium bicarbonate is the most important preventive measure. Recommended regimen for volume replacement for patients undergoing contrast administration include normal saline administered at 1 mL/kg/h for 3–12 hours pre-procedure and continued for 6–12 hours post-procedure. There is no clear evidence to guide the choice of the optimal rate and duration of fluid infusion in CI-AKI prevention. Recently published PRESCRIBE Trial concluded that there was no significant benefit of intravenous sodium bicarbonate over intravenous sodium chloride among patients who were undergoing angiography for the prevention of death, need for dialysis, or a persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury. Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion. Thus, hydration with oral fluids alone is not recommended.

Extracellular volume expansion counteracts both the intrarenal vasoconstriction and the direct tubulotoxic effects of contrast agents that play a role in the pathophysiology of CI-AKI. Volume expansion may also directly reduce cellular damage by dilution of the contrast medium and decreases viscosity, particularly in the medullary tubular segments.

“Renal Guard therapy” is an automated and personalized hydration system that has shown superiority in preventing CI-AKI by ensuring a stable urine volume without a reduction in body’s hydration during treatment using contrast media. This system monitors the infusion rate of fluids, urine volume from the catheter, and weight changes. This system allows a high urine flow rate (≥300 mL/h) to be achieved, while simultaneously balancing urine output and venous fluid infusion volume of normal saline to prevent hypovolemia until 4 h after cardiac catheterization.

POSEIDON trial showed that left ventricular end-diastolic pressure (LVEDP) guided fluid administration is safe and effective method of preventing contrast-induced acute kidney injury in patients undergoing cardiac catheterisation.

Role of N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is an excellent antioxidant and scavenger of free oxygen radicals. However, it has failed to show conclusive evidence of a protective effect in CI-AKI. Various meta-analyses have shown insignificant results regarding the efficacy of NAC in CI-AKI. The second arm of the PRESERVE trial also showed no benefit of oral acetylcysteine over placebo in terms of endpoints. Recently published Japanese guidelines also concluded that the strength of the evidence concerning the preventive effect of NAC on CI-AKI is low, and recommend against the routine use of NAC as a preventive strategy. NAC is inexpensive and appears to be safe but, it may have some detrimental effects on myocardial and coagulation function at a higher dosage. Hence, oral NAC (600-1200mg twice a day for 2-3 days) can be given along with intravenous volume expansion.

Role of Statins

The proposed hypothesis for the role of statins in reducing the risk of CI-AKI is by their anti-inflammatory and antioxidant properties. A majority of studies that compared statins with placebo had a target population who had a normal renal function, and only a few studies enrolled patients with renal failure. PROMISS (Prevention of radiocontrast medium induced nephropathy using short term high dose simvastatin in patients with renal insufficiency undergoing coronary angiography) study failed to show any significant difference between simvastatin and placebo arms. Meta-analyses of various studies on the effectiveness of statins showed a risk of bias and weak evidence and thus need for future studies. Therefore, the routine use of statins for CI-AKI prevention cannot be recommended at present.

Role of Other Pharmacological Agents

Other agents like atrial natriuretic peptide (ANP), ascorbic acid, theophylline, and fenoldopam have failed to show any benefit against CI-AKI and thus, are not recommended.

ANP has been reported to be beneficial in AKI post-cardiac surgery due to its natriuretic, vasodilatory (particularly on afferent arteriole) and anti-RAS effects. A study by Morikawa et al showed that systemic protocol of continuous intravenous hydration along with ANP is a safe and effective method of preventing CI-AKI but it was a non-blinded single-center study. A recent study by Okumura et al showed that ANP had no prophylactic effect against CI-AKI. Therefore, the use of ANP for prophylaxis of CI-AKI is not recommended.

Ascorbic acid has antioxidant properties. But recent meta-analysis of 6 randomized control trials failed to show any significant difference in risk reduction of CI-AKI by ascorbic acid and the strength of evidence was low. So, its use is not yet recommended for the prevention of CI-AKI.

The efficacy of Theophylline, an adenosine antagonist, in preventing CI-AKI has been compared by two major meta-analysis, one in 2005 (nine RCTs, 585 patients), and another in 2008 (six RCTs, 629 patients). Both of these showed an insignificant trend toward a protective effect of theophylline against CI-AKI.

Similarly, the use of Fenoldopam which is a selective dopamine A1 receptor agonist is not recommended. It might increase renal medullary blood flow, but the prospective randomized trials have shown no significant effects.

Role of Prophylactic Dialysis Modalities

Nephrologists quite often get consults from other clinicians for dialysis therapy soon after the administration of contrast material. Many clinicians perceive that extracorporeal therapies can potentially remove contrast agents and thus prevent CI-AKI. It could theoretically be anticipated that high-flux membranes used in hemodiafiltration (HDF) modalities should be able to remove contrast media more efficiently than low-flux membranes used in routine intermittent hemodialysis (HD). Cruz et al in their meta-analysis of 11 studies (8 of HD and 3 of HDF) concluded that there are no beneficial effects of these modalities as compared to standard fluid hydration.
renal dysfunction and low cardiac output, fluid hydration is generally done at a very lower rate of infusion to avoid the risk of pulmonary edema and overhydration, whereas pre-dilution hemofiltration can safely provide required hydration to such patients. In post hoc analysis by Cruz et al, renal replacement therapies were found to be associated with a harmful trend in CKD stage 3 while no clear benefit could be demonstrated in reducing the risk of CI-AKI in CKD stages 4-5 patients.37

However, there is no conclusive evidence that prophylactic IHD or HDF will prevent renal injury and therefore these modalities are not recommended.17,42 HD should of course be performed for other routine indications such as hyperkalemia, fluid overload etc. rather than as a tool for removing contrast agents to prevent CI-AKI.

Should ACEI/ARB be stopped before the use of iodinated contrast agents?

There is no conclusive evidence that RAAS inhibitors (ACE inhibitors and angiotensin receptor blockers) increase the risk of CI-AKI.43,44 In various recent meta-analyses, the use of RAAS inhibitors have not shown any significant effect on CI-AKI in patients undergoing cardiac interventions.35,46 Therefore, discontinuation and reduction in the dosage of these drugs are not recommended.27

Should Biguanides (metformin) be stopped before the use of iodinated contrast agents?

