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Clinical profile of hypoglycemia in diabetic patients : A prospective study in a tertiary care hospital

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Abstract

Background: Hypoglycemia refers to a clinical condition resulting from an abnormally low plasma glucose level ≤40 mg/dl without symptoms and <50mg/dl with symptoms. Clinically, it is characterized by varying degree of neurological dysfunction and is responsive to the administration of glucose. Hypoglycemia is commonly caused by drugs used to treat diabetes mellitus.

Objective: To study the clinical profile, precipitating factors and outcome in the patients of hypoglycemia.

Material and Methods: This hospital based 2 years prospective study was conducted in the Department of Medicine, Kasturba Medical College and hospital, Manipal, Karnataka. Clinical profile of 100 diabetic patients on OHA's or Insulin treatment with the diagnosis of hypoglycemia were analyzed. The criteria for hypoglycemia was blood glucose level of <40mg/dl without symptoms and <50mg/dl with symptoms.

Results:

Out of 100 patients, 30 (30%) patients were of type 1 diabetes mellitus and 70 (70%) patients of type 2 diabetes mellitus. The male:female ratio was 1:1.7. The most common precipitating factor was found to be delaying or skipping meals (80%), followed by decreased carbohydrate intake (70%), increase in insulin or OHAs dosage (54%), decrease in insulin requirement (10%). The most common autonomic symptom was sweating (90%) followed by palpitation (80%). Neuroglycopenic symptoms were observed at much lower blood glucose level. Majority of hypoglycemic patients (68%)

had blood glucose in the range 31-40 mg/dl. 64 patients (64%) were on only insulin therapy and 16 (16%) patients were on OHAs. 20 (20%) patients were on combination (insulin+OHAs) therapy. Maximum incidence of hypoglycemia was reported among patients who were on combination of short acting plus intermediate-acting (i.e Premix – 30/70) Insulin. However, within the set of patients developing hypoglycaemia due to OHA's, the frequency was much higher (62.5%) with a combination therapy of OHA's as compared to monotherapy (37.5%). All hypoglycaemic patients received IV dextrose (25%) and responded well to treatment. Present study did not show any mortality due to hypoglycemia.

Conclusion:

Hypoglycemia is the most common acute metabolic complication of diabetes mellitus on treatment. Elderly diabetics, patients with chronic kidney disease and patients on long acting insulin/sulfonylureas (used either alone or in combination) are more prone to develop hypoglycemia. Diabetic patients should be familiar with hypoglycemia symptom profile so that they can perceive the early onset of hypoglycemia and an appropriate action can be taken immediately.

Key words: Hypoglycemia, Blood sugar, OHAs (oral hypoglycemic agents)

INTRODUCTION

Hypoglycemia is the most common endocrine emergency faced by clinicians globally. It results when the blood glucose drops to less than 50mg/dl accompanied with neuroglycopenic symptoms or less than 40mg/dl without symptoms.[1] For a physician, hypoglycemia is more concerning than hyperglycemia as it can lead to death. In diabetic patients, it has been implicated as a cause of death in “dea-in-bed” syndrome. Hypoglycemia delays safe achievement of optimal glycemia and can sometimes be severe. Severe hypoglycaemia, classified as the sudden dip in glucose level which require the assistance of another person – is a clinical red flag. [1]

Hypoglycemia is one of the main and serious iatrogenic cause of morbidity in diabetic patients.[2]

Large clinical trials conducted across the globe have shown a higher mortality in patients treated intensively to achieve glycemic control .[3],[4] Hence, the American Diabetes Association (ADA) guidelines emphasizes on individualizing targets to reduce the risk of hypoglycemia in patients with long duration of diabetes and co-morbidities.[5] In patients with Type 1 Diabetes and Type 2 Diabetes, the targeted HbA1c levels should be tailored to the individual, balancing the micro-vascular complication with risk of hypoglycemia. [6-9] The ADA’s most recent guidelines still recommend HbA1C goal for most adults to be <7 %, but also stresses on less stringent levels like <8% for patients with a history of severe hypoglycemia, advanced complications, associated

comorbidities and limited life expectancy. [10] The main objective of this study is to know the clinical facts of hypoglycaemia, precipitating factors, symptomatology, early recognition and correction, Prevention of recurrent episodes of hypoglycemia will reduce morbidity and mortality of diabetic patients.

