Study of Oral Hypoglycemic Agent-induced Hypoglycemia in Type 2 Diabetes Mellitus in a Tertiary Care Center

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ABSTRACT

Introduction: Diabetes prevalence is increasing rapidly; estimates from the International Diabetes Federation put the number at 381 million people have diabetes. Hypoglycemia is a commonly encountered complication in diabetic patients, which, in the short-term, can lead to mortality and, in the long-term, precludes maintenance of euglycemic control. Over 65.2% of patients have reported at least one incidence of severe and nonsevere hypoglycemia when on oral hypoglycemic agents (OHA) at an annual crude incidence density of 35.1 events per year per person. Insulin more commonly causes hypoglycemia than OHA. However, this study was done with the aim of studying the hypoglycemia specifically caused by OHA—clinical profile of patients, medications causing hypoglycemia, and the outcome.

Materials and methods: This prospective observational study was conducted in the Department of Medicine at a tertiary care hospital in Western Maharashtra. Data was collected over a period of 18 months from indoor patients on admission having hypoglycemic symptoms with strip blood sugar levels of <70 and on OHAs. Patients on insulin were excluded from the study.

Results: There were 60 patients with hypoglycemia with a mean age of 53.65 years and a higher incidence of hypoglycemia in females, 35 (58.3%) compared to males. There was a statistically significant difference between outcome (i.e., discharged or death) and urine protein–creatinine ratio (UPCR), a deranged liver function, that is, serum albumin, serum glutamic oxaloacetic transaminase (SGOT)/aspartate transaminase, and serum glutamic pyruvic transaminase (SGPT)/alanine transaminase (p < 0.05). However, there was no statistically significant difference between outcome (discharged or death) and mean age, gender, mean duration of diabetes mellitus (DM), GCS scoring, and drug type of study subjects (p > 0.05).

Conclusion: The risk factors for hypoglycemia were middle-aged patients. Females are at higher risk of hypoglycemia than men. Hypoglycemia due to OHAs is known to have a recurrence of hypoglycemia due to the long half-life of the drug; however, patients who were hospitalized were well monitored and did not have any recurrence of hypoglycemia. Deranged liver function or raised UPCR have high mortality after OHA-induced hypoglycemia.

INTRODUCTION

Globally, an estimated 422 million adults are living with diabetes mellitus (DM), according to the World Health Organization. Diabetes prevalence is increasing rapidly; the International Diabetes Federation puts the number at 381 million people having diabetes. The number is projected to almost double by 2030. Type 2 diabetes makes up about 85–90% of all cases. Increases in the overall diabetes prevalence rates largely reflect an increase in risk factors for type 2, notably greater longevity and being overweight or obese to treat type 2 diabetes.1

In India, there are 77 million people with diabetes and 25 million per diabetics.

Definition of hypoglycemia, according to American Diabetes Association (ADA): hypoglycemia is defined by the presence of hypoglycemic symptoms with low sugar on a blood test, which improves with the administration of sugar.2

Hypoglycemia remains a major barrier to tight glycemic control and a common complication of diabetes treatment. For patients with type 1 diabetes and type 2 DM (T2DM), hypoglycemia remains one of the most enduring issues.3

Over 65.2% of patients have reported at least one incidence of severe and nonsevere hypoglycemia when on oral hypoglycemic agents (OHAs) at an annual crude incidence density of 35.1 events per year per person.4

Hypoglycemia tops the list of hurdles in preventing tight glycemic control and is often observed in patients on insulin or insulin secretagogue (like sulfonylurea) therapies. Recent studies have demonstrated that though strict glycemic control results in reduced microvascular complications, it is associated with increased cardiovascular events and even mortality (ACCORD).5

Further recurrent episodes of hypoglycemia result in hypoglycemia unawareness.6 Hypoglycemic episodes may result in significant psychosocial dysfunction and lower quality of life. In spite of the knowledge about the importance of hypoglycemia, it is still a relatively neglected complication in diabetes care in our setting.7

Given the significance of hypoglycemia in patients with T2DM and the limited knowledge of its frequency in patients on OHAs, this study was conducted with the aim to evaluate OHAs induced hypoglycemia in T2DM with respect to clinical profile, risk factors, and outcome of patients having OHA-induced hypoglycemia.