Biguanides (Metformin) can increase the risk of developing lactic acidosis with a transient impairment in kidney function which occurs after the use of iodinated contrast agents. About 8% of the total cases of metformin-induced lactic acidosis had an association with CI-AKI.47

While administering an iodinated contrast media, it is recommended that we should temporarily discontinue or reduce the dosage of biguanides to prevent lactic acidosis.27,48

### Nephrotoxicity of Gadolinium (Gd) Chelates Used In MRI

Gd chelates are widely used as MRI contrast agents and are considered to have a good overall safety profile as compared to iodinated contrast media. However, Perazella et al summarized many recent studies which raised the possibility of its nephrotoxicity.31 After that, the US FDA requests all the new labels of Gd based contrast describe the risk for nephrogenic systemic fibrosis (NSF) following exposure in patients with a GFR ≤ 30 ml/min per 1.73 m2. In CKD stage 5 patients, the half-life of Gd is increased up to 30 hours, but the relatively small molecular weight (500 Da), a small volume of distribution, and minimal protein binding make Gd chelates ideal for removal with hemodialysis (HD). So, patients on maintenance HD should be considered for dialysis post-exposure.17 However, there is no data that supports prevention of NSF or nephrotoxicity after hemodialysis.

### Conclusion

Contrast induced acute kidney injury continues to be one of the most common causes of AKI in hospitalized patients. Patients with pre-existing renal dysfunction, diabetes, advanced age, and intra-vascular volume depletion are at high risk for developing CI-AKI. There is no definitive treatment available once AKI sets in and therefore, prevention strategies (Table 3) and risk stratification are very important. Extracellular volume expansion with intravenous normal saline is the best available solution for the prevention of CI-AKI. Recent studies have failed to show the benefit of NAC but as it is inexpensive and relatively safe, oral NAC can be considered together with intravenous fluid hydration. Finally, there is no benefit of pre-emptive or prophylactic dialysis therapy and it is not recommended. We require more trials to probe the role of HDF (hemodiafiltration) in the prevention of CI-AKI. In high-risk patients, we should consider a safer alternative imaging strategy. MRI gadolinium-based contrasts are relatively safer, though there is a risk of nephrogenic systemic fibrosis in patients with renal dysfunction when the estimated GFR is ≤ 30 ml/min/1.73 m². To avoid the risk of NSF in dialysis patients with no residual renal function (no urine output) if contrast administration is required, CT is clearly preferred over MRI.

### References


Mycetoma

Himmatrao Saluba Bawaskar¹, Pramodini Himmatrao Bawaskar²

A twenty years old male from tribal community accompanied with father, enter in outpatient department with limping gait. He complained chronic pain, unable to flex and eversion of right foot since last 14 years. Progressive increased in swelling over dorsum of foot and around the right ankle, with multiple nodules and recurrent discharging sinuses. He recollected that long days ago before this swelling he had severe pain at right heal due to un-notice prick of big acacia thorn. He removed the thorn. One week of thorn prick he noticed small small nodule over closed to site of prick there was painless gradually nodules are increased in number, many of them are conglomerated together. Gradually edema of around ankle is increased with restriction of movement at ankle. He applied some herbal remedies and quack tried to puncture the nodules resulted in infection, throbbing pain and non-healing discharging yellow, blackly granules sinuses. He was examined by many quacks, ayurvedic, unanani, homeopath and mantrik, applied varies ointment, powders and oral antibiotic. There was transient improvement and relapse. He denied history chronic febrile illness except local pain and restriction movement at ankle joint, anorexia, and weight loss. He was non diabetic, non-smoker but alcholico and tobacco chewer. Investigations showed hemoglobin 12.8 mg/dl, white cells count was 6100,HIV negative.

On examination there were multiple nodular tumors with black crust (Figure 1A), inversion, eversion, flexion and extension movements at right ankle were restricted. There was woody, non tender, non pitting swelling around the right ankle and dorsum of foot. X-ray right foot did not show any bony lesion. He denied to further investigations such as MRI, ultrasonography, culture and sensitivity due to lack of funds. He was prescribed oral doxycycline 100 mg twice and itroconazole 200mg twice for 30days and follow up after one month. He improved within 15 days and stop taking treatment due to lack of money. We repeatedly call him on phone but failed to respond, finally author (HSB) visited his resident 60 KM from Mahad. There were multiple sinuses, tender swelling, and yellow, blackish color pus was draining from multiple sinuses (Figure 1B). He was unable to walk and had febrile illness. We gave him three months course of doxycycline 100 mg twice a day and itroconazole 100 mg twice day. At the end of three months there was complete cure of lesion with fibrosis, loss of edema and movements at ankle joints were no more restricted and he walk without limp (Figure 2C). He was followed for every six month for next 18 months without any recurrence. Pus was examined under microscope showed multiple fungus hype and budding of actinomycosis (Figure 1D).

Mycetoma was recognized by the WHO as neglected tropical disease. Mycetoma or Madura foot was first described by Vandyke carter in 1860 in Madurai, India.

Mycetoma is a potentially serious, devastating, chronic inflammatory disease cause by microaerobic actinomycetic bacteria (actinomycetoma or fungus (eumycetoma) Heavy rainfall, high humid and hot climate flourished the organism responsible for mycetoma in coastal region of Maharashtra.

“Mycetoma belt” runs from India to Yemen and goes through sudan, Senegal and onto south America and Mexico. Mycetoma caused by actinimycetoma microaerophilic bacteria responds to antibiotic and eumycetoma fungal infection responds to anti fungal agents. Surgical intervention s is only done if there is bone involvement. With continuation of drug therapy till there is complete improvement (Figure 1C).

Madura foot is not a contagious disease. If neglected May result in life time disability due to amputation of affected part usually foot.
A 71 year old male patient presented with progressive dyspnoea for 2 months duration. His ECG showed old inferior wall myocardial infarction.

Transthoracic Echocardiography revealed a large pseudoaneurysm at the base of the inferior wall (Figure 1). The body of the pseudoaneurysm was 4.5 cm with a narrow neck of 0.9cm. Thrombus was present adherent to its wall. The communication between the body of the pseudoaneurysm and left ventricular chamber was confirmed by a colour Doppler (Figure 2). The patient expired the next day while waiting for surgery.

