Severe Hypoglycemia in Type II Diabetes at Nakornping General Hospital: A Study on Clinical Risk Factors

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Objective: *To study clinical risk factors of severe hypoglycemia in type II diabetes*
Material and Method: *Fifty-one type II diabetes with severe hypoglycemia admitted between October 2006 and September 2008 and 359 nonhypoglycemic type II diabetes were evaluated in this case-control study. Medical records were retrospective reviewed for age, sex, duration of diabetes, previous diabetes registration, concomitant diseases, HbA_1c level and current diabetes therapy in both groups. Acute illness, blood glucose, hypoglycemic episodes, symptoms and length of stay (LOS) were assessed in hypoglycemic group. Univariate and multivariate logistic regression were used to determine risk factors of severe hypoglycemia.*
Results: *Fifty-one hypoglycemic and 359 nonhypoglycemic patients were analyzed. The authors found that 40% of severe hypoglycemic cases were recurrent. The average LOS was six days. Intercurrent illness was the major leading cause of hypoglycemia (54.9%). Mean blood glucose level was 37.2 mg/dl (SD = 13.5). Twenty-three of fifty-one (45%) patients presented with unconsciousness. Predisposing risk factors associated with severe hypoglycemia were old age ($p = 0.026$), insulin therapy ($p = 0.001$), cirrhosis ($p = 0.020$), cerebrovascular disease ($p = 0.040$), and no diabetes registry ($p = 0.015$). Sex, HbA_1c level, hypertension and chronic kidney disease were not risk factors associated with severe hypoglycemia.*
Conclusion: *Risk factors associated with severe hypoglycemia in type II diabetes were elderly, insulin therapy, cirrhosis, previous cerebrovascular disease, lack of standard diabetic care and team approach. Self-monitoring of blood glucose and individual case management should be considered in those with previous hypoglycemic events.*

Keywords: *Type II diabetes, severe hypoglycemia, recurrent hypoglycemia, risk factors*

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Hypoglycemia is the most common endocrine emergency. It has a significant economic impact and impairs quality of life in diabetic patients[1].

Hypoglycemia is common in diabetes and non-diabetes but patients with type I diabetes have a higher rate of severe hypoglycemia than those in Type II[2-4]. An episode of severe, disabling hypoglycemia, at least temporally, occurred approximately once a year. In type II diabetes, the frequency of severe hypoglycemia is quite low[5,6]. Nevertheless, it is the leading limiting factor in the glycemic management of type I and insulin-treated type II diabetes[7]. Risk factors for hypoglycemia include 1) endogenous insulin deficiency 2) a history of hypoglycemia, or hypoglycemic unawareness 3) aggressive glycemic control per se as evidenced by lower glycemic goals, lower HbA_1c levels, or both 4) recent moderate or intensive exercise 5) sleep and 6) renal failure[7,8]. Insulin use, oral hypoglycemic agent especially sulfonylurea, alcohol or intensive glucose tight control had strong evidences related to hypoglycemia[6,9,10]. The clinical syndrome of hypoglycemia is documented by Whipple's triad[11] and includes hypoglycemic symptoms, low plasma glucose level and symptoms relieved when plasma glucose concentration is normal. These symptoms include palpitations, tremor, sweating (neurogenic or autonomic symptoms) or neuroglycopenic symptoms such as behavior changes, confusion, seizure, or coma. Severe hypoglycemia refers to event requiring assistance of another individual[12]. The concept of hypoglycemia-associated autonomic failure (HAAF) in type1 DM explained defective glucose counter regulation and hypoglycemia unawareness in Type1 DM as well as in advanced type II DM.

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In Thailand, previous studies on severe hypoglycemia in type II diabetes were limited. Information on severity, predisposing risk factors of severe hypoglycemia in type II DM in clinical practice has not been well described. In order to optimize the goal of treatment and balance tight glycemic control with risk of hypoglycemia, potential risk factors were needed to identify.

The purpose of the present study was to assess the severity and risk factors of severe hypoglycemia in type II DM treated in Nakornping General Hospital, Thailand.

Material and Method

The present study was approved by the Ethics Review Committee for Research of the hospital. The authors evaluated adult type II diabetes aged more than 18 years. Fifty-one type II diabetic patients admitted with severe hypoglycemia in Medical Department at Nakornping Hospital between October 2006 and September 2008 were studied. Documented symptomatic hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied with plasma glucose $\leq$ 70/dl and severe hypoglycemia was defined as low blood glucose level and requiring assistance from another person[12]. The control subjects were non-hypoglycemic diabetic patients who received diabetes treatment at the out patient department in the same hospital during the same period.

Study design

Case-control study design was used.