MATERIAL AND METHODS

The study was conducted on patients admitted in Department of Medicine, Kasturba Medical College and hospital, Manipal, Karnataka during a span of 2 years (2016-2107). A total of 100 diabetic Patients (diabetes diagnosed as per American diabetes Association criteria) with Hypoglycemia (as per inclusion criteria) were selected for the study. The detailed history, clinical examinations and relevant laboratory investigations done for all the patients were evaluated and analyzed in detail. (Using Accu-Chek Nano Glucose meter, Roche Diagnostics, USA, Beckman Coulter Auto analyzer, USA and COBAS 6000, Auto Analyzer, Roche Diagnostics, USA). Study was conducted after institutional ethical committee approval. The statistical analysis was done using SPSS program.

INCLUSION CRITERIA

Plasma glucose ≤40mg/dl without symptoms and <50mg/dl with symptoms.

Exclusion criteria

Non-diabetic patients with hypoglycaemia secondary to systemic illness.

RESULTS

Out of 100 patients of diabetes (under treatment) included in study, 30 (30%) patients were suffering from type 1 diabetes mellitus and 70 (70%) patients from type 2

diabetes mellitus. The male:female ratio was 1:1.7. The maximum number of patients (44%) were in age group of 41 to 60 years. Majority of hypoglycemic patients (n=68, 68%) had blood glucose in the range 31-40 mg/dl and 26 (26%) had blood glucose between 21-30 mg/dl. Only 6 (6%) patients had blood glucose <20 mg/dl.

The most common symptom was sweating (90%) followed by palpitation (80%), incoordination (80%) and altered sensorium (64%). 6% of patients had tremors. Hunger and speech difficulty were reported in 50% of patients. Visual disturbance and headache were present in 40% of patients. 10% of patients had nausea. Two patients of hypoglycemia presented with hemiplegia but it recovered completely on treatment. (Figure 2)

The most common precipitating factor was found to be delaying or skipping meals (80%), followed by decreased carbohydrate intake (70%). In 54% patients, precipitating factor for hypoglycemia was increase in insulin or dose of oral hypoglycemic agent. In 10% of patients, hypoglycemia was due to decrease in insulin requirement due to clearance of infection, reduced renal clearance of Insulin (progression to chronic kidney disease). Most of the patients had more than one precipitating factor. (Figure 1)

Out of 100 patients, 64 (64%) were on only insulin therapy (short acting–regular insulin, mixture of short acting+intermediate acting insulin (30/70) and combination) and 16 (16%) patients were on oral hypoglycemic agents (Sulfonlyureas, biguanides, thiazolidinediones). 20 (20%) patients were on combination (insulin+OHA) therapy. Out of 64 patients who were on insulin therapy alone, 36 (56.25%) were on mixture of short

acting+intermediate acting insulin (i.e Premix Insulin 30/70) and 18 (28.12%) patients were on short acting (regular insulin).

Out of 16 patients who were on oral hypoglycemic agents alone, 6 (37.5%) patients were on Sulfonylureas (Glibenclamide) and other 10 (62.5%) patients were on various combination of oral hypoglycemic agents. None of the patients was on biguanide monotherapy. All hypoglycemia patients recovered fully following treatment without any neurological sequelae.

DISCUSSION

One of the limiting factors in the glycemic management of diabetes mellitus is Iatrogenic hypoglycemia. [5] Other than being sometimes fatal, it leads to recurrent symptomatic and sometimes temporary disabling episodes in patients with type 1 diabetes as well as in those with advanced type 2 diabetes.[11] Drug induced hypoglycemia is reported more frequently in older patients with underlying hepatic or renal dysfunction.[12]

Present study showed that 70% hypoglycemic patients had Type 2 diabetes as compared to 30% patients with type 1 diabetes. In conformity with our observations, Heller [13] has reported that risks of hypoglycemia are higher during insulin treatment and are less in type 2 diabetes mellitus patients. Hepburn *et al.* [14] in their study found that when matched for duration of insulin therapy (mean duration 12 years) and HbA_{1C}, the frequency of severe hypoglycemia is similar in Type 1 and Type 2 diabetes mellitus patients. Higher incidence of hypoglycemia in type 2 diabetic patients in the present study may be due to the fact that some of these patients were admitted for surgical

intervention and were temporarily put on insulin therapy as a part of pre-operative management of diabetes. The mean age of patients in this study was 57.68 years. Although, any age group is prone to hypoglycemia on treatment, however elderly patients on long acting preparations are more susceptible to hypoglycemic episodes. This may be attributed to multi-factorial causes like reduced clearanace of anti-diabetic drugs because of reduced eGFR (Diabetic nephropathy), bed ridden state reduced oral intake, co-morbidities, drug interactions, etc. Hypoglycemia recognition can sometimes be difficult in elderly due to predominance of neurological (dizziness, weakness and confusion) rather than autonomic symptoms (sweating tremors). Symptoms of hypoglycaemia tend to be less specific with increasing age. Independent risk factors for severe hypoglycemia include recent hospitalization, advanced age and polypharmacy.