Pseudoaneurysm is an uncommon complication of myocardial infarction. When the myocardium ruptures, the blood entering the pericardial space is contained by clot formation in the vicinity of the rupture. Thus the body of the pseudoaneurysm is made up of pericardium only while its neck is made of ruptured ends of the myocardium. The neck of the pseudoaneurysm is always narrow. In contrast, the neck of an aneurysm is wide and the body is made of myocardium. Because of the high risk of rupture such pseudoaneurysms require emergency surgery.
Deprescribing for Better Patient Outcomes in Chronic Long-Term Care and Role of Clinical Pharmacological Review

Shambo Samrat Samajdar¹, Shatavisa Mukherjee¹, Santanu Kumar Tripathi¹, Jyotirmoy Pal², Shashank Joshi³

Abstract
Prescribing is always a risky proposition with a varied degree of vulnerability embedded in the act. It is therefore important to do a perfect balancing in favor of benefit against harm. Deprescribing is the planned and supervised process of dose reduction or stopping of prescribed medications, aimed at correcting inappropriate polypharmacy and improving patient outcomes. Informed reconciliation for potential deprescribing need should be a norm in all patients receiving many medications for multiple chronic comorbidities and is best done in partnership with the prescribing physician. Judicious deprescribing through clinical pharmacological review ensures better patient outcomes. We present here a case series from our experience in clinical pharmacology outpatients’ department (OPD), highlighting how de-prescribing helps achieving better patient outcomes.

“YOU MAY HAVE NEEDED THE MEDICINE THEN; IT MIGHT NOT BE THE BEST CHOICE NOW!”

Optimizing medication use through targeted deprescribing is crucial for better and safer management of chronic conditions. Deprescribing, an important component of medication reconciliation, is the planned and supervised process of dose reduction or stopping of prescribed medications, aimed at correcting inappropriate polypharmacy and improving patient outcomes.[1,2] For certain medications the dose reduction should be done slowly to avoid withdrawal effects. [3] Deprescribing is best done in partnership with the prescribing physician, following the “no blame, and no shame” principle, and guarding primary physician’s professional dignity. We present here a case series from our experience in clinical pharmacology outpatients’ department (OPD), highlighting how de-prescribing helps achieving better patient outcomes.

Case 1

AJ, a 56 years old, obese (BMI 36 kg/m²) female, on multiple medications for long-term treatment of her chronic ailments – hypertension, type 2 diabetes, osteoarthritis knee, and finding it too challenging to adhere to such treatments, visited our clinical pharmacology OPD, seeking reconciliation support. On presentation, she had knee pain and severe weakness for 5 days, and history of pedal swelling for 5 months. She was on daily glimepiride 4mg, metformin 2gm, pioglitazone 15mg, amlodipine 5mg, and rose hip extract, as well as FDCs of pregabalin+ methylcobalamine, rosuvastatin+aspirin, tramadol+paracetamol, glucosamine+diacerein, calcium carbonate salt from her long list of medications, in consultation with the primary prescribers. She was instead introduced with once weekly GLP1RA injection dulaglutide, and metformin 1gm once daily, initially 2 weeks with glargine followed by canagliflozin 100mg OD. Also calcium citrate+vitD3 FDC was prescribed along with continuation of rosuvastatin+aspirin and pantoprazole+domperidone. Lifestyle modification, physiotherapy and orthopedic consultation were advised. After 6 months, her BMI reduced to 28 kg/m² with much decrease in pain and no pedal swelling. Investigations suggested; Cr-1.2 mg/dl, eGFR-50.5ml/min/1.73m², HbA1c-6.7%.

Her pedal edema could have resulted from the long-term use of pregabalin, pioglitazone and amlodpine, and the same might have been further contributed by compromise in kidney function secondary to repeated spells of diclofenac intake in the last few years, can explain. Prescribing frusemide for pedal swelling without addressing the iatrogenic factors was inappropriate and it led to hyponatremia. This was an example of prescribing cascade which could be well managed by deprescribing.¹ Weight loss is important for osteoarthritis management in obese patients. Anti-diabetes drugs like glimepiride and pioglitazone that are known to increase weight, were therefore replaced with other more suitable options. With eGFR below 45ml/min/1.73m², metformin dose was halved, dulaglutide and

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Acute Flaccid Quadriplegiasis Because of a Rare Systemic Cause

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Abstract

Sjogren’s syndrome is a chronic slowly progressive autoimmune disease characterized by lymphocytic infiltration of exocrine glands resulting in xerostomia and dry eyes. The syndrome has wide clinical spectrum from organ specific exocrinopathy to systemic manifestation. The disease can present alone or with other autoimmune diseases like RA, SLE, Scleroderma, autoimmune thyroid disease etc. Prevalence of primary Sjogren’s is 0.5–1% and of secondary Sjogren’s is 5-20%. Renal involvement is rare and can either be tubulointerstitial or glomerular. Based on biopsy reports in the available literature, tubulointerstitial nephritis (TIN) is the most common histological abnormality, followed by glomerulonephritis as a distant second.1 Distal Renal tubular Acidosis is the most common manifestation of TIN.

We report a case of a 35 year female with acute onset motor weakness (quadriplegiasis) with hypokalemia with NAGMA with distal RTA. Patient was diagnosed with Secondary Sjogren’s and managed accordingly.

Reference


Introduction

Distal RTA is usually associated with a genetic defect or anatomic abnormality of the urinary system.2 dRTA indicates a failure of the intercalated cells in the kidney collecting ducts to secrete hydrogen ions.3,4 If the secretion of protons is severely impaired, the secretion of other cations, including potassium, is increased to maintain electroneutrality. This explains why complete dRTA is

and motor weakness. Hypokalemic muscle cramps, fractures, renal colic. The patient complained of generalized weakness, which may present as Distal RTA with renal potassium loss, which often accompanies hypokalemic paralysis. Renal involvement is not commonly defined in Sjögren syndrome but if involved it mostly causes TIN. Hypokalemic paralysis is the initial symptom in seven percent of patients with Sjögren’s syndrome. The presence of high anti-Ro/SSA titers has also been associated with a greater likelihood of earlier disease onset and extra-glandular involvement. In this case report, a 35 year old woman had first episode of quadriparesis without bowel and bladder and cranial nerve involvement. Since she was found to have severe hypokalemia, a diagnosis of hypokalemic paralysis with distal RTA with secondary Sjögren’s syndrome was made. Also the association of SS and autoimmune thyroid diseases (AITD) has been largely documented, suggesting that AITD could be overrepresented in patient with SS with respect to general population and vice versa. Interestingly, Rojas-Villarraga et al. analyzing prevalence of multiple autoimmune syndromes in 1,083 patients belonging to four autoimmune disease cohorts described AITD and SS as the most frequent coexisting autoimmune disorders in single patients. Overall, then, it has been hypothesized that common genetic, immunologic, and biologic factors may be implied in SS and AITD, leading to the coexistence of these two conditions. Moreover, both SS and AITD may lead to the development of non-Hodgkin’s lymphoma (NHL) highlighting the relationship between similar autoimmunity pathways and lymphoproliferation.

