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Temporal patterns of inpatient hypoglycaemia are treatment-dependent

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Abstract

Background: Inpatient hypoglycaemia has been well studied around the world, and more tools are being developed to understand and predict hypoglycaemic episodes. Most published data, however, focuses on patient characteristics and predictions of whether a patient would have a hypoglycaemic episode during inpatient stay. There is a paucity of data concerning the timing, as well as types of diabetic medications used, surrounding a hypoglycaemia episode.

Objectives: To characterise inpatient hypoglycaemia episodes by time and associated diabetes medications, on top of baseline patient characteristics.

Design: Retrospective observational study of 425 hypoglycaemia episodes, over a 2 month period from two general internal medicine wards, in a tertiary medical hospital.

Methods: A discrete hypoglycaemic episode is defined as a capillary blood glucose (CBG) reading of <4 mmol/L. Hypoglycaemic episodes were further sub-analysed by dividing them into three time frames – day (0801–1600), evening (1601–2359) and night (0000–0800).

Results: In total, 425 hypoglycaemia episodes from 207 patients were analysed. Sulphonylurea (SU), premixed, basal and basal-bolus insulin regimens were associated with 31.8%, 30.4%, 15.1% and 5.9% of the hypoglycaemia episodes, respectively. All agents revealed significant intra-day differences ($p < 0.05$) except for the basal-bolus insulin regimen ($p = 0.76$). Basal insulin and sulphonylurea-associated hypoglycaemia occurred mostly in the midnight timeframe (0000–0800) at 65.6% and 47.4%, respectively, whereas premixed insulin-associated hypoglycaemia occurred mostly in the evening timeframe (1601–2359) at 51.2%. In total, there were significant differences in the distribution of hypoglycaemia across the three time frames associated with different diabetes medications ($p < 0.05$).

Conclusion: There are marked differences in the medications associated with inpatient hypoglycaemia at differing time points. These time points offer insight into appropriate CBG testing timings for different diabetes medications. Hence, stratified monitoring and strategic 3 a.m. testing of CBG for patients on sulphonylurea and basal insulin should be considered in tackling inpatient hypoglycaemia.

Plain language summary

Understanding the timing and medications linked to low blood sugar in hospital patients

This study looked at the problem of low blood sugar (hypoglycaemia) in hospital patients with diabetes. Low blood sugar is a common issue for patients staying in hospitals, especially those receiving treatment for diabetes. Typically, low blood sugar occurs in episodes. Most research focuses on who is likely to experience low blood sugar during their hospital stay, but there is limited information on when these episodes occur and which diabetes medications are most likely to cause them. The goal of this study was to analyse the timing of low blood sugar episodes in hospital patients and to understand

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which diabetes medications were involved. We reviewed 425 instances of low blood sugar in 207 patients over two months in two medical wards of a large hospital. The study found that certain medications were linked to low blood sugar at specific times of the day. For example, sulphonylurea (a type of diabetes pill) and basal insulin (an injectable long-acting insulin) caused most episodes during the night, while premixed insulin (an injectable with two kinds of insulin) caused most episodes in the evening. These results suggest that hospitals should adjust their blood sugar testing schedules based on the type of diabetes medication a patient is receiving. In particular, testing for blood sugar at 3 a.m. might be helpful for patients taking sulphonylurea or basal insulin to prevent dangerous drops in blood sugar during the night.

Keywords: hypoglycaemia, insulin, pre-mixed, sulfonylurea

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Introduction

Inpatient hypoglycaemia is associated with increased morbidity, mortality, length of stay and healthcare costs.[1–3] Many observational studies suggest that optimal inpatient glycaemic control is associated with reduced infections and mortality rates[4], and this has been supported by a few randomised clinical trials performed in the Intensive Care setting.[5] Despite clear therapeutic goals set out by various professional societies,[6] the rates of inpatient hypoglycaemia remain high, as shown by National Diabetes Inpatient Audit in the UK with inpatient hypoglycaemia accounting for 69.5% of diabetic-related harms.[7] However, there is a paucity of data from Asia on inpatient hypoglycaemia, with the exception of one study performed in Indonesia,[8] which evaluated the risk factors of inpatient hypoglycaemia in 475 subjects. While management of hypoglycaemia is hospital/institution dependent, the treatment goals and principles in Asia largely mirror those of recommendations from Europe and North America.