MATERIALS AND METHODS

We conducted a prospective observational study at a tertiary care hospital in Mumbai, Maharashtra, India, between April 2019 and September 2020 after obtaining clearance from the local ethical committee. Around 60 type 2 diabetic patients on admission having hypoglycemic symptoms with strip blood sugar levels of <70 and OHAs were enrolled in the study. Hypoglycemia in nondiabetic and type one diabetic patients found to have other drugs which may cause hypoglycemia (like β-blocker, aspirin, and tricyclic antidepressants [TCA]), and patients on insulin therapy alone or along with OHA were excluded from the study as insulin is the most common cause of hypoglycemia.

Demographic details of the patients, like age, sex, occupation, and residence were noted. Disease history in detail of duration, a medication used in detail, and a previous episode of hypoglycemia, presenting complaints with duration, vitals were assessed. A detailed examination was done. Patients were classified into mild, moderate, severe, and a previous episode of hypoglycemia.
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Results

A total of 60 type 2 diabetic patients on admission having hypoglycemic symptoms with strip blood sugar levels <70 and on OHAs were recruited in the study. Of 60 study subjects, 35 (58.3%) were female and 25 (41.7%) were male. The demographic and baseline characteristics of the study subjects are presented in Table 1. The mean ± SD age was 53.65 ± 10.52, ranging from 38- to 91-year-old subjects. The majority of study subjects, 50 (83.4%), had altered level of consciousness, six (10%) had giddiness, two (3.3%) patients had left-sided hemiparesis, and one patient (1.7%) had right-sided hemiparesis, one (1.7%) patient had only sweating palpitation. According to the grade of hypoglycemia, most of the study subjects, 50 (83.3%), had severe hypoglycemia, followed by nine (15%) had moderate hypoglycemia, and one (1.7%) had mild hypoglycemia. Mild hypoglycemia: 70–54 mg/dL blood sugar, moderate hypoglycemia: <54 mg/dL of the blood sugar level, and severe hypoglycemia: blood sugar <50 mg/dL.

Table 1: Baseline and demographic profile of study subjects

<table>
<thead>
<tr>
<th>Baseline and demographic profile</th>
<th>Number of study subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>53.65 ± 10.52</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>41.7%</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>58.3%</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>27</td>
<td>45.0%</td>
</tr>
<tr>
<td>6–10</td>
<td>17</td>
<td>28.3%</td>
</tr>
<tr>
<td>11–15</td>
<td>9</td>
<td>15.0%</td>
</tr>
<tr>
<td>&gt;15</td>
<td>7</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

Clinical profile of study subjects

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of study subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered consciousness</td>
<td>50</td>
<td>83.4%</td>
</tr>
<tr>
<td>Giddiness</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>Left-sided hemiparesis</td>
<td>2</td>
<td>3.3%</td>
</tr>
<tr>
<td>Right-sided hemiparesis</td>
<td>1</td>
<td>1.7%</td>
</tr>
<tr>
<td>Only sweating and palpitation</td>
<td>1</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Hypoglycemia:
- Mild hypoglycemia: blood sugar 70–54 mg/dL
- Moderate hypoglycemia: blood sugar 54–47 mg/dL
- Severe hypoglycemia: blood sugar <47 mg/dL

Neurogenic symptoms:
- Altered sensorium

GLP-1 receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase IV (DPP-IV) inhibitors do not cause hypoglycemia.

Of 24 patients on FDC, 12 patients were on metformin 500 mg + glimepiride 1 mg, five patients were on metformin 500 mg + glimepiride 1 mg, four patients on metformin 1000 mg + glimepiride 2 mg, two patients on metformin 500 mg + voglibose 0.2 mg. Daily doses were once or twice a day of these FDCs.