Case Report

A 35-year-old female with no known comorbidities presented to the casualty with complaints of weakness in all four limbs and inability to pass stools for 2 days. Weakness was sudden in onset, developed first in lower limbs which progressed to involve both upper limbs within 2 days. She had symmetrical and total weakness in both upper and lower limbs with no associated diurnal variation (vide Myasthenia Gravis). There was no history of sensory loss or bladder involvement. No history of trauma, backache, fever, vomiting, diarrhea, headache, convulsions, speech difficulty, facial weakness, abnormal body movement, root pain or exposure to STD. On repeated enquiry, history of painful swollen bilateral wrist joint was elicited. The joint pain persisted throughout and was only relieved after medication. Also on and off history of dry mouth and swelling of both jaw region since 2 years was noted. No history of similar episodes in the past, tuberculosis, diabetes, hypertension, thyroid disorders, seizure disorder and surgical intervention was present. The patient was vegetarian by diet and is non alcoholic and non smoker and had good appetite. No similar complaints were present in other family members.

On examination, the patient was conscious but confused, blood pressure was 110/70 mmHg, respiratory rate was 20/min and pulse rate was 50/min. General physical examination revealed pallor and dry oral cavity. Clubbing, cyanosis or lymphadenopathy was absent. From the aforementioned history, I examined the Neurological system first. Neurological examination revealed decreased tone in all four limbs with the power of 1/5 in all limbs and bilateral plantar reflex was mute. Both superficial and deep tendon reflexes were absent. No sensory and cranial nerve involvement, autonomic disturbance, or involvement of bladder was there. On P/A examination, abdomen was soft, nontender but bowel sounds were decreased. The rest of the systemic examination was within normal limits. After history and clinical examination, we sent the patient for routine blood investigations and NCCT head. The CT report was WNL and blood investigation revealed Hypokalemia. From the above mentioned reports we suspected hypokalemia as a cause of the patient’s acute motor weakness and the patient was further evaluated for the same. Arterial blood gas shows pH of 7.2, HCO3- 11 mmol/L, pCO2 17 mmHg,
Na+ 140 mmol/L, K+ 1.9 mmol/L, Cl- 114 mmol/L and anion gap of 14 mmol/L. The blood and urine parameters of the patient are tabulated under Table 1.

So after getting the ABG report, diagnosis of Normal anion gap hyperchloremic metabolic acidosis with severe hypokalaemia was made. Potassium replacement was started. Gradually (after 2 days) patient's power started improving (Patient was able to sit and walk without support).

Further urine evaluation revealed urinary Na+124 mmol/L, K+18 mmol/L and Cl- 114 mmol/L with urine anion gap of 28 mmol/L (highly positive) s/o Distal RTA (type 1). Further evaluation revealed 5. TSH 15.3 uIU/ml, FT3 2.79 pg/ml and FT4 0.65 ng/dl s/o AITD and patient was started on L-Thyroxine 50ug OD. Patients RF came out to be positive and ANA quantitative index value was 5.43 (Positive). After the above investigations, Reflex to ENA profile was sent (suspecting autoimmune cause for Distal RTA). The profile revealed speckled pattern with strongly positive SS-A, Ro-52 and SS-B/La. Schirmer's Test revealed tear flow of 15mm in RE and 17mm in left eye (Normal Schirmer’s Test). Final diagnosis of Hypokalemic quadriparesis with distal RTA with secondary Sjogren syndrome associated with autoimmune thyroid disorder was made. The patient was started on sodium bicarbonate and KCl infusion resulting into improvement of hypokalaemia and metabolic acidosis. This condition might have been precipitated by underlying urinary tract infection, which may increase the bicarbonate requirement and cause volume depletion and potassium loss.

**Discussion**

Sjögren's syndrome is one of many fascinating, pluriform autoimmune entities whose underlying pathophysiology remains incompletely understood. This case illustrates presentation of severe symptomatic hypokalaemia in the context of distal RTA associated with underlying Sjögren's syndrome. Our report emphasizes that although Sjögren's syndrome is most often associated with chronic sicca symptoms, it may present for the first time with extraglandular manifestations which may be life threatening conditions. In distal (type 1) RTA the nephrons lack the ability to secrete H+ ions and hence acidify the urine normally during spontaneous or induced metabolic acidosis. Distal RTA can be inherited or acquired. Inherited forms include autosomal-dominant, autosomal-recessive, or X-linked recessive, of which autosomal-dominant form causing mutations in the basolateral chloride-bicarbonate exchanger (AE1) has been identified as the most common form of inheritance. Acquired causes include hypergammaglobulinemic states, such as hypergammaglobulinemic purpura, cryoglobulinemia, fibrosing alveolitis, Sjögren syndrome, lupus, chronic active hepatitis, thyroiditis, Graves' disease, primary biliary cirrhosis; disorders of calcium metabolism, e.g., primary hyperparathyroidism, vitamin D intoxication, idiopathic hypercalciuria, familial absorptive hypercalciuria, medullary sponge kidney. Tubulo-interstitial diseases include leprosy, hyperoxaluria, chronic pyelonephritis, obstructive uropathy; and genetic diseases like Ehler Danlos syndrome, hereditary eliptocytosis, South Asian ovalocytosis, sickle cell disease, carbonic anhydrate II deficiency.

In distal RTA, the urinary ammonium excretion is inappropriate low for the level of acidosis as the defect in acidification decreases ion trapping required for ammonia secretion. Hence urinary anion gap (UAG = urinary Na+ + K- - Cl-) is positive. This differentiates from chronic diarrhea in which the UAG is negative due to enhanced renal ammonium excretion. In distal RTA, there is a tendency for renal calcii formation, nephrocalcinosis due to hypercalciuria, and hypocitraturia. Severely depressed plasma bicarbonate levels with a corresponding inappropriate urinary pH >5.5 differentiates from type 2 RTA. Finally the requirement of patient to maintain plasma bicarbonate levels near normal was less than 1mEq/kg body weight which pointed towards distal RTA.