Many inpatient hypoglycaemia studies focus on patient characteristics and the use of insulin versus sulphonylureas (SU). There is, however, a lack of studies on the effects of premixed, basal and short-acting insulin in hypoglycaemia, which gives us more granularity on this important subject. Most evidence focuses instead on nocturnal hypoglycaemia as an outcome and is often done in the setting of clinical trials.[9] Hence, in this study, we aim to elucidate the occurrence of inpatient hypoglycaemia at different times of the day, and how these episodes of hypoglycaemia are associated with different diabetes medications.

Methods

Ethical review

This study received ethical approval from the SingHealth CIRB (CIRB Ref 2018/2437) in 2018. As an IRB-approved retrospective study, all patient information was de-identified and patient consent was not required.

Participants and data

A retrospective cohort study was performed using data extracted from electronic health records (Sunrise Clinical Manager), over a consecutive 2-month period (between May and June 2018) for patients admitted to the internal medicine wards in Singapore General Hospital, a tertiary hospital with over 1900 beds. There were no exclusion criteria. We included patients who have a recorded hypoglycaemic event, defined as a capillary blood glucose (CBG) reading of <3.9 and <3.0 mmol/L as per Level 1 and 2 hypoglycaemia in accordance with IHSG guidelines. CBG readings were taken either as regular premeal three times daily or if there was suspicion of hypoglycaemia as guided by patients' symptoms. Briefly, nurses will perform CBG testing if patients exhibit symptoms such as palpitations, dizziness, headache, sweating, unceasing hunger, weakness, blurring of vision, slurred speech, confusion and seizures. The CBG machine used is

the Accu-Chek Instant, Device Number 973 (Roche Diabetes Care).

Demographics, clinical and biochemical data were also extracted. Recurrent hypoglycaemia is defined as consecutive hypoglycaemic events occurring within a 1-h window.

Statistical analysis

p-Values were calculated using Welch's ANOVA or Chi-square test (specified). Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and R v4.2.2, with packages onewaytests and stats.

Results

Data were collected from 207 (96 males) subjects with a mean age of 70.0 ± 11.8 years old, who experienced a total of 425 recorded episodes of hypoglycaemia (Table 1). Of note, the mean Charlson Comorbidity Index (CCI)[10] was 6.8 ± 2.7, and the mean CBG and glycated haemoglobin (HbA1c) were 3.3 ± 0.5 mmol/L and 8.3% ± 2.2%, respectively. Approximately 34.1% of events were recurrent hypoglycaemia, and 21.2% of events were recorded as Level 2 hypoglycaemia.

To further characterise the hypoglycaemic events, events were subdivided into three time frames: day (0801–1600), evening (1601–2359) and night (0000–0800). This is summarised in Table 2. Comparison between patients on different diabetes medications revealed significant differences in mean age, CCI, HbA1c and events occurring at different time frames ($p < 0.05$). There were significant differences in the distribution of hypoglycaemic events across the three time frames ($p < 0.001$), with most hypoglycaemic events occurring at night. Notably, hypoglycaemic events at night were associated with higher mean age and higher CCI. Of note, there were no significant differences in BMI, length of stay or depth of hypoglycaemia between patients across the three time frames. Recurrent hypoglycaemia occurred at a higher rate during the day compared to evening and night, at 53.0%, 29.2% and 31.4%, respectively ($p = 0.002$).

Overall, there were significant differences in the distribution of hypoglycaemia events associated with different diabetes medications across the three time frames ($p < 0.001$). None of these diabetes medications were newly initiated. Of note, SU contributed most to night events (33.5%) while premix insulin contributed most to both day and evening events (42.2% and 39.3%).

A further analysis was performed to look at the characteristics of hypoglycaemic patients associated with different diabetes medications and

Table 1. Clinical characteristics of the 425 hypoglycaemic episodes included in this study.

