Original Article

A retrospective study on epidemiology of hypoglycemia in Emergency Department

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ABSTRACT

Background: Hypoglycemia is one among the leading causes for Emergency Department (ED) visits and is the most common and easily preventable endocrine emergency. This study is aimed at assessing the incidence and elucidating the underlying causes of hypoglycemia. **Materials and Methods:** A retrospective, observational study which included patients registering in ED with a finger prick blood glucose ≤ 60 mg/dl at the time of arrival. All patients aged above 15 years with the above inclusion criteria during the period of August 2010 to July 2013 were selected. The study group was categorized based on diabetic status into diabetic and nondiabetic groups. **Results:** A total of 1196 hypoglycemic episodes encountered at the ED during the study period were included, and of which 772 with complete data were analyzed. Underlying causes for hypoglycemia in the diabetic group (535) mainly included medication related 320 (59.81%), infections 108 (20.19%), and chronic kidney disease 61 (11.40%). Common underlying causes of hypoglycemia in nondiabetic group (237, 30.69%) included infections 107 (45.15%), acute/chronic liver disease 42 (17.72%), and malignancies 22 (9.28%). Among diabetic subjects on antidiabetic medications ($n = 320$), distribution over 24 h duration clearly reported two peaks at 8th and 21st h. The incidence of hypoglycemia and death per 1000 ED visits were 16.41 and 0.73 in 2011, 16.19 and 0.78 in 2012, 17.20 and 1.22 in 2013 with an average of 16.51 and 0.91, respectively. **Conclusion:** Bimodal distribution with peaks in incidences of hypoglycemic attacks at 8th and 21st h based on hourly distribution in a day can be correlated with the times just before next meal. None of the patients should leave ED without proper evaluation of the etiology of hypoglycemia and the problem should be addressed at each individual level. Increasing incidence of death over the years is alarming, and further studies are needed to conclude the root cause.

Key words: Diabetes, Emergency Department, etiology, hypoglycemia

INTRODUCTION

Hypoglycemia is one among leading causes for Emergency Department (ED) visits. It is also the most common and easily preventable endocrine emergency. With increasing incidence of diabetes and with various modalities of intensive control of blood glucose levels, there is always a risk of a proportional increase in the incidence of hypoglycemia. As prolonged duration of hypoglycemia may lead to significant morbidity and even mortality, each hypoglycemic episode should be addressed accurately in the aspects of etiological diagnosis and preventive measures.

The incidence of severe hypoglycemia (SH) varied from 0.038 to 3.2 episodes per patient per year in patients

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with Type 1 diabetes mellitus (DM)[1-5] and from 0.0004 to 0.96 episodes per patient per year in patients with Type 2 DM.[3,4] Mild hypoglycemia is characterized by unpleasant autonomic and neuroglycopenic symptoms.[6] SH is usually defined as an episode requiring the assistance of another individual for recovery.[7] Causes include drugs, endocrine disorders, malignancies, malnutrition, and renal insufficiency, etc., However, hypoglycemic agents used in DM are the most common cause of hypoglycemia.[8] The causes of hypoglycemia may also depend on the medical facilities in the region, and on the sociocultural and economic status of the population. A high morbidity and mortality are still associated with hypoglycemia, and accurate diagnosis and early treatment may improve the prognosis.[9,10]

Previous studies on hypoglycemia do not reflect much on the nondiabetic patients, and most of them were from outside the Indian subcontinent. These studies do not represent Indian population with much more diversities in genetic constitution, food habits, sensitivity to various drugs, socioeconomic status, epidemiology of infectious, and noninfectious diseases, etc., With this in the background, this study was done to find out the incidence of hypoglycemia in patients admitted through ED and to describe the epidemiological profile, etiology, and incidence of death in hypoglycemia.

MATERIALS AND METHODS

This study was done at a tertiary care medical college hospital in South India. The institutional ethical clearance was taken before the study. Patients aged more than 15 years at the time of arrival to ED with a random blood glucose level of ≤60 mg/dl during the period of August 2010 to July 2013 were included in the study. Those with the inadequate data were excluded from the analysis of the cause of hypoglycemia.

Sample size calculation
The sample size was calculated based on small prior data showing 17 hypoglycemic patients in the duration of 11 days with a total ED attendance of 1650. Required sample size is calculated from the following values and the formula.