The study cases (n = 51) were the patients with severe hypoglycemia.

The authors expected 80% of power to calculate sample size with a 95% confidence interval. The controls (n = 359) were type II diabetes without severe hypoglycemia.

The authors selected the controls from nonhypoglycemia type II diabetic patients who attended on the same day of previous visits of the cases before they developed severe hypoglycemia (proportion 1:7). Inclusion criteria were 1) type II diabetic patients that presented with severe hypoglycemia, 2) type II diabetes with no history of clinical hypoglycemia that were followed-up during the same period.

Exclusion criteria were 1) type II diabetic patients admitted with any disease but had normal blood glucose and developed hypoglycemia during their admissions, 2) type II diabetic patients that did not regularly attend at Nakornping Hospital.

The subjects of both groups were assessed personal data, duration of diabetes, diabetes registration (completeness of standard for examination and diabetic education by DM care team), concomitant diseases such as hypertension, previous stroke, cirrhosis, congestive heart failure and chronic kidney disease (serum creatinine $\geq$ 1.5 mg/dl), glycemic control (evaluated by HbA_1c level in the past 6 months), current insulin therapy and adjustments of dosage of anti-diabetic medications in previous visits.

In the hypoglycemic groups, additional data on intercurrent illness within two weeks before admission, symptoms leading to the hospital, level of blood glucose, episodes of severe hypoglycemia and length of stay (LOS) were assessed.

Statistical analysis

The subjects' demographic data and baseline characteristics were described using means, SD, frequency, and percentage.

Statistical analysis of the data was performed using Stata version 10. The Chi-square or Fisher's exact probability and Student's t-test were used to compare differences where appropriate. Univariate and multivariate logistic regression were used to determine the risk factors (Odds ratio OR) for severe hypoglycemia with 95% confidence interval (95% IC). Statistical significance was accepted if p-value was less than 0.05.

Results

Fifty-one and 359 diabetic patients with and without hypoglycemia respectively were included in the present study. The characteristics of subjects were similar between the two groups (Table 1). The average ages of the study group and control group were 63.4 (SD = 11.6) and 58.6 (SD = 10.6) years (p-value = 0.003). Durations of diabetes in both groups were 6.1 (SD = 4.19) and 6.0 (SD = 4.33) years, respectively. The majority of patients in the present study and control group had hypertension (74.50% and 74.37%).

In the hypoglycemic group, 51 patients with severe hypoglycemia (26 males and 25 females) were presented with palpitation, syncopy and unconsciousness or seizure. Unconsciousness was the presenting symptoms of 45% (23/51) of cases. Blood glucose level taken at emergency room varied from 10 to 61 mg/dl. Mean blood glucose was 37.2 mg/dl (SD = 13.5). The range of length of stay (LOS) was 1 to

Table 1. Demographic data of severe hypoglycemia (cases: n = 51) and nonhypoglycemia type II diabetes patients (controls: n = 359)

Characteristics	Cases (n = 51)	Controls (n = 359)	p-value
Sex (n, %)			
Male (140)	26 (51.0)	114 (31.8)	0.007
Female (270)	25 (49.0)	245 (68.2)	
Age (years)			
Mean ± SD	63.4 ± 11.6	58.6 ± 10.6	0.003
Age group (n, %)			
< 60 years	21 (41.2)	217 (60.4)	0.025
61-70 years	16 (31.4)	85 (23.7)	
> 71 years	14 (27.4)	85 (23.7)	
Duration of treatment (years)			
Mean ± SD	6.1 ± 4.2	6.0 ± 4.3	0.865
DM Registration (n, %)	38 (74.5)	332 (92.7)	<0.001
Underlying diseases (n, %)			
Hypertension	38 (74.5)	267 (74.4)	0.983
Chronic kidney disease	19 (37.2)	66 (18.4)	0.002
Cirrhosis	7 (13.7)	11 (3.06)	0.003
Previous cerebrovascular disease	7 (13.7)	21 (15.8)	0.066
Congestive heart failure	7 (13.7)	11 (3.1)	0.003
Coronary heart disease	3 (5.9)	16 (4.5)	0.178
Medications			
Increasing dosage (n, %)	16 (31.4)	42 (11.7)	<0.001
Insulin use (n, %)	28 (55.0)	53 (14.8)	<0.001
Insulin with oral hypoglycemic drugs (n, %)	15 (29.4)	36 (10.0)	<0.001
HbA1c level (n, %)			
≤ 7 %	11 (32.4)	151 (44.8)	0.163
> 7 %	23 (67.6)	186 (55.2)	
Mean ± SD	8.63 ± 2.35	7.44 ± 1.62	

21 days. Mean LOS was six days (SD = 4.5). Twenty-eight of subjects (54.9%) had intercurrent illness that included sepsis, urinary tract infection and pulmonary tuberculosis before hypoglycemic admission. Hypoglycemic event was the first episode in 56.9% (29/51 cases), second and third episodes in 23.5% and 19.6% respectively.

