

Original Article

Hyperglycemic Crisis in Prapokklao Hospital

VibhuVijara M.D.*

WarapornPolamaung M.D.*

บทคัดย่อ

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วิภู วิหาระ พ.บ.*

วรารณ พลเมือง พ.บ.*

* กลุ่มงานอายุรกรรม โรงพยาบาลพระปกเกล้า จันทบุรี

วารสารศูนย์การศึกษาแพทยศาสตร์คลินิก โรงพยาบาลพระปกเกล้า 2556;30:133-145

ความเป็นมา

ภาวะคีโตซีส (Diabetic ketoacidosis, DKA) และภาวะโคม่าจากน้ำตาลในเลือดสูง (hyperosmolar hyperglycemic state, HHS) ถือเป็นภาวะแทรกซ้อนที่สำคัญและพบได้บ่อยของโรคเบาหวาน ซึ่งในผู้ป่วยกลุ่มนี้พบอัตราการเสียชีวิตและทุพพลภาพค่อนข้างสูงเมื่อเปรียบเทียบกับผู้ป่วยเบาหวานทั่วไป การวิจัยในครั้งนี้จึงมีจุดประสงค์เพื่อเก็บข้อมูลผู้ป่วย ปัจจัยกระตุ้น และวิเคราะห์ปัจจัยต่างๆ ที่มีผลต่ออัตราการเสียชีวิตและทุพพลภาพในผู้ป่วยที่พบภาวะดังกล่าวในโรงพยาบาลพระปกเกล้า จันทบุรี

รูปแบบการศึกษาวิจัย

การศึกษาวิจัยแบบพรรณนาย้อนหลัง

ขั้นตอนการวิจัย

เริ่มมีการเก็บข้อมูลผู้ป่วยที่มีภาวะคีโตซีสและภาวะโคม่าจากน้ำตาลในเลือดสูง ที่เข้าได้กับเกณฑ์การวินิจฉัยของ ADA guideline โดยอิงตามฐานข้อมูลอิเล็กทรอนิกส์ของโรงพยาบาลพระปกเกล้าและข้อมูลจากเวชระเบียนผู้ป่วยเบาหวานเฉียบพลัน (hyperglycemic crisis registry หรือ DM care map) ในช่วงระหว่างเดือน มกราคม พ.ศ. 2552 จนถึงเดือนธันวาคม พ.ศ. 2553

* Department of Internal Medicine, Prapokklao Hospital, Chanthaburi Province, Thailand.

ผลการวิจัย

พบผู้ป่วยที่ได้รับการรักษาทั้งหมด 49 ครั้ง (43 ราย) โดยพบเป็นผู้ป่วยที่เข้ารับการรักษาด้วยภาวะคีโตซิส 36 ครั้ง ภาวะโคม่าจากน้ำตาลในเลือดสูง 11 ครั้ง และผู้ป่วยที่พบทั้งสองภาวะร่วมกัน 2 ครั้ง ส่วนมากพบเป็นผู้ป่วยเบาหวานประเภทที่สองร้อยละ 65.3, เบาหวานประเภทที่หนึ่งร้อยละ 26.5 และผู้ป่วยเบาหวานชนิดอื่นๆ ร้อยละ 8.2 อายุเฉลี่ยพบอยู่ในช่วง 50.53 ± 19.35 ปี (45.97 ± 17.29 ปี ในภาวะคีโตซิส DKA, 66.09 ± 18.49 ปี ในภาวะโคม่าจากภาวะน้ำตาลในเลือดสูง และ 47.00 ± 25.46 ปีในกลุ่มที่พบทั้งสองภาวะร่วมกัน) พบในเพศหญิงและเพศชายเท่าๆ กันคือในอัตราส่วน 1.05:1 ปัจจัยกระตุ้นที่สำคัญคือการติดเชื้อและการหยุดยาเบาหวานโดยพบร้อยละ 40.9 และ 20.4 ตามลำดับการติดเชื้อทางเดินปัสสาวะพบมากที่สุดซึ่งพบถึงร้อยละ 35 รองลงมาคือการติดเชื้อในระบบทางเดินหายใจพบร้อยละ 30 ภาวะแทรกซ้อนระหว่างนอนโรงพยาบาลที่สำคัญคือภาวะโพแทสเซียมในเลือดต่ำ ซึ่งพบถึงร้อยละ 53.06 โดยเกิดจากการได้รับโพแทสเซียมไม่เพียงพอระหว่างการรักษา แต่ไม่พบอันตรายจากหัวใจเต้นผิดจังหวะจากภาวะโพแทสเซียมต่ำดังกล่าว พบผู้ป่วยเสียชีวิตทั้งสิ้น 6 ราย หรือร้อยละ 12.24 (3 ราย เสียชีวิตจากปอดติดเชื้อ, 1 รายจากติดเชื้อแบคทีเรียแกรมลบในกระแสเลือด, 1 รายจากภาวะเลือดออกในทางเดินอาหารอย่างรุนแรง และ 1 รายจากภาวะตับอ่อนอักเสบรุนแรงเฉียบพลัน) โดยในกลุ่มผู้ป่วยโคม่าจากน้ำตาลในเลือดสูงมีอัตราการเสียชีวิตสูงกว่ากลุ่มคีโตซิส (ร้อยละ 36.36 และ 5.56 ตามลำดับ)