Prevalence from pilot study (p) $= 17/1650 = 0.0103 = 1.03\%$ and q=1-p

Margin of error (d) $= 0.5\%$ or 0.005

Confidence level 95% corresponds to Z-score= 1.96

Sample size $= z^2 \times p \times q/d^2 = 4 \times 0.0103 \times 0.99/(0.005)^2 = 1566.$

Data collection methods
Patient hospital identification numbers were noted from the triage register along with time, date of arrival, glucometer random blood sugar (GRBS) values, and age and gender of the patient. Patient's clinical data were retrieved from software used for storing patient information. Data of the patients were entered manually into Microsoft Excel Spreadsheet. All the data were verified twice, once at the time of entry from ED triage register, and second, at the time of chart verification from Clinical WorkStation through software. This two level data verification gave a satisfactory level of data accuracy for further analysis. Completed data were analyzed by special Statistical Package for Social Science (SPSS) version 10.0 (Inc., Chicago IL) for Windows. Descriptive statistics are presented as a mean ± standard deviation.

Study procedure
The whole study group was divided into diabetic and nondiabetic groups. The hypoglycemic attack was defined as patient's random glucose levels ≤60 mg/dl at the time of his/her arrival to ED. Blood sugar levels are recorded from handheld glucometer machine as a routine checkup in ED triage. Common presenting symptoms included in the study were giddiness, sweating, palpitations, altered mental status, seizures, syncope, paresthesia, numbness, and motor deficits.

Positive history of DM was confirmed from other hospital's old medical records, through our clinical workstation history sheets, and drug history. The history of chronic kidney disease (CKD), constitutional symptoms such as soft tissue edema, decreased urine output, creatinine, urea values, creatinine clearance levels, ultrasonography, or computed tomography evidence was considered for admitting positive history of CKD. Additional information such as biopsy, blood and other body fluid culture, and radiological tests were also noted. Etiological diagnosis of hypoglycemic attack due to precise control of blood sugar levels with oral hypoglycemic drugs or insulin or both were considered as a diagnosis of exclusion depending on the modality of treatment.

Infection was diagnosed based on the history of fever, localizing symptoms, raise in total counts with left shift in differential counts, other organ involvement, urine analysis, culture of blood or body fluids, etc., Diagnosis of malignancies was confirmed based on cumulative analysis

of clinical history and investigations. The inconclusive diagnosis was categorized into unknown. Death of patient with hypoglycemic episode was considered if it occurred during patient's ED stay or within 24 h from the time of arrival at ED if the patient later got admitted in the hospital.

RESULTS

One thousand one hundred and ninety-six reports with hypoglycemic attack were retrieved from ED triage register. For analysis of the cause of hypoglycemia and for calculation of death rate, 772 patients with complete documentation were considered. Primary profiling of these 1196 patients revealed that 751 (62.8%) were males and 445 (37.2%) were females. Mean age distribution was 57 ± 14.7 years; the youngest being 16 years old and the oldest 98 years of age. Mean GRBS value in diabetic patients was 39 mg/dl and in nondiabetic patients was 40.6 mg/dl.

Of the total 772 hypoglycemic attacks in the final analysis, 535 (69.3%) episodes occurred in diabetic patients and 237 (30.7%) episodes in nondiabetic patients. Three hundred and thirty-seven (62.99%) male and 198 (37.01%) female patients were in the diabetic group, 161 (67.93%) male and 76 (32.07%) female were in the nondiabetic group. Death occurred in 13 diabetic patients and 36 nondiabetic patients [Table 1].

Among diabetic patients, 342 (60.63%) presented with decreased conscious levels, 64 (22.00%) with giddiness, 20 (3.54%) with sweating/palpitations, 8 (1.42%) with seizures, 6 (1.06%) with motor deficits/paresthesia, and 124 (11.35%) with other/nonspecific symptoms. In the nondiabetic group, symptoms were decreased conscious levels 138 (56.33%), giddiness 15 (6.12%), sweating/palpitations 5 (2.04%), seizures 6 (2.45%), and other/nonspecific symptoms 81 (33.06%) [Table 2].

Underlying causes for hypoglycemia in diabetic group included intensive control of blood sugars by oral hypoglycemic agents (OHAs) 204 (38.13%), intensive control of blood sugars by insulin 103 (19.25%), intensive control of blood sugars by with both insulin and OHAs 13 (2.43%), infections 108 (20.2%), CKD 61 (11.4%), acute/chronic liver dysfunction 13 (2.43%), malignancies 10 (1.87%), drugs/toxins 3 (0.56%), other factors 13 (2.43%), and unknown 7 (1.31%). Whereas in nondiabetic group, causes were infections 107 (45.16%), acute/chronic liver dysfunction 42 (17.72%), malignancies 22 (9.28%), CKD 1 (0.42%), drug overdose/toxins 9 (3.80%), other factors 16 (6.75%), reactive hypoglycemia 1 (0.42%), and unknown 39 (16.45%) [Table 3].