By comparison between both groups, the present study revealed that the proportion of previous diabetes registration was lower in the severe hypoglycemic group (74.5% and 92.7% p-value < 0.001). The mean HbA_1c level of hypoglycemic and non hypoglycemic patients was 8.6% (SD = 2.3) and 7.4% (SD = 1.6) respectively, the hypoglycemic group reached the glycemic control target ($HbA_1c \leq 7.0$) in lower proportion than that in the control (32.34% vs. 44.8%) but it was not statistically significant (p = 0.163). Insulin therapy and increasing anti-diabetic drug dosages were predominant in hypoglycemic diabetes (55% vs. 14.8% and 31.4% vs. 11.7%) (p < 0.001). Univariate logistic regression showed that impaired renal function, cirrhosis, congestive heart failure and previous cerebrovascular disease were significant comorbid diseases associated with severe hypoglycemia (Table 2).

However, by multiple logistic regression, independent risk factors associated with severe hypoglycemia were old age, insulin therapy, no previous diabetic registration, cirrhosis and previous cerebrovascular disease (Table 3).

Discussion

The present study demonstrated that almost half of the patients with severe hypoglycemia presented with unconsciousness as a result of very low blood glucose. The incidence of recurrent severe hypoglycemia was relatively high in Nakornping Hospital. It is possible that the patients could not recognize or were not aware of neuro-hypoglycemic or autonomic symptoms of hypoglycemia. Hypoglycemic

Table 2. Univariate analyses of risk indicators of severe hypoglycemia in type II DM, odd (OR) ratios and 95% confidence interval (CI)

Risk indicators	Crude OR	95% CI	p-value
Sex (n = 410)			
Female	1	-	-
Male	2.24	1.24-4.04	0.008
Age group (years)			
< 60 years	1	-	-
61-70 years	1.95	0.96-3.92	0.058
> 71 years	2.54	1.20-5.35	0.011
No DM registration (n = 40)	4.37	2.07-9.21	<0.001
Medications			
Insulin use (n = 81)	7.03	3.58-13.76	<0.001
Increasing dosage (n = 58)	3.45	1.63-7.04	<0.001
Insulin with oral drugs (n = 51)	3.74	1.72-7.80	<0.001
Comorbid diseases (n = 168)			
Chronic kidney disease	2.64	1.32-5.13	0.002
Congestive heart failure	5.03	1.56-15.00	<0.001
Cirrhosis	5.03	1.56-15.00	<0.001
Previous cerebrovascular diseases	2.56	0.87-6.70	0.037

Table 3. Multiple logistic regression of risk factors related to severe hypoglycemia in type II DM

Risk indicators	Adjusted OR	95% CI	p-value
Age group (years)			
< 60	1		
61-70	2.58	1.17-5.68	0.019
> 71	2.62	1.12-6.13	0.026
Insulin use (n = 81)	6.67	3.40-13.08	0.001
Comorbid disease			
Cirrhosis	4.14	1.26-13.66	0.020
Previous cerebrovascular diseases	2.98	1.05-8.43	0.040
No DM Registration	2.933	1.23-7.00	0.015

unawareness from glucose counterregulation defect in patients experienced of frequent hypoglycemic events was described particularly in advanced type II diabetes and poor control diabetes[7,8,13]. The authors also learn that severe hypoglycemia was leaded by acute illnesses.

From the present study, non hypoglycemic group had better glycemic control ($HbA_1c \leq 7.0\%$) and less frequent severe hypoglycemia than hypoglycemic group. Diabetes Control and Complications Trial (DCCT) reported that intensive glycemic therapy both decreased the frequency of long-term complications and increased the frequency of hypoglycemia[3,14]. In the present study, however, severe hypoglycemia was not related to intensive glucose control as described in previous studies[15,16]. This is because the mean HbA_1c level of both groups was more than 7.0%. However, older age and insulin therapy were significant risk factors for severe hypoglycemia similar to other studies[16,17].

Increasing of medication dosage did not show a correlation with severe hypoglycemia. Comorbid disease related to severe hypoglycemic risk was cerebrovascular disease. It may be related to history of long-term poor glycemic control. HbA1c was a strong predictive factor for macrovascular complications of diabetes[18,19] but it was limited in patients with high variability of blood glucose or recurrent hypoglycemia. It has been recommended that for patients prone to glycemic variability especially

in type 1 or type II diabetic patients with severe insulin deficiency, glycemic control is best judged by the combination of results of self-monitoring blood glucose (SMBG) and HbA1c.