สรุป

จากการศึกษาพบว่า การติดเชื้อเป็นปัจจัยกระตุ้นสำคัญและพบบ่อยที่สุดที่ทำให้เกิดภาวะฉุกเฉินในโรคเบาหวาน และยังเป็นสาเหตุหลักของการเสียชีวิต การหยุดยาเป็นอีกปัจจัยที่พบรองลงมาซึ่งสามารถป้องกันได้โดยการให้ความรู้อย่างถูกต้องแก่ผู้ป่วย ร้อยละ 50 ของผู้ป่วยทั้งหมดเกิดภาวะโพแทสเซียมในเลือดต่ำในระหว่างการรักษาซึ่งอาจสามารถแก้ไขได้โดยการปฏิบัติตามแนวทางการรักษาผู้ป่วยฉุกเฉินทางเบาหวานอย่างเคร่งครัด

คำสำคัญ หัวใจล้มเหลว การกลีบมานอนโรงพยาบาลซ้ำ

Background : Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most serious acute complications of diabetes and associated with significant morbidity and mortality in diabetic patients. The objective of this study is to describe the clinical characteristics, precipitating factors morbidity and mortality of patients with hyperglycemic crisis in Prapokklao hospital.

Study design : A retrospective descriptive study

Material and methods : A retrospective descriptive study was conducted from January

2009 to December 2010. All data which met the ADA diagnostic criteria for DKA and HHS were collected from hyperglycemic crisis registry (DM care map) and electronic data base of Prapokklao hospital.

Results : There were 49 episodes of hyperglycemic crisis (DKA 36, HHS 11, and mixed DKA/HHS 2) in 43 patients in this study. The percentage of T2DM, T1DM and other type of diabetes were 65.3 percent, 26.5 percent and 8.2 percent respectively. The overall mean age was 50.53 ± 19.35 years (45.97 ± 17.29 years in DKA, 66.09 ± 18.49 years in HHS and 47.00 ± 25.46 years in mixed DKA/HHS) with a female to male ratio of 1.05:1. Infection and self-discontinuation of medication were the two most common precipitating causes of hyperglycemic crisis (40.9 percent and 20.4 percent). Urinary tract and respiratory tract infections were the major sources of infection (35.0 percent and 30.0 percent). We found that 53.06 percent of study population developed hypokalemia during admission due to under-treatment with potassium supplement. No significant cardiac arrhythmia associated with hypokalemia was observed. The overall mortality rate from hyperglycemic crisis was 12.24 percent (3 cases from severe pneumonia, 1 case from gram-negative septicemia, 1 case from massive UGIH and 1 case from severe acute pancreatitis). Syndrome specific mortality was 5.56 percent for DKA and 36.36 percent for HHS.

Conclusions : Infection was the most important precipitating cause of hyperglycemic crisis and the leading cause of death. The second most common and preventable cause of hyperglycemic crisis was self-discontinuation of medication. Hypokalemia was found in approximately half of the patients. Adherence to DKA/HHS treatment protocol could help prevent this complication.