Delaying or skipping meals was observed as the most important precipitating factor for hypoglycemia (80% of patients). Decreased carbohydrate intake as a causative factor was found in 70% of patients. These patients were eating less as compared to their regular diet during sick days or had anorexia due to their primary illness. All the patients were on hospital supplied diabetic diet. Increase in insulin or OHA dosage to achieve good glycemic control was the precipitating cause for hypoglycemia in 54% of patients. Decrease in insulin requirement was found in 10% of patients. This decrease was due to clearance of the primary infection like treatment of diabetic foot or delayed insulin clearance due to progression to Chronic kidney disease.

Symptom profile provoked by hypoglycemia is idiosyncratic and varies in character, pattern and intensity between individuals.[14] Symptoms of hypoglycemia vary depending on the age of the individual but the symptoms appear to be similar whether

induced by sulfonylureas, insulin analogues, animal or human insulin.[15] Although, no single symptom is present consistently during hypoglycemia in all patients with diabetes, some symptoms are more common than other.[16] In the present study sweating was the most common autonomic symptom (90%) followed by palpitation and inco-ordination (80%), altered sensorium (64%), tremors (60%), hunger and speech difficulty (50%), visual disturbances and headache (40%). Consistent to our results, McAulay *et al.* [17] have reported similar prevalence of symptoms in their study with sweating in 80% of patients, palpitation (55%), incoordination (75%), altered sensorium (40%). Hunger and slurred speech were present in 60% and 40% of patients respectively. Visual disturbance in 20% and headache in 30% of patients. There is no single symptom that is exclusive to hypoglycemia alone. However, hypoglycemia unawareness is a major clinical problem in the management of Diabetic patients on Insulin therapy. The risk of severe episode of hypoglycemia increases 6-7 folds in these patients.[18]

Moreover, Pennebaker *et al.* [19] have found that no single symptom correlate significantly with a specific blood glucose concentration in humans. Hence, it is important that diabetic patient on treatment should be familiar with their own symptom profile, so that they can perceive the early onset of hypoglycemia and know what appropriate action has to be taken.

Our study showed insulin therapy was the most common cause of hypoglycemia accounting for 64% of diabetic patients. Carroll *et al*. [2] also reported insulin treatment of diabetes as the most common cause of severe hypoglycemia in adults. United Kingdom Prospective Diabetes Study (UKPDS) [20] reported severe hypoglycaemia in 11.2% of

patients treated with insulin. In the present study, the majority of hypoglycaemia cases were receiving combination of OHA's rather than monotherapy. And the most common monotheraupeutic offending agent was sulfonylurea. United Kingdom Prospective Diabetes Study (UKPDS) [20] has reported severe hypoglycemia due to sulfonylureas in 3.3% of patients and 2.4% of those treated with bigunanides. Jennings *et al.* [22] have found, varied level of hypoglycemia in patients receiving sulfonylurea treatment but were reported as high as 20% over a 6 month treatment period. Shorr *et al.* [23] described a crude rate of serious hypoglycemia which includes hospitalization, emergency department admission or death of 1.23 per 100 person-years in users of sulfonylureas aged 65 years or older.

All hypoglycemic patients recovered fully following treatment without any neurological sequelae. Zero mortality rate was seen in this study. Usually, death from cerebral edema caused by hypoglycemia is extremely rare. [16] However, hypoglycemia had been implicated in "dead-in-bed" syndrome and in chronic cognitive impairment. [24] Klatt *et al.* [25] found 0.2% of death due to hypoglycemic coma. Macleod *et al.* [26] found "dead-in-bed" syndrome may account for 6% of deaths in diabetic patients under the age of 40. Sartor [27] reported the highest incidence of mortality in childhood onset insulin dependent diabetes between 15-19 years of age. In our study, 100% recovery rate may be attributed to the fact that all patients had hypoglycemia in the hospital, so early detection and effective treatment was given. All hypoglycaemic patients received IV dextrose (25%) and responded well to treatment. Blood sugar monitoring was done following correction of hypoglycaemia.