In the present study, non diabetes registration is a significant risk factor of severe hypoglycemia. Those who are registered will receive complete standard diabetic care from physician-coordinated team. The team includes physicians, nurses, dietitian, pharmacists, rehabilitation, and mental health profession. The registry program included standard of cares and annual eye and dental examination and diabetes self-management education. It showed that those registered patients achieved better glycemic control and were less likely to suffer from severe hypoglycemic events. Awareness of hypoglycemic symptoms, self-care for diabetic management in special situations of these patients might be better than those who were not registered.

Severe hypoglycemia is not only a significant barrier to good glycemic control in diabetes but can also be fatal. In order to achieve goal of DM management and reduce hypoglycemic events in type II diabetes in Nakornping Hospital, glucose monitoring by SMBG and HbA_1c measurement every three months should be added to monitor patients with high risk and previous hypoglycemia[20].

Diabetic care team should educate patients and family members to be aware of hypoglycemia when there is a serious acute illness. Individual goal of treatment and the case manager is needed particularly in diabetic patients who have a history of hypoglycemia.

Conclusion

Risk factors of severe hypoglycemia were old age, insulin therapy, previous cerebrovascular disease, cirrhosis and lack of standard diabetic care and team approach. DM care team should consider more strategies to prevent severe hypoglycemia including education for family members in patients with high-risk type II DM, particularly those with previous hypoglycemic events. Individual goal of hypoglycemic control and SMBG should be recommended.

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Potential conflicts of interest

None.

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ปัจจัยเสี่ยงต่อการเกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรงในผู้ป่วยเบาหวานชนิดที่ 2 ที่รักษาในโรงพยาบาลนครพิงค์

ทิพยา แสนไชย, ชยันตร์ธร ปทุมานนท์

วัตถุประสงค์: *เพื่อศึกษาปัจจัยเสี่ยงของ ภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง ในผู้ป่วย เบาหวานชนิดที่ 2*
รูปแบบการศึกษา: *เป็นแบบ case-control study*
สถานที่ศึกษา: *โรงพยาบาล นครพิงค์ จังหวัดเชียงใหม่*
วัสดุและวิธีการ: *ศึกษาลักษณะผู้ป่วยเบาหวานชนิดที่ 2 ที่เกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง 51 ราย และในกลุ่มที่ไม่เกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง 359 รายในช่วงเดือนตุลาคม พ.ศ. 2549 ถึงเดือนกันยายน พ.ศ. 2551 ลักษณะที่ศึกษาคือ อายุ เพศ ระยะเวลาการเป็นเบาหวาน การผ่านการลงทะเบียนจากคลินิคเบาหวาน โรคที่พบร่วม ระดับ HbA1c ลักษณะการใช้ยาในกลุ่มที่เกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง เก็บข้อมูลเพิ่มเรื่องอาการนำมาโรงพยาบาล ประวัติการเจ็บป่วยเฉียบพลัน ระดับน้ำตาลแรกรับ ลำดับครั้งที่เกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง และระยะเวลาที่นอนโรงพยาบาล*
ผลการศึกษา: *ภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง เป็นการเกิดซ้ำ ถึง ร้อยละ 40 วันนอนเฉลี่ย 6 วัน ระดับน้ำตาลเฉลี่ย 37.2 mg/dl มีการเจ็บป่วยเฉียบพลันนำมา ร้อยละ 54.9 ปัจจัยที่เพิ่มความเสี่ยงต่อภาวะน้ำตาลในเลือดต่ำอย่างรุนแรงคือ อายุมาก การใช้อินซูลิน ตับแข็ง ประวัติโรคหลอดเลือดสมอง และการไม่ผ่านการลงทะเบียนจากคลินิกโรคเบาหวาน ส่วนความดันโลหิตสูง และไตเสื่อมไม่เพิ่มความเสี่ยงต่อการเกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรง*
สรุป: *ปัจจัยเสี่ยงต่อภาวะน้ำตาลในเลือดต่ำอย่างรุนแรงในผู้ป่วย เบาหวานชนิดที่ 2 ได้แก่ผู้สูงอายุ การใช้อินสุลิน ตับแข็ง ประวัติโรคหลอดเลือดสมอง และการขาดการดูแลเบาหวานจากทีมสหสาขา สำหรับผู้ที่มีเคยมีประวัติการเกิดภาวะน้ำตาลในเลือดต่ำอย่างรุนแรงมาก่อน ควรพิจารณาเพิ่มการตรวจด้วย self monitoring of blood glucose (SMBG) และวางแผนการดูแลปัญหาเฉพาะราย*