Introduction

Diabetes is a global health problem and trends to grow up with time. The disease directly affects the individual health, well-being and increases mortality from microvascular and macrovascular complications.

Diabetic ketoacidosis and hyperosmolar

hyperglycemic state have been the two most serious acute complications which associate with significant morbidity and mortality in diabetic patients. The annual incidence is about 4.6-8 episodes per 1000 diabetic patients.¹ They also results in a huge economic burden on medical system.² There has been little data

on the epidemiology of hyperglycemic crisis in Thailand, especially in Chanthaburi province.

Objectives

The objective of this study is to describe the clinical characteristics, precipitating factors, morbidity and mortality of patients with hyperglycemic crisis who presented at Prapokklao tertiary care hospital Chanthaburi, Thailand.

Materials and Methods

Study population

All adult diabetes patients, who were diagnosed with diabetic ketoacidosis or hyperosmolar hyperglycemic state, and admitted in Prapokklao hospital from January 2009 to December 2010.

Definitions

Diabetic ketoacidosis (DKA) – according to the American Diabetes Association criteria 2009³, Diabetic ketoacidosis is defined as a casual plasma glucose > 250 mg/dL, a high anion gap metabolic acidosis (anion gap >12, serum $\text{HCO}_3^- < 15$ mmol/L, and pH < 7.3) and plasma ketone positive in moderate level.

Hyperosmolar hyperglycemic state (HHS) – defined as a plasma glucose > 600 mg/dL, increased serum effective osmolality (> 320 mOsm/kg), anion gap < 12, no significant acidosis ($\text{HCO}_3^- < 15$ mmol/L, pH < 7.3)

Mixed DKA/HHS – defined as a presentation with acidosis ($\text{HCO}_3^- < 15$ mmol/L, pH < 7.3), ketosis and effective osmolality > 320 mOsm/kg.

Inclusion criteria

- Age more than 15 years
- Diagnosis of DKA, HHS or hyperglycemic crisis

Exclusion criteria

- Not meet the ADA diagnostic criteria for DKA, HHS or mixed DKA/HHS.
- Incomplete data

Study design

This is a retrospective descriptive study, conducted over a two-year period from January 2009 to December 2010, using hospital medical records. Patients, included in this study, were those who were treated in adult medical wards and intensive care unit with discharge summary diagnosis specified in International Classification of Disease – 10th Modification Diagnosis code (ICD 10) coding system, as follows: Insulin-dependent diabetes mellitus (E10), non-insulin-dependent diabetes mellitus including HHS (E11), other specified diabetes mellitus (E13), unspecified diabetes mellitus (E14), DKA (E11.1), and diabetic coma (E11.0). Most of the patient's medical records were collected from DKA/HHS registry and electronic data base.

Data collection and measurements

All collected data included patient demographics, past medical history, onset and duration of diabetes, type of diabetes, drug and substance used, presence of a co-existing medical disease (hypertension, dyslipidemia,

renal insufficiency, coronary artery disease, cerebrovascular disease, gout and hyperuricemia, cancer, etc.), presence of risk factors for development of a hyperglycemic syndrome (infection, acute stress, non-compliance in current medication, etc.). Laboratory data and other parameters assessed on admission to hospital included the followings: hematocrit, white blood cell count and differential count, platelet level, glucose level, electrolyte level, arterial pH, effective osmolality, presence of ketone (serum and/or urine), lactate level and culture reports. The complications of treatment were collected from a hospital discharge summary and admission chart review. The cause of death was determined in accordance with the death certificate.

All data was recorded in the diabetic form. No financial support was provided for this research.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0. Mean, standard

deviation and frequency were used to describe demographic data. Paired t-test was used to compare means between two different groups. Continuous variables were compared using analysis of variance (ANOVA). A p-value < 0.05 was considered statistically significant.