The mean incidence of hypoglycemia per 1000 ED visits were 16.41 in 2011 (343 hypoglycemic episodes among 20,897 ED visits), 16.19 in 2012 (531 episodes among 32,805 ED visits), and 17.20 in 2013 (322 episodes among 18,726 ED visits). The overall incidence of hypoglycemia was 16.51 per 1000 ED visits (1196 hypoglycemic episodes among 72,428 ED visits). The overall incidence of death was 0.91 per 1000 ED visits (49 deaths among 772 hypoglycemic episodes for which complete data were available), with 53,747 ED visits on these days wherein hypoglycemia patients with complete data reported to the ED [Table 4].

DISCUSSION

In the current study, although whole study population has been categorized into diabetic and nondiabetic groups, they cannot be compared as baseline characters among these two study groups have significant variations. As expected, hypoglycemia mostly manifested in middle and elderly age group. In a Taiwanese study, 79.83% of the hypoglycemic episodes with ED attendance occurred in diabetics.[11] Female patients with hypoglycemia were in low number compared to male population due to less number of females in the study group.

Among diabetic subjects on medications (*n* = 320), distribution over 24 h duration clearly reported two peaks at the 8th and 21st h [Figure 1]. This bimodal distribution of hypoglycemia episodes over time may be correlated

Table 1: Demographic characteristics and bimodal peaks

Parameter	Diabetic (*n*=535)	Nondiabetic (*n*=237)
Age	60.3±25.2	50.5±34
Sex		
Male	337	161
Female	198	76
Time of arrival in hours for bimodal peaks in diabetics on medications (*n*=320)	0800-0900 2000-2100	-
GRBS	39.04 (12-58)	40.6 (10-59)
Sodium	132±6.2	130±7.5
Potassium	4.0±1.0	4.3±1.1
Expired (%)	13 (2.43)	36 (15.19)

GRBS: Glucometer random blood sugar

Table 2: Presenting symptoms

Presenting symptom(s)	Diabetic, *n* (%)	Nondiabetic, *n* (%)	Total, *n* (%)
Giddiness	64 (11.35)	15 (6.12)	79 (9.77)
Sweating/palpitation	20 (3.54)	5 (2.04)	25 (3.09)
Decreased conscious levels	342 (60.63)	138 (56.33)	480 (59.33)
Seizures	8 (1.42)	6 (2.45)	14 (1.73)
Motor deficit/paresthesia	6 (1.06)	0.00	6 (0.74)
Others/nonspecific	124 (22.00)	81 (33.06)	205 (25.34)
Grand total	564 (100)	245 (100)	809 (100.00)

Table 3: Etiology of hypoglycemia

Etiology of hypoglycemia	Eren *et al*.	Feher *et al*.	Cheng-Chuan Su		Current study	
			Diabetic	Nondiabetic	Diabetic *n*=535 (%)	Nondiabetic *n*=237 (%)
Intensive control of sugars with OHA (%)	41.7		78.6	2.1*	204 (38.13)	
Intensive control of sugars with insulin (%)	24.4	17			103 (19.25)	
Intensive control of sugars with both OHA and insulin (%)	4				13 (2.43)	
Liver disease (%)	0.9		0.6	13.1	13 (2.43)	42 (17.72)
Renal dysfunction (%)		1	6.6	10.9	61 (11.4)	1 (0.42)
Malignancies (%)	4.9		2.1	10.9	10 (1.87)	22 (9.28)
Reactive hypoglycemia (%)	11.6				0	1 (0.42)
Missing meal (%)		51				
Others (%)	9		1.7	34.8	13 (2.43)	16 (6.75)
Drugs/toxins (%)		19	2.1		3 (0.56)	9 (3.80)
Unknown reasons (%)	3.5	12			7 (1.31)	39 (16.45)
Infection/sepsis (%)			8.5	28.2	108 (20.2)	107 (45.16)
Total (%)	100	100	100	100	100	100
Individual sample size	225	86	182	46	535	237
Total sample size	225	86	228		772	

OHA: Oral hypoglycemic agent

Table 4: Incidence of hypoglycemia and death rate over the years

Year	Total ED attendance*	Number of episodes of hypoglycemia*	Considered population with complete data for calculation of death rate**	ED attendance on relevant days**	Number of deaths**	Incidence (/1000)	
						Hypoglycemia*	Death**
2011	20,897	343	100	8186	6	16.41	0.73
2012	32,805	531	381	28,340	22	16.19	0.78
2013	18,726	322	291	17,221	21	17.20	1.22
Total	72,428	1196	772	53,747	49	16.51	0.91