Of 30 patients on multiple OHAs, 11 were on metformin 500 mg and glimepiride 1 mg, eight patients were on metformin 500 mg and voglibose 0.2 mg. Daily doses were once or twice a day.

Of six patients on a single drug, two were on gliclazide 60 mg per day, two patients were on glimepiride 2 mg per day, one patient was on glimepiride 30 mg per day, and one patient was on metformin 1500 mg per day.

Table 2: Clinical profile of study subjects

Table 3: Type of medication

<table>
<thead>
<tr>
<th>Drug type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDC</td>
<td>24</td>
</tr>
<tr>
<td>Multiple pills</td>
<td>30</td>
</tr>
<tr>
<td>Single pill</td>
<td>6</td>
</tr>
</tbody>
</table>
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Total patients on dipeptidyl peptidase 4 inhibitors: One
Total patients on α-glucosidase inhibitors (voglibose): One

The various laboratory data are presented in Table 4. Blood glucose at admission was 37.28 mg/dL on average, which ranged from 15 to 68 mg/dL. After withdrawing OHAs, the patient had an increase in blood sugar on average to 170.74 mg/dL on day 2 and 200.34 mg/dL on day 4.

In RFTs, 26 patients had a raised creatinine (glomerular filtration rate below 60 mL/minute/1.73 m²), and patients had an average creatinine of 1.5 mg/dL (glomerular filtration rate: 42 mL/minute/1.73 m²), however, the range is wide from 0. to 3.9 mg/dL.

In the LFT, most parameters were, on average, in the normal range. The mean total serum bilirubin was 1.01 mg/dL, the mean total serum protein was 7.20 gm/dL, and the mean serum albumin was 3.59 mg/dL; however, liver enzymes were mildly raised, mean serum glutamic-oxaloacetic transaminase (SGOT) or aspartate transaminase was 57.1 mg/dL and mean SGOT or alanine transaminase was 69.43 mg/dL.

Mean HbA1c was 7.35%, with a range from 5.7 to 14.3%. The mean UPCR was 1.99 mg/dL.

The outcome of the study was assessed as discharged or expired (Fig. 2). Out of 60 patients, 52 were discharged, that is, 86.7%, and mean SGOT or alanine transaminase was 57.1 mg/dL and mean SGPT/alanine transaminase between the discharged and the expired, with a p-value of <0.001, <0.003, and <0.001, respectively. Unpaired t-test showed a statistically significant difference (p-value of 0.021) seen between UPCR, with the mean UPCR of expired patients being 3.328 mg/dL and discharged patients being 1.80 mg/dL.

The association of outcome with clinical profile and lab parameters is given in Table 6. Among 60 patients who had hypoglycemia, their sugar at admission, on day 2 or 4, did not correlate with the outcome as discharged or expired (p > 0.05). RFT [i.e., blood urea nitrogen (BUN) and creatinine] and outcome did not show any significant difference (p > 0.05). There was a statistically significant difference with serum albumin, SGOT/aspartate transaminase, and SGPT/alanine transaminase between the discharged and the expired, with a p-value of <0.001, <0.003, and <0.001, respectively.
A total of 52 patients who survived had regained full sensorium at discharge. Eight patients who expired were due to complications of hypoglycemia. Five subjects developed hypoglycemic encephalopathy (or hypoglycemic coma), and three patients died of aspiration pneumonia.

**Discussion**

The present prospective observational study was done among 60 type 2 diabetic patients, on hospital admission having hypoglycemic symptoms with strip blood sugar levels <70 and on OHAs with the objective of finding predisposing factors and outcome of hypoglycemia due to OHAs in T2DM patients.

In this study, we found the mean age of study participants was 53.65 years, with a higher incidence of hypoglycemia in females 35 (58.3%). Similarly, Shorr et al. and Samaya et al. found more incidence of hypoglycemia in females, 82 and 73.3%, respectively.

The mean duration of diabetes in our study was 8.49 years, and Samaya et al. found 6.82 years.