Variable	Value (*n* = 425)
Age (years)	70.0 ± 11.8
Sex (% male)	39.8
BMI (kg/m^2)	25.3 ± 5.3
Capillary blood glucose (mmol/L)	3.3 ± 0.5
HbA1c (%)	8.3 ± 2.2
Level 2 hypoglycaemia (%)	21.2
LOS (days)	13.9 ± 13.7
CCI	6.8 ± 2.7
Reason for admission (episodes)	
Infectious	
Respiratory infections	75
Genitourinary infections	37
Gastrointestinal infections	29
Skin infections	31
Other infections	61
Non-infectious	
Cardiovascular	59
Renal	10
Metabolic	34
Others	89
Steroid use (episodes)	22

Level 2 hypoglycaemia as defined by IHSG guidelines – <3.0 mmol/L.
CCI, Charlson comorbidity index; HbA1c, glycated haemoglobin; LOS, length of stay.

Table 2. Clinical and pharmacological characteristics for hypoglycaemic episodes occurring during the day (0801–1600), evening (1601–2359) and night (0000–0800).

Variable	0000–0800	0801–1600	1601–2359	*p*-Value
No. of hypo episodes ($n=425$)	191 (44.9%)	66 (15.5%)	168 (39.5%)	<0.001[a]
Age	71.4 (11.4)	67.0 (11.8)	69.6 (12.1)	0.031
BMI	24.8 (5.3)	25.4 (4.8)	25.7 (5.6)	0.25
Creatinine	231.1 (194.3)	249.3 (249.0)	214.1 (181.8)	0.49
HbA1c	8.0 (1.9)	8.7 (2.7)	8.5 (2.2)	0.042
LOS	13.4 (12.9)	16.0 (15.6)	13.6 (13.9)	0.48
Charlson comorbidity index	7.1 (2.7)	6.7 (3.2)	6.4 (2.4)	0.037
CBG reading (first hypo)	3.3 (0.5)	3.3 (0.6)	3.3 (0.5)	0.93
Level 2 hypoglycaemia	40 (20.9%)	16 (24.2%)	34 (20.2%)	0.81
Medical regimen				<0.001[b]
Premix	35 (18.3%)	28 (42.2%)	66 (39.3%)	
Basal	42 (22.0%)	8 (12.1%)	14 (8.3%)	
Basal bolus	7 (3.7%)	8 (12.1%)	10 (6.0%)	
SU	64 (33.5%)	15 (22.7%)	56 (33.3%)	
SU + Insulin	25 (13.1%)	1 (1.5%)	11 (6.5%)	
SCSI	15 (7.9%)	3 (4.5%)	10 (6.0%)	
Others	3 (1.6%)	3 (4.5%)	1 (0.6%)	
Recurrent hypoglycaemia	60 (31.4%)	35 (53.0%)	49 (29.2%)	0.0032

Unless (%) shown, numbers in bracket show standard error. (%) shows proportion of episodes from total for number of episodes, Level 2 hypoglycaemia and Recurrent hypoglycaemia. (%) shows proportion within time frame for Medical regimen. Recurrent hypoglycaemia is defined as consecutive hypoglycaemic events occurring within a 1 h window. Level 2 defined as CBG <3.0 mmol/L. Other categories include oral hypoglycaemics such as metformin and DPP-IV inhibitors.
[a]Using Chi-squared test.
[b]Using Chi-square test with Monte Carlo simulations.
Basal, long-acting insulin; Basal Bolus, long-acting insulin + pre-meal short-acting insulin; CBG, capillary blood glucose; HbA1c, glycated haemoglobin; LOS, length of stay; Premix, premixed short + long-acting insulin; SCSI, Sliding Scale Insulin, defined as bolus insulin dosage contingent on CBG readings; SU, sulphonylureas; SU + Insulin, patients prescribed both insulin (in any formulation) alongside sulphonylurea.

results are summarised in Table 3. SU, premixed, basal and basal-bolus insulin regimens were associated with 31.8%, 30.4%, 15.1% and 5.9% of the hypoglycaemia episodes, respectively. SU-associated hypoglycaemia occurred mainly at two peak periods in the evening and at night (41.5% and 47.4%). Over half of premixed insulin-associated hypoglycaemia occurred in the evening (51.2%), in contrast to less events at night and during the day (27.1% and 21.7%). Basal insulin-associated hypoglycaemia occurred predominantly at night (65.6%). Basal-bolus insulin regimen-associated hypoglycaemia was more evenly distributed in the 24 h period as compared to premixed and basal insulin, with no within-group statistical significance between the time frames ($p=0.756$). A graphical representation can also be found in Figure 1; the propensity

Table 3. Time distribution and clinical characteristics for episodes attributed to different pharmacological regimens.