Results

Of 72 dockets screened for study inclusion, 49 met the diagnostic criteria for DKA, HHS and mixed DKA/HHS (Figure 1). There were 43 patients with 49 episodes of hyperglycemic crisis (DKA 36, HHS 11 and mixed DKA/HHS 2 episodes). The percentage of T2DM, T1DM and other types of diabetes were 65.3 percent, 26.5 percent and 8.2 percent respectively. The mean age of all our patient population was 50.53 ± 19.35 years with a female to male ratio of 1.05 to 1. About twenty six point five percent of patients were newly diagnosed of diabetes (T1DM 6.12 percent, T2DM 20.41 percent). Mean length of hospital stay was 10.78 ± 8.68 days, incurring average medical cost of 38,088.41 baht.

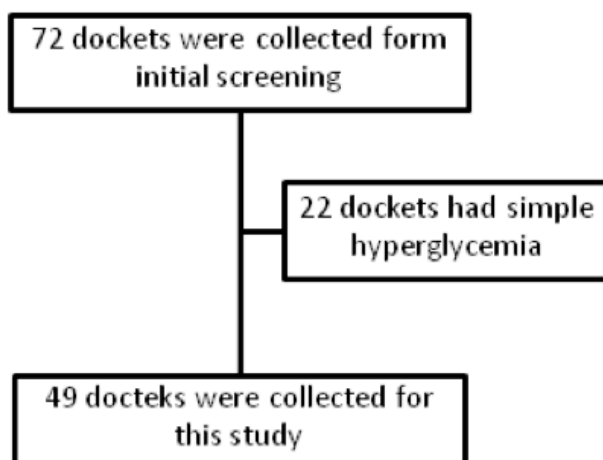


Figure 1 Data collection

Of the study population, 73.5 percent were DKA, 24.4 percent HHS and 4.1 percent mixed DKA/HHS. Mean age of HHS patients (66.09 ± 18.49 years) was significantly higher than DKA patients (45.97 ± 17.29 years) ($p=0.03$) and also higher than mixed DKA/HHS (47.00 ± 25.46 years)

DKA patients had female to male ratio of 1.25:1 and had T2DM, T1DM and other DM type at frequencies of 61.1 percent, 30.6 percent and 8.3 percent respectively. HHS

patients had female to male ratio of 1.2:1 and frequencies of T2DM, T1DM and other DM type were 81.8 percent, 9.1 percent and 9.1 percent respectively. All patients with mixed DKA/HHS were male, having T1DM and T2DM in the ratio of 1:1.

Of type 1 DM-patients, 84.6 percent (11/13) presented with DKA. Presentations with HHS and mixed syndrome were equal in frequency at 7.7 percent. There were no precipitating causes in 15.4 percent.

Table 1. Patient characteristic

	Hyperglycemic crisis	DKA	HHS	DKA/HHS
Incidence (episodes)	49	36	11	2
Female: male	1.05:1	1.25:1	1.2:1	1:1
Mean age (years)	50.53 ± 19.35	45.97 ± 17.29	66.09 ± 18.49	47.00 ± 25.46
Type of DM				
T1DM	26.5%	30.6%	9.1%	50%
T2DM	65.3%	61.1%	81.8%	50%
Other type of DM	8.2%	8.3%	9.1%	-
Newly diagnosed	26.5%	6.12%	20.41%	-
Laboratory data				
WBC count ($10^3/\mu\text{L}$)	16.01 ± 6.48	16.96 ± 6.57	14.16 ± 4.67	9.68 ± 11.63
Neutrophil (%)	82.72 ± 7.23	83.21 ± 7.04	81.55 ± 7.45	80.55 ± 13.51
Plasma glucose (mg/dL)	758.51 ± 308.51	622.63 ± 171.71	$1,031.55 \pm 293.99$	$1,431.00 \pm 306.88$
Potassium (mmol/L)	4.74 ± 1.03	4.86 ± 0.89	4.35 ± 1.27	4.73 ± 2.09
Bicarbonate (mmol/L)	11.87 ± 6.29	9.80 ± 4.22	19.25 ± 6.59	6.65 ± 0.92
Anion gap (mmol/L)	21.85 ± 7.30	23.14 ± 5.97	16.14 ± 7.01	31.35 ± 13.79
pH	7.22 ± 0.14	7.21 ± 0.13	7.31 ± 0.12	7.00 ± 0.09
Calculate Osm.(mOsm/L)	307.32 ± 29.83	292.76 ± 14.85	348.21 ± 26.70	322.70 ± 0.08
Infection precipitated	41.7%	33.3%	63.6%	50%