We found the maximum number of patients (50) had come to the emergency in an altered sensorium (83.4%). The second most common symptom was giddiness, which affected six patients, accounting for 10%, that is, six patients. Three patients (5%) had hemiparesis (two left-sided and one right-sided). One patient had a fever. The study by Shorr et al. studied symptoms of hypoglycemia. Alerted sensorium (49%), lethargy (34%), irrational behavior (6%), seizure (5%), and transient ischemic attack (10%).

We have tried to study if there is any difference between the outcome of having a FDC vs having separate tablets of OHAs. Out of the 60 patients, six patients were on only a single OHA, and 54 patients were on two or more hypoglycemic agents, either as a FDC or as different pills. The most common class of drugs that cause hypoglycemia are sulfonylureas or glinides, but in our study, 59 patients were on sulfonylureas, and no patient in our study was on glinides. Metformin, thiazolidinediones, α-glucosidase inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-IV inhibitors do not cause hypoglycemia. Among eight patients who died in the study, a FDC of multiple pills or a single pill did not make any difference in terms of outcome in our study (p > 0.05).

Among the 60 patients with hypoglycemia, the maximum had a Glasgow Coma Scale (GCS) of 3–8, that is, 45 patients or 75% of patients. Only three patients (5%) had a GCS between 9 and 12. A total of 12 patients (20%) had a good GCS between 13 and 15. There was no statistically significant difference between GCS at admission and outcome as expired (eight patients) vs discharged (52 patients) (p > 0.05).

Of the various laboratory data collected, the mean blood glucose at admission was 37.28 mg/dL, which ranged from 15 to 68 mg/dL. After withdrawing OHAs, the patient had an increase in blood sugar on average to 170.74 mg/dL on day 2 and 200.34 mg/dL on day 4. For patients who had hypoglycemia, their sugar at admission, on day 2 or on day 4, did not correlate with the outcome as discharged or expired (p > 0.05).

Shorr et al. and Burg et al. reported that the mean blood sugar level on admission was 33 and 40 mg/dL, respectively.

In the RFT, the mean serum creatinine was 1.5 of the 60 subjects, with a mean glomerular filtration rate (GFR) of 42 mL/minute/1.73 m². The number of subjects with creatinine >2 mg/dL (n = 11) were put on insulin. Of subjects with a creatinine of 1.1–1.9 mg/dL, 28% were put on insulin, 7% expired, and 18% were put off any anti-diabetics. This is because in diabetic patients with renal failure, the half-life of insulin increases, leading to more risk of hypoglycemia.

Liver function tests (LFT) showed that patients in the study had normal total bilirubin and total albumin. However, transaminases like SGOT and SGPT were elevated in a few of them, and the mean SGOT and SGPT were 57.17 and 69.43 IU/dL, respectively.

However, nine patients (15%) had SGOT and SGPT raised (above 45 U/L); in our study, raised transaminase is a risk factor for mortality in hypoglycemia due to OHAs. Mean HbA1c was 7.35%, with a range from 5.7 to 14.3% in our study. HbA1c is not a risk factor for mortality in hypoglycemic patients; however, strict diabetic control is associated with the risk of hypoglycemia. Burg et al. reported mean HbA1c was 8.6%.

The mean UCR is 1.99 mg/dL. UPCR with the mean UPCR of expired patients was 3.328 mg/dL and discharged patients being 1.80 mg/dL. This shows that proteinuria correlates with the outcome of the patients (p < 0.05).

Eight patients who expired were due to complications of hypoglycemia. Five subjects developed hypoglycemic encephalopathy (or hypoglycemic coma), and three patients died of aspiration pneumonia.

In conclusion, patients, mainly middle-aged patients and females, are at higher risk of hypoglycemia than men. Hypoglycemia due to OHAs is known to have a recurrence of hypoglycemia due to the long half-life of the drugs; however, patients who were hospitalized were well monitored and did not have any recurrence of hypoglycemia. Mortality correlation shows that the deranged LFT has a poor outcome. Proteinuria is a significant prediction for mortality in such patients.

**References**