**Conclusion**

Hypokalemic periodic paralysis as a presenting complaint of Sjogren’s syndrome is an uncommon entity. Sjogren’s syndrome should be considered as a strong differential diagnosis while evaluating hypokalemic paralysis associated with metabolic acidosis. Early treatment along with proper evaluation is essential to prevent recurrence of episodes of hypokalemic paralysis which can be life-threatening. Our case report adds to the existing literature on renal involvement in a patient with Secondary Sjogren’s syndrome.

**Consent**

Informed written consent was taken from the patient’s husband for case report writing.

**References**

Saul Adler (1895-1966) was born in Czarist Russia in 1895. He immigrated to Britain as a child and settled in Leeds with his parents. After receiving scholarship to study medicine, he entered Leeds University and qualified in medicine in 1917.

He was commissioned as an officer in the British Royal Army Medical Corps and served in Mesopotamia (Iraq) until 1920. On being demobilized he went to the Liverpool School of Tropical Medicine, where he received a Diploma. He also worked at Alfred Lewis Jones Laboratory in Sierra Leone (1921-24). He next immigrated to the Mandatory Palestine (now Israel) in 1924. Adler came to the Hebrew University in 1924, about the time of its founding, and was appointed assistant in the Department of Microbiology. He became Associate Professor in 1928 and Professor of Parasitology in 1934, holding this position until his death. He also served as Dean of the Medical School and was an active member of Israeli Academy of Sciences.

Adler’s scientific reputation rests on a wide range of achievements in basic biology of parasites, their classification and taxonomy. Major among these was work on leishmaniasis including sandflies, and various aspects of medical entomology. He was one of the first and most important investigators of this group of maladies. Adler devoted much time to leishmaniasis and made a major contribution to the epidemiology of leishmaniasis and the problem of its transmission along with Theodor. He also showed that it was possible to infect human volunteers with leishmania from artificially-infected sandflies and thus proved that sandflies are the vectors of leishmaniasis. Saul went on to distinguish the sandfly species, and identified different leishmanial strains.

Adler’s investigations led to the local recognition of certain tick-borne fevers in cattle and introduction of vaccination against the diseases of cattle in Israel and made its dairy industry to flourish. He succeeded in breeding wild Syrian hamsters in captivity in his Jerusalem laboratory and introduced this valuable animal to the world. He also introduced a reliable method for classification of ticks. His contribution to malariology was fundamental; both in the human disease and in developing laboratory models for research. Adler’s investigations into relapsing fever exposed him to the disease and led to his infection with Rickettsial fever.

In 1957 he was elected Fellow of the Royal Society. Saul Adler won many awards, and had more than 200 scientific publications to his credit. He died in January, 1966.
In Stent Restenosis (ISR) after percutaneous coronary intervention (PCI) has been attributed to procedure related factors, as well as individual susceptibility for the same. The inflammatory process plays an important role, not only in initiation and progression of atherosclerosis, but also in development of ISR. We tried to assess if readily available markers of inflammation could be associated with ISR, when using drug eluting stents (DES) in patients with acute coronary syndrome. We conducted a prospective study from September 2017 to March 2019, of 86 consecutive patients of ACS, who had undergone PCI, using second generation DES. We excluded patients who had history of bypass surgery, left main artery stenosis or chronic total occlusions. Pre-procedural clinical profile, laboratory parameters (ESR, hs CRP, eosinophil count), and angiographic parameters (pre- and post-stenting parameters determined by quantitative coronary angiography) were recorded. All patients underwent repeat coronary angiography 9.7 ± 2.3 months after PCI. We defined ISR as > 50% diameter detection, including 5 mm proximal or distal to the stent edge.

In this study cohort of 86 patients, there was a male predominance of 67.4% and the age was 54.2 ± 11.3 years. Of the 86 patients, 14 (16.3%) underwent multivessel stenting, comprising 12 patients with double vessel stenting and 2 patients with triple vessel stenting. Thus, totally 102 arteries were stented; left anterior descending in 57, left circumflex in 20, obtuse marginal in 3 and right coronary artery in 22 patients. In 19 arteries, two stents were implanted while in the remaining 83 arteries, a single stent was implanted; this amounted to a total of 121 stents. The repeat coronary angiography was performed 9.8 ± 2.4 months after the stenting. There was ISR in 5/86 (5.81%) patients. There was no difference between the 2 groups with respect to age, ESR or follow up duration (Table 1). The ISR Group was found to have higher hsCRP compared to non ISR group (2.3 ± 0.4 µg/ml vs 1.7 ± 0.4µg/ml, p=0.01). There was also relation seen between eosinoplin count and ISR (0.24 ± 0.03 *10³/µl vs 0.19 ± 0.07 *10³/µl, p = 0.007). No correlation was found between the vessel treated/ lesion type and ISR. We did not find any significant relation between ISR for single stent vs two stents or for stent length. Post-PCI parameters were inferior in ISR group, such as minimum luminal diameter (2.64 ± 0.25 mm vs 2.94 ± 0.34 mm, p=0.01) and post-PCI percent diameter stenosis (7.9 ± 2.4% vs 4.8 ± 1.3%, p < 0.00001). Multivariate binary logistic regression was performed to test likelihood for causing ISR; this was done to exclude the confounding factors and to screen independent risk factors of ISR. Regression analysis identified only post-PCI residual stenosis as an independent predictor for ISR.