CONCLUSION

Delaying or skipping meals was found to be the most common precipitating factor for hypoglycemia. Insulin treatment alone was the most common causative factor for hypoglycemia. Among sulfonylureas, glibenclamide was the most common offending agent causing hypoglycemia in elderly. Elimination of hypoglycemia from the lives of people with diabetes will likely be accomplished by new treatment methods that provide plasma glucose-regulated insulin secretion with newer treatment modalities such as automated insulin pumps and artificial/ bionic pancreas.[21]

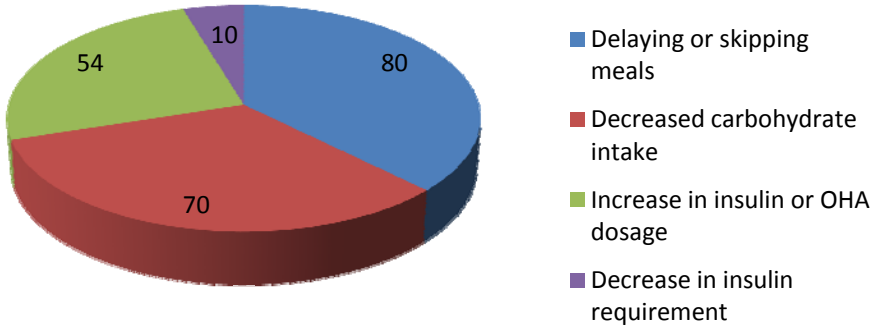

Figure 1. Precipitating factors for hypoglycemia

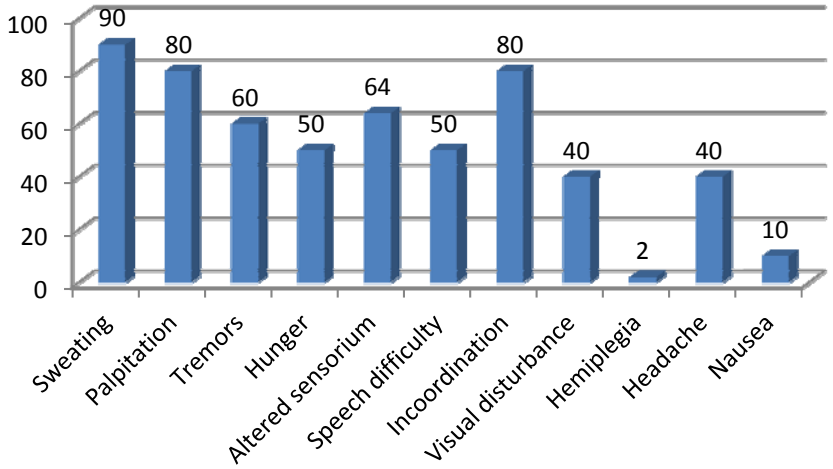

Figure 2. Symptomatology in patients with hypoglycemia (%age)

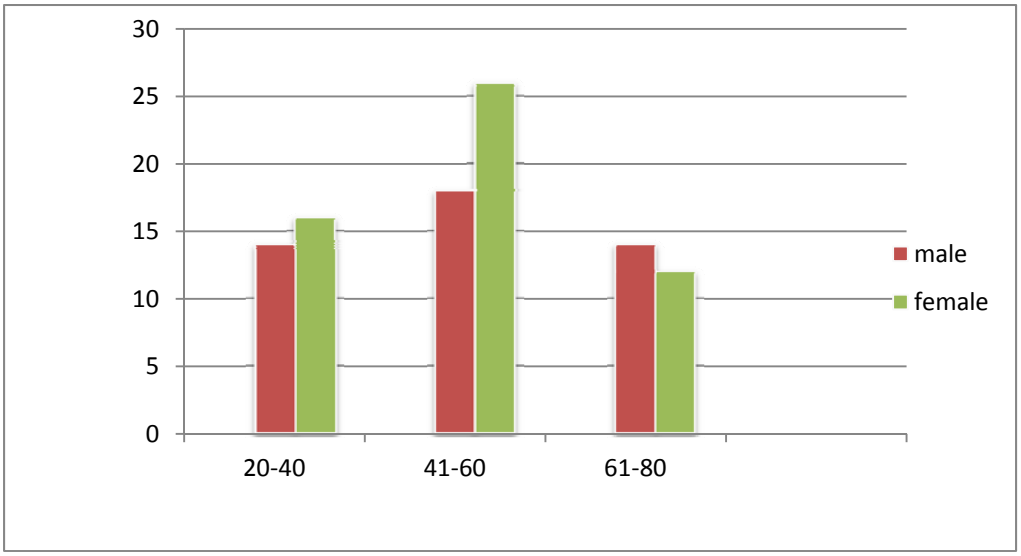

Figure 3. Age & Sex distribution in patients with Hypoglycemia

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