Variable	Premix	Basal	Basal bolus	SU	SU + Insulin	SCSI	Others	*p*-Value
No. of hypo episodes ($n = 425$)	129 (30.4%)	64 (15.1%)	25 (5.9%)	135 (31.8%)	37 (8.7%)	28 (6.6%)	7 (1.6%)	
Number of hypo events								
0000–0800	35 (27.1%)	42 (65.6%)	7 (28.0%)	64 (47.4%)	25 (67.6%)	15 (53.6%)	3 (42.9%)	<0.001[a]
0801–1600	28 (21.7%)	8 (12.5%)	8 (32.0%)	15 (11.1%)	1 (2.7%)	3 (10.7%)	3 (42.9%)	<0.001[a]
1601–2359	66 (51.2%)	14 (21.9%)	10 (40%)	56 (41.5%)	11 (29.7%)	10 (35.7%)	1 (14.7%)	<0.001[a]
Age	68.5 (12.2)	72.2 (10.4)	62.6 (13.4)	71.4 (11.4)	71.2 (9.1)	68 (14.0)	71.71 (9.3)	0.024
Creatinine	253 (231)	232 (184)	170 (110)	200 (173)	300 (223)	202 (200)	146.86 (115.8)	0.023
HbA1c	8.7 (2.2)	7.8 (1.8)	8.8 (2.5)	7.6 (1.4)	9.4 (2.8)	8.7 (2.7)	11.4 (3.5)	<0.001
Charlson comorbidity index	6.9 (2.6)	7.7 (2.6)	6 (2.4)	6.5 (2.7)	6.6 (2.4)	6.1 (3.6)	6 (1.5)	0.032

Abbreviations and definitions as per Table 2. Unless (%) shown, numbers in brackets show standard error. (%) shows proportion of episodes from total for Number of episodes, and proportion within Medical regimen for each time frame.
[a]Chi squared test.

for hypoglycaemia episodes occurring at night can be clearly seen for SU (yellow), SU with Insulin (brown) and basal insulin (turquoise).

There were also significant differences in the characteristics of the hypoglycaemic patients attributable to the different diabetes medications. One of the most striking differences was that patients with SU-associated hypoglycaemia had significantly tighter background glycaemic control, evidenced by the lowest HbA1c (7.6% ± 1.4%) as compared to patients on other diabetes medications. Moreover, patients with SU-associated hypoglycaemia were older than most other groups, except for patients with basal insulin-associated hypoglycaemia; yet even with a comparable age range, basal insulin was only associated with 15.0% of hypoglycaemic events compared to 31.8% for those on SU.

Discussion

Out of the 425 cases of hypoglycaemic events recorded in this study, 44.9%, 15.5% and 39.5% of events occurred at night, day and evening time frames, respectively. This highlights that there is a temporal aspect towards the occurrence of hypoglycaemia in patients, and is particularly relevant in the inpatient setting. It is also reasonable to assume that the staffing of healthcare professionals, including both nurses and doctors, is at its lowest in the early hours of the day. With such limited resources, there is an increased risk of harm to patients with hypoglycaemia at such hours. While a diversion of staffing may circumvent this issue and increase the quality of care for such hypoglycaemic issues, this in turn incurs an opportunity cost for other acutely ill patients. Furthermore, there is an increased risk of hypoglycaemic events going undetected for patients who are asleep during the early hours of the day, thus increasing the chances of untimely treatment.