Cheng G et al\(^1\) studied 1132 cases with ACS, and concluded that elevated hsCRP and homocysteine level after PCI, history of diabetes, coronary bifurcation lesions, and greater stent length were associated with higher ISR risk. Yip et al\(^2\) found no association between an elevated hsCRP concentration and late

<table>
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<th>Table 1: Demographic, clinical, laboratory and angiographic parameters with respect to presence of in-stent restenosis</th>
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<tr>
<td>Demographic &amp; clinical characteristics</td>
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<td>Diabetes Mellitus</td>
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<td>Average follow up (months)</td>
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<td>C-reactive protein (CRP) (µg/ml)</td>
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<td>Angiographic parameters</td>
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<td>Stent per lesion</td>
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Mental Health Assessment of Health Care Workers in Covid-19 pandemic in SRN Hospital Prayagraj

Sarita Bajaj1, Anurag Varma2, Anubha Srivastava3, Richa Singh4, Rajendra Kumar Singh5

1Professor and Head of Department, Dept. of Medicine, 2Consultant Psychiatrist, Dept. of Psychiatry, 3Associate Professor, Dept. of Medicine, 4Assistant Professor, Dept. of Social and Preventive Medicine, 5Junior Resident, Dept. of Medicine, MLN Medical College, Prayagraj, Uttar Pradesh

Sir,

In the wake of Covid-19 pandemic there has been a spate of publications on the subject. In this correspondence I would like to emphasize on the Psychiatric morbidity faced by health care workers.

Health care workers managing Covid designated hospitals and exposed to coronavirus disease (COVID-19) are at higher risk of being psychologically stressed and developing psychiatric morbidity. Hence this study was designed for Mental health assessment of health care workers working in Level 3 COVID Hospital SRN associated with MLN Medical College, Prayagraj.

A cross-sectional survey was carried using Survey Monkey to minimise risk of personal exposure and to fulfill social distancing norms. Study collected demographic data and mental health parameter from 224 health care workers in our COVID designated L3 tertiary care hospital from May1, 2020 to August 31, 2020. The symptoms of depression, anxiety, insomnia were assessed by the 9-item Patient Health Questionnaire, 7-item Generalized Anxiety Disorder scale, the 7-item Insomnia Severity Index respectively. Multivariable logistic regression analysis was performed to identify factors associated with mental health outcomes.

Figure 1 shows the Data observed in this study of Depression, Anxiety and Sleep disorders. It can be seen that minor depressive complaints, problems of anxiety and Insomnia have been commonly reported but the symptoms have not been significant to cause Psychiatric illness according to DSM-V and there was no statistical difference among the various studied groups on assessment of anxiety on GAD 7 scale, insomnia on ISI scale and depression on PHQ 9 scale.

Most of the health workers engaged in duties also report a sense of fulfillment and pride and a good peer support system of COVID -19 Warriors has emanated which has led to increased bonding in the workplace and with families in spite of occasional problems of duty rostering, shortage of safety kits, increased workload and novel challenges which were not expected in their specialities of work, this is especially true for doctors who make up the majority of our survey. Health care workers have always stood up to difficult challenges, they have been used to working with limited resources and their resilience has again shown through in spite of themselves turning COVID-19 Positive and hearing of sad losses of their colleagues due to this pandemic. The self-actualisation and religious affiliation, familial, friend and co-workers support too may have been significant factors and the very fact that working itself prevents Acute and Post Traumatic stress can be argued to have had a protective influence.

With no signs of the COVID 19 pandemic ending, uncertainty about Vaccine efficacy, new mutant variants emerging and evidence of reinfection we feel that Psychiatric morbidity is going to increase not just in health care workers but also in COVID-19 patients and the general population also a longer study period and follow up of our own sample may show more positive correlation as Psychiatric illnesses have an incubation period and more such studies need to be done on health care workers specifically working with COVID-19 patients.

References


Acute Kidney Injury in Hornet Sting: Two Cases from East India

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Insect sting is a very common occurrence in tropical countries like India. These can occur as an accident or may be an occupational hazard (e.g. for those working in forests). In most cases, insect sting causes local
Involvement 1. But practically, one potential to cause severe multiorgan the venom of insects like wasp have the male who presented on the 2nd day after getting stung by multiple hornets presented to the emergency after insect sting. Cases of such grave consequences of multiple stings. We here present two in severe envenomation resulting from multiple stings. We here present two cases of such grave consequences of insect sting.

We recently had two patients who presented to the emergency after getting stung by multiple hornets (Beng, Vimrul). One was a 60 year old male who presented on the 2nd day after the stings. He got stung by hornets while clearing weed from his garden. He had burning pain at the sites of sting and facial edema. He was at first managed as a case of acute anaphylaxis to insect venom. But the facial edema did not decrease with adrenaline or steroids, which were administered at the primary health centre and thus, he was referred to higher centre. On admission to our hospital, he had moderate facial edema. More than 20 sting marks were noted all over his body (Figure 1). It was also noted that he had decreased urine output and the urea/creatinine came as 120/4.8 mg/dl respectively. Urine RE/ME revealed WBC 6-8/Hpf and RBC 1-2/Hpf. By the same evening, the urea/creatinine rose to 148/6 mg/dL. There was no body ache. His urine output started improving after 7th day. Urea/creatinine on 7th day was still 58/5.78 mg/dl. Ultrasonography of abdomen revealed normal sized kidneys with normal echotexture. Serum CPK normalized by 10th day. This patient also needed multiple hemodialysis sessions over 15 days.

Both of these patients had no prior history of diabetes, hypertension or any kidney disease. They were not known to be allergic to any insects. For both of them, blood hemoglobin levels remained normal throughout.

Common stinging insects of the tropical countries include bees, wasps and rarely, hornets. These stings cause significant local inflammatory reaction and occasionally, IgE mediated allergic reactions. Rarely, significant systemic involvement has also been reported. In contrast to animal or snake bite, in case of insect stings, the envenomation and extent of systemic involvement is often determined by the number of stings. In both of our patients, multiple hornet stings were followed by acute kidney injury (AKI).

The pathophysiology of renal injury after insect stings is complex and multi-factorial. Direct toxic effect of the injected venom on renal tubules may be responsible. But other factors like insect venom induced intravascular hemolysis, rhabdomyolysis, arterial hypotension and venom induced catecholamine release are also responsible to an equal extent. In the two cases presented here, the 2nd one had evidence of rhabdomyolysis. But hemolysis was not documented in either case.

The medical consequences of hymenoptera sting has not been studied adequately in India. In a recent study from Himachal Pradesh, it was seen that out of 32 cases of Hymenoptera sting victim, more than 90% needed hemodialysis and mortality was 31%. Since, unlike snake bite, no specific anti-venom is available, treatment is mainly supportive and early aggressive therapy can reduce morbidity to a large extent.

Cases similar to ours has been reported from Nepal. Dongol et al reported three cases of AKI following hornet sting in the Kathmandu valley. Two of these three cases also had evidence of Disseminated Intravascular Coagulation in the form of raised PT and aPTT. One patient needed multiple hemodialysis sessions over 38 days for recovery. Thus, the course of AKI after insect sting can be as prolonged as snake bite, or even more.