*Total number of episodes (1196) and ED attendance during 1 year for incidence rate, **Considered sample (772 for which complete data are available) for incidence of death and death rate; Relevant days are the days wherein hypoglycemia patients with complete data for analysis (772) reported to the ED. ED: Emergency Department
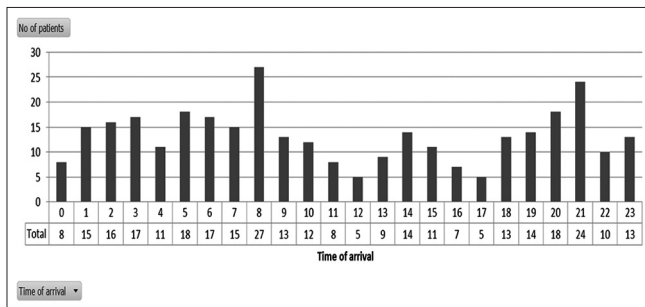

Figure 1: Incidence of hypoglycemia among diabetics on medications (*n* = 320)

with the times just before next meal. However, it should be noted that the patient flow to the ED varies during different hours of the day, and this could affect the study findings. Murata *et al*.[12] found that an omitted meal led to the highest number of hypoglycemic episodes at 5 pm. Krnacova *et al*.[13] study showed that most hypoglycemic episodes were experienced by patients between 2 pm and 6 pm. Another study reported that the lowest glycemia occurred just before the evening meal.[14]

Similar to the reports of Eren *et al*.,[15] the leading cause of hypoglycemia in diabetic patients in this study has been observed to be intensive control of blood glucose levels

with antidiabetic drugs. Current study differed from Feher *et al*.,[16] which reported missed meal as the predominant cause of hypoglycemia. In nondiabetic hypoglycemia attacks, Su study[11] reported hypoglycemia mainly due to infections, liver and kidney disease, and malignancy. Results of the current study also support this evidence. Moreover, the current study reports the proportion of hypoglycemia in diabetic patients caused by renal impairment was much higher than in nondiabetic patients. Renal disease may reduce gluconeogenesis and insulin degradation and thus be associated with hypoglycemia.

In diabetic patients, the leading source of infection was from genitourinary system followed by surgical causes, respiratory, hepatobiliary, and gastrointestinal causes. However, in the nondiabetic population, the predominant focus of infection was hepatobiliary followed by surgical sites. Further studies need to get specific associations with individual foci of sepsis.

Swanson *et al*.,[17] Halton, Ontario, reported the incidence of hypoglycemia as 37.5/1000 patients in overall emergency ambulance calls. Overall incidence in this study was 16.51/1000 ED visits (1196 hypoglycemic episodes among 72,428 ED visits) and is much less compared to the

afore-mentioned study. The current study reported an increase in the incidence of hypoglycemia over successive years from 2011 to 2012 and a decrease from 2012 to 2013. Both of these studies have been done on near to similar population based on services required but in different regions. Leese *et al*.[3] reported the incidence of SH as 2.09, which included both emergency ambulance calls and direct ED visits. Compared to the current study, incidence report is very low even though it covered both pre-ED and ED hypoglycemia.

The overall incidence of death was 0.91/1000 ED visits (49 deaths among 772 hypoglycemic episodes for which complete data were available). Mortality of patients with SH seen in EDs ranged between 0.3% and 8.3% in other studies.[18-21] Technically above studies cannot be compared with a current study due to differences in study settings.

The incidence of recurrent admissions for hypoglycemia suggested that 15 out of 1196 patients got admitted more than once in a fortnight. Furthermore, 12 patients were readmitted within a month. Twenty-six patients with hypoglycemic attack were admitted more than once in a calendar year. The previous studies also reported that hypoglycemia occurs more often than previously reported in insulin-treated Type 2 diabetes and with sufficient frequency to cause significant morbidity.

The current study included large sample size which may minimize bias due to retrospective data collections. In this study, additional information obtained included categorizing the whole study group into diabetic and nondiabetic patients and calculation of incidence and death rates. The main limitation was the retrospective nature of the study. History or evidence of alcohol consumption precipitating hypoglycemia was not taken into account in this study. Variations in the patient flow to the ED during different hours of the day could compound the calculation of the bimodal peaks among diabetics on antidiabetic drugs, and the significance of this peak is not calculated statistically. Moreover, a bimodal distribution of hypoglycemia overtime cannot be considered completely accurate as these times might not correlate exactly with the onset of symptoms. These timings were the only time of arrival of patients at the ED.

Conclusion

Hypoglycemia is mainly medication related in diabetics and infection is the leading cause in nondiabetics. Among diabetic subjects on medications, bimodal distribution

with peaks in incidences of hypoglycemic attacks at the 8th and 21st h based on hourly distribution in a day can be correlated with the times just before next meal. This problem needs to be addressed by treating physician from the perspective of patient education, and possibly by modification of medications as well. None of the patients should leave ED without proper evaluation of the etiology of hypoglycemia and the problem should be addressed at each individual level. Increasing incidence of death over the years is alarming, and further studies are needed to conclude the root cause.

Conflicts of interest
There are no conflicts of interest.

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