There have been consistent reports of inpatient hypoglycaemia with peak incidence between the range of 0000–0600 h.[11–13] This observation has been validated by our data, with 44.9% of events occurring in a similar time frame (0000–0800 h). We also note that there are two other peak incidences at 1100–1200 and 1700–1800 h (Figure 1); these peaks correspond to pre-meal timings and have also been similarly observed in other studies.[13] Interestingly, we observed that patients with hypoglycaemic events at night (0000–0800 h) were older and with higher CCI. This is important as these vulnerable patients have the highest risk of hypoglycaemia at a time when staffing is at its lowest at night in most acute care hospitals.

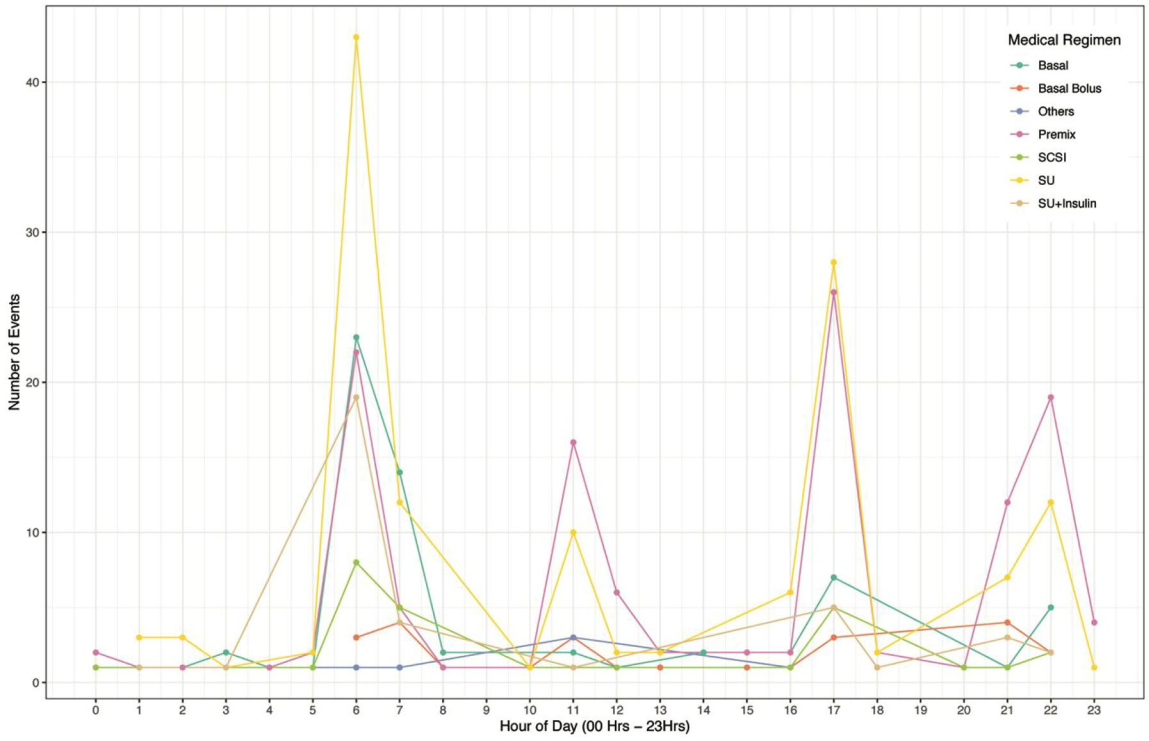

Figure 1. Hourly distribution of hypoglycaemic episodes grouped by pharmacological regimens showing medication-specific temporal patterns. *X*-axis: time, shown in 1 h ticks. *Y*-axis: Number of hypoglycaemic episodes per Medical regimen (colour).

Furthermore, patients on SU were older, with a higher propensity for developing hypoglycaemia at night. Moreover, this group of patients may have reduced oral intake while they are unwell, and an unadjusted dose of SU will increase the risk of hypoglycaemia. Considerations should thus be given to reduce the doses of SU in inpatients with reduced oral intake.