Our main idea behind presenting these two cases is to sensitize clinicians to the potential serious consequences of insect exposure. Especially, stings by hymenoptera species should always be managed aggressively and regular clinical and biochemical monitoring is needed in the early stages to detect any complication like AKI.

References

“Chin on Palms Sign”
to Diagnose Traumatic Anserine Folliculosis: An Observational Analysis

Konchok Dorjay¹, Surabhi Sinha², Soumya Sachdeva³
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Sir,

Traumatic anserine folliculosis is a rarely reported but commonly encountered condition. In 1977, it was first named “Traumatic anserine folliculosis” by Padilha-Goncalves. It is most commonly seen on the chin, jaws or neck. Repeated friction and/or pressure is believed to be the causative factor.1 Here, we report a case series of 8 patients with traumatic anserine folliculosis. We also propose the “Chin on Palms Sign” as a pointer towards the diagnosis of this under reported condition.

Eight patients with asymptomatic skin-colored keratotic papules on chin presented to the Dermatology outpatients department of our tertiary care hospital between July 2018- June 2019. Five patients were females and 3 were males with a mean age of onset at 18 years. The chin was the only affected site and none of the patients had a history of atopy. All our patients were students with a characteristic history of resting their chin on the palms while studying. Five patients also frequently rubbed their chin with fingers. Half of the patients noted aggravation of lesions during examinations. Cutaneous examination revealed multiple tiny, skin-colored, discrete but closely set, grouped, follicular papules over the chin with normal surrounding skin (Figures 1, 2). Topical tretinoin 0.05% gel was prescribed in all patients but this led to improvement only if coupled with abolition of the habit of “chin on palms”. The demographic details of the patients are summarized in Table 1.

Traumatic anserine folliculosis is an uncommonly reported entity characterized by the presence of follicular “goose like skin” papules. The cause is believed to be repeated friction or pressure on the skin in children, adolescents and young adults while studying, watching television, drawing and even playing one handed mobile phone games.2,4

A history of atopy is frequently reported.2 But none of our patients were atopic. Clinically, anserine folliculosis presents with grouped yellow to white or skin colored papules with or without surrounding erythema. White yellow colored spine shaped bodies can be appreciated on dermoscopy.4,5 Histopathology reveals dilated follicular openings and presence of retained keratic material.2,3

It is important to differentiate traumatic anserine folliculosis from other follicular disorders. They include keratosis pilaris, trichostasis spinulosa, lichen spinoelulosus, erythromelanosis follicularis faciei et colli.3 Keratosis Pilaris is characterized by unevenly affected follicular papules possessing a protruding keratin spine. Perifollicular erythema may be present. The cheeks and preauricular areas, extensor surface of arms, thighs and buttocks are commonly affected sites.5 Lichen spinulosus presents as spiny keratotic papules at friction prone area such as knees and elbows and trichostasis spinulosa presents as comedones like follicular papules commonly on the nose.6,7 The peculiar history and site of traumatic anserine folliculosis can distinguish it from other follicular disorders.

The prognosis is generally good. If the factors causing friction or pressure are removed complete resolution of the lesions can occur. Topical keratolytics, topical corticosteroids and topical vitamin D analogue are reported to be useful adjuncts.

Only Cases report and series have been reported in literature. We however believe that these numbers belief the actual incidence which may be higher. Therefore, to aid in the diagnosis we propose the “Chin on Palms sign” to be asked by clinicians when faced with patients with such presentations.

To conclude, the follicular lesions of the skin pose a diagnostic challenge to the physician. Appropriate history, examination and investigation can distinguish between them. The peculiar history and site of lesions can easily diagnosed traumatic anserine folliculosis. Avoiding friction may suffice in most of the cases thus avoiding unnecessary treatments and the related side effects.

References


Table 1: Demographic and epidemiological profile of the cases

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients characteristics</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Female – 5/8 (62.5%)</td>
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<tr>
<td></td>
<td>Male(3/8) 37.5%</td>
</tr>
<tr>
<td>Age of patients (mean)</td>
<td>19.75 years</td>
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<tr>
<td>Awareness of Disease</td>
<td>5/8 – 62.5%</td>
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<tr>
<td>Age of onset (mean)</td>
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<tr>
<td>Site</td>
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</tr>
<tr>
<td>History of symptoms like Itching</td>
<td>None</td>
</tr>
<tr>
<td>Occupation</td>
<td>Students (8/8=100%)</td>
</tr>
<tr>
<td>History of Atopic</td>
<td>None</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>None</td>
</tr>
<tr>
<td>History of Neurocutaneous findings</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1: Demographic and epidemiological profile of the cases

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female – 5/8 (62.5%)</td>
</tr>
<tr>
<td></td>
<td>Male(3/8) 37.5%</td>
</tr>
<tr>
<td>Age of patients (mean)</td>
<td>19.75 years</td>
</tr>
<tr>
<td>Awareness of Disease</td>
<td>5/8 – 62.5%</td>
</tr>
<tr>
<td>Age of onset (mean)</td>
<td>18 years</td>
</tr>
<tr>
<td>Duration of disease (mean)</td>
<td>8.37 months</td>
</tr>
<tr>
<td>Family History</td>
<td>None</td>
</tr>
<tr>
<td>Site</td>
<td>Chin (8/8=100%)</td>
</tr>
<tr>
<td>History of symptoms like Itching</td>
<td>None</td>
</tr>
<tr>
<td>Occupation</td>
<td>Students (8/8=100%)</td>
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<td>History of Atopic</td>
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<tr>
<td>History of Neurocutaneous findings</td>
<td>None</td>
</tr>
</tbody>
</table>
KEEP THE BRAIN-GUT BOND STRONG

In IBS with anxiety

Librax®
Chlordiazepoxide 5 mg • Clidinium Bromide 2.5 mg Tablets

Established safety & efficacy profile
Textbook recommended
Over 3 decades of trust
Globally available in over 50 countries

For the use only of registered medical practitioners or a hospital or a laboratory. | This e-communication is being sent in view of COVID-19 exigency and the need for social distancing, and is intended for RMPs only. Please do not forward. | You have consented to receive this email. To opt out, please message "No" to the sender.