We further analysed the types of medical regimens that contributed to hypoglycaemic events. Use of insulin and SU have been reported in previous studies on inpatient hypoglycaemia,[14] but it is unclear which types of insulin are implicated, except for basal insulin which has been studied separately.[15] We have shown that premixed insulin use was associated with nearly a third of hypoglycaemic events (30.4%) while basal (15.1%) and basal-bolus (5.9%) regimens were associated with less hypoglycaemic events. This is not surprising as changes in meals and appetite of acutely ill medical patients on premixed insulin may have contributed to the occurrence of hypoglycaemia; this is on top of any fasts for medical reasons, of which 5.7% of patients had indications. Thus, special consideration should also be given to inpatients with reduced oral intake while on premixed insulin. One strategy would be to reduce the dose of premixed insulin, but a conversion to basal-bolus insulin may also be considered for severely unwell patients with a significant reduction of oral intake. This must be done with caution, however, as the conversion to basal bolus is not entirely risk-free, and healthcare professionals need to be educated for safe conversions.

Hour-by-hour analyses also revealed further insights regarding the timing of hypoglycaemia (Figure 1). Two kinds of patterns can be concluded: a triphasic pattern following meal times, and a biphasic pattern with peak incidences occurring in the evening or night. SU, SU and insulin and basal insulin use all fall under the biphasic pattern, and thus more attention should be diverted to catching late-night hypoglycaemic events; whereas premix and basal-bolus regimes follow the triphasic pattern. These patterns are built on top of the current understanding of nocturnal hypoglycaemia, where the lack of dietary intake throughout the night predisposes to

nocturnal hypoglycaemia on top of behavioural and pharmacological factors. Taken together, this information may be helpful in planning and establishing strict CBG monitoring guidelines in accordance with different diabetes medications. A helpful suggestion would be to implement a strategic 3–4 a.m. CBG test for patients under SU, SU and insulin and basal insulin regimens. This would increase the monitoring of this at-risk group of early morning hypoglycaemic patients.

The use of continuous glucose monitoring (CGM) has been explored extensively in outpatient settings,[16] and has recently gained traction for inpatient diabetes management, showing some potential benefits and improvement in outcomes.[17,18] Indeed, CGM may allow increased capture of hypoglycaemic episodes, but the path to improved outcomes from CGM will require further work on implementation.[19] Education of nursing teams, data interpretation of CGM and technological assimilation to patient management will be important for inpatient CGM use. Given the highly standardised protocols of hypoglycaemia management in response to CBG readings, we foresee that the results of this study are immediately applicable to many institutions, and will assist in the future implementation of CGM use.

One of the limitations of our study is that we have neither collected information on diabetic patients yet, nor normoglycaemic patients in the same inpatient setting. With such information, it would be possible to compare the clinical characteristics of patients who are normoglycaemic and hypoglycaemic, specifically when they are prescribed the same pharmaceutical regimen. This will be taken into account for future studies. Furthermore, we did not calculate statistical power for sample size. This is a limitation that we hope to address in a larger-scale study in the future.

In summary, this study has demonstrated that different medical regimens contribute to different kinds of temporal patterns for hypoglycaemic events. Night-time hypoglycaemia warrants specific attention, and medications should be adjusted if there is reduced oral intake. CBG monitoring guidelines should also be adjusted to reflect different needs according to the patient's medications.

Declarations

Ethics approval and consent to participate

This study received ethical approval from the Singhealth CIRB (CIRB Ref 2018/2437) in 2018. This is an IRB-approved retrospective study, all patient information was de-identified and patient consent was not required. Patient data will not be shared with third parties.

Consent for publication

Not applicable.

Author contributions

Wharton O. Y. Chan: Formal analysis; Investigation; Project administration; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Paik Shia Lim: Conceptualisation; Data curation; Writing – review & editing.

Alcey Li Chang Ang: Formal analysis; Methodology; Visualisation; Writing – original draft.

Su-Yen Goh: Conceptualisation; Resources; Writing – review & editing.

Yong Mong Bee: Conceptualisation; Resources; Writing – review & editing.

Ming Ming Teh: Conceptualisation; Investigation; Project administration; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The participants of this study did not give written consent for their data to be shared publicly, even if anonymised, so due to the sensitive nature of the research supporting data is not available.

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