Abbreviated Prescribing Information
CHLORDIAZEPOXIDE & CLIDINIUM BROMIDE TABLETS | Librax | COMPOSITION: Each sugar-coated tablet contains Chlordiazepoxide 1.5 mg and Clidinium Bromide USP 2.5 mg. | INDICATION: Indicated for the treatment of organic manifestations of anxiety and tension in gastrointestinal and genitourinary tracts. The conditions may (but not limited to) include irritable bowel syndrome, dysmenorrhoea, gastric & duodenal ulcer, gastro-duodenitis, intestinal spasms, ureteric spasm, biliary dyskinesia etc. | DOSAGE, DURATION AND METHOD OF ADMINISTRATION: Adults: 1-2 tablets 3-4 times daily. Elderly or debilitated: 1-2 tablets daily initially, then may increase gradually. In dysmenorrhoea, the drug should be taken three to four days prior to menstruation or as directed by the physician. Children: Not recommended, Elderly or debilitated patients and Special patient groups: In elderly patients, renal or hepatic insufficiency, dosage adjustment is required. Treatment must be as brief as possible. The indication will be re-evaluated regularly, especially in the absence of symptoms. The total duration of treatment should not exceed 8 to 12 weeks for the majority of patients. | CONTRAINDICATIONS: Hypersensitivity to the active substances or to any of the excipients, pathological subjects aged over 65 years, patients aged over 75 years and children under 6 years, risk of angle-closure glaucoma, risk of urinary retention associated with urethra-prostatic disorders, severe respiratory insufficiency, severe, acute or chronic hepatic insufficiency (risk of occurrence of encephalopathy), myasthenia gravis. | WARNINGS AND PRECAUTIONS: Cautiously used in patients with alcohol and drug abuse, major depression, prostatic hypertrophy. Rebound reactions, tolerance, dependence, withdrawal symptoms may be observed. | PREGNANCY AND LACTATION: Librax is contraindicated in pregnancy. An increased risk of congenital malformations has been reported with the use of chlordiazepoxide during the first trimester of pregnancy. Patients should be advised that if they become pregnant during therapy or intend to become pregnant. Both Clidinium and chlordiazepoxide can appear in the breast milk. Clidinium may decrease milk secretion and it may also pass into milk. This can result in atropinic effects in the child. Therefore, the use of Librax is not recommended during breast feeding. | ADVERSE REACTIONS: Most common adverse effects include sedation, ataxia, fatigue, somnolence, dizziness, and balance disorder. The elderly are particularly sensitive to the effects of centrally-depressant drugs and may experience confusion. General: - Dry mouth, fatigue. CNS: - Sedation, dizziness. GI: - constipation. CVS: - Palpitations, tachycardia. Hepato-biliary: - Raised bilirubin, SGPT, SGOT levels. Renal: - urinary retention. For full prescribing information, please contact: Medical Sciences Division, Abbott Healthcare Private Limited, Floor 17, Godrej BKC, Plot No. C - 68, BKC, Near MICA Club, Bandra (E), Mumbai - 400 051.
In Stage I hypertension

Initiate Olmesar

Olmesartan Medoxomil 10 / 20 / 40 mg Tablets

Offers 5.6 mmHg greater SBP reduction than Telmisartan

A Class Apart

Best in Class

Olmesar CH
Olmesartan Medoxomil + Chlorthalidone Tablets

20/40 8.25

20/40 12.5

TriOlmesar-CH
Olmesartan Medoxomil + Candesartan 16 mg / Chlorthalidone 12.5 mg Tablets

Olmesar-M
Olmesartan Medoxomil 10 mg + Metoprolol Tartrate 50 mg Tablets

Olmesar Plus
Olmesartan Medoxomil 20/40 mg + Amlodipine 8 mg Tablets

Abridged Prescribing Information:
Composition: Each Olmesar 10/20/40mg tablet contains Olmesartan 10/20/40 mg.
Indication: Hypertension.
Dosage: Adult: 20 mg once daily when used individually, increase to 40 mg after 2 weeks of therapy if required. Children (age of 6 to 16 years): 10 mg once daily for patients who weigh < 35 kg or 20 mg once daily for patients who weigh > 35 kg. Increase to a maximum of 20 mg for patients who weigh < 35 kg or 40 mg once daily for patients who weigh > 35 kg after 2 weeks of therapy if required.
Contraindications: Hypersensitivity to Olmesartan, co-administration with aliskiren in diabetic patients, 2nd and 3rd trimester of pregnancy, biliary obstruction. Special Precautions: Assess renal function, BP & volume status during initiation of therapy & dose escalation periodically thereafter. Use with caution in elderly. Children < 1 year of age must not receive Olmesartan for hypertension. In patients whose renal function may depend on activity of the renin-angiotensin-aldosterone system (eg, patients with severe CHF), treatment may be associated with oliguria &/or progressive azotemia, rarely resulting in acute renal failure &/or death. Symptomatic hypotension may be anticipated after initiation of treatment in patients with an activated renin-angiotensin system, such as volume &/or salt-depleted patients. In patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN may occur. Adverse Drug Reaction: most commonly observed adverse reaction is Hyperkalaemia. Dizziness, Headache other ADRs may be Rhinitis, Pharyngitis, Cough, Pain, Angioedema, Pruritus, Rash, Urticaria, Hyperkalaemia, Hypotension & Muscular spasm. Full prescribing information is available on request.
Efficacy meets Affordability
Bioequivalent to the Innovator brands

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**DAJIO**
(Dapagliflozin 10 mg Tablets)

Delivers Powerful Outcomes

**DAJIO-M₅₀₀**
(Dapagliflozin 10 mg + Metformin 500 mg SR Tablets)

**DAJIO-M₁₀₀₀**
(Dapagliflozin 10 mg + Metformin 1000 mg SR Tablets)

In T2DM patients with uncontrolled PPBG,

**Voglinorm-R 0.5/1.0**
(Voglibose 0.3mg + Repaglinide 0.5/1.0 mg)

Rapid Action... Better Control

Time to Show Red card to Uncontrolled PPBG

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- 7 International Clinical Trials in 1910 RTI Patients
  • 94.4% bacterial eradication in RTI
  • 100% success rate as switch over therapy

- Robust Indian Data in AECOPD
  77.36% Clinical Success & Decreased exacerbations from > 1.5 /2 to avg. 1.3

- USFDA approved