As shown in table 1, white blood cell count was significantly higher in DKA than in HHS ($p<0.01$) and also significantly higher in the infection-precipitated group. ($p=0.03$). There were 4 cases (8.16 percent) whose white blood cell counts were greater than

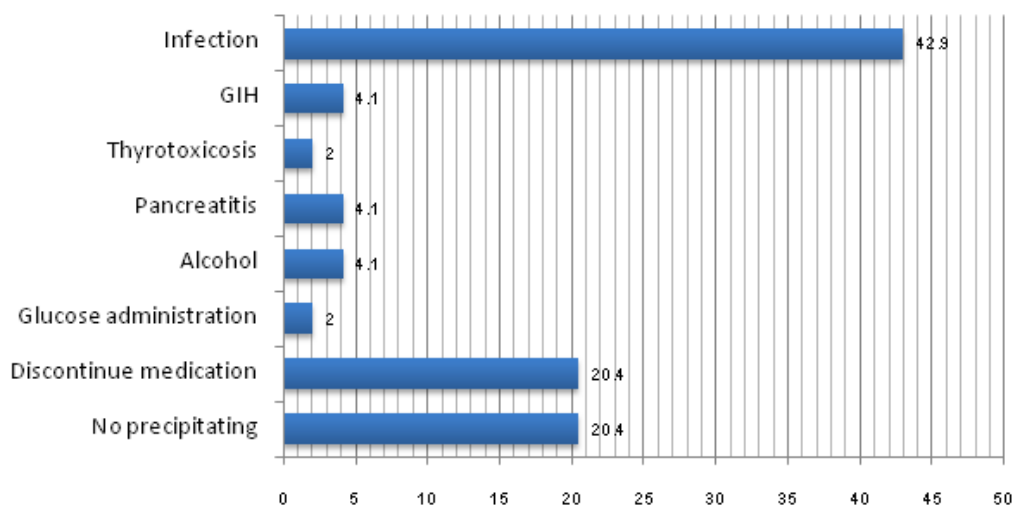
25000/ μL and there was only one case that had culture-proven infection as the precipitating cause. Predominant neutrophil counts were found in all subgroups without significant difference. ($p=0.84.$)

Table 2. Precipitation factors

	DKA (%)	HHS (%)	DKA/HHS (%)	Hyperglycemic crisis(%)
Infection	36.1	63.6	50	42.9
Pneumonia	8.3	27.3	-	12.2
Urinary tract infection	11.1	18.2	50	14.3
GI infection	5.6	-	-	4.1
Skin and soft tissue infection	5.6	9.1	-	6.1
CNS infection	-	9.1	-	2.0
Bacteremia	2.8	-	-	2.0
Illness				
Gastrointestinal hemorrhage	2.8	9.1	-	4.1
Thyrotoxicosis	2.8	-	-	2.0
Pancreatitis	2.8	-	50	4.1
Drugs and toxin				
Alcohol	5.6	-	-	4.1
Glucose administration	-	9.1	-	2.0
Discontinued from medications	27.8	-	-	20.4
No precipitating cause	22.2%	18.2%	-	20.4%

Infection and self-discontinuation from medication were the two most common precipitating causes of hyperglycemic crisis (42.9 percent and 20.4 percent). Urinary tract and respiratory tract infection were the major sites

of infection (35.0 percent and 30.0 percent) (Table 2) Newly diagnosed thyrotoxicosis, which precipitated hyperglycemic crisis, was found in one case (2.8 percent).

**Figure 2** Precipitating factor for hyperglycemic crisis (%)

Complications of treatment during hyperglycemic crisis led to increase of morbidity and mortality. There were 26 cases (53.06 percent) who developed hypokalemia during treatment due to under treatment with potassium supplement. Severe hypokalemia was also found in this study. Eleven cases (23 percent) had serum potassium lower than 3.3 mmol/L, and three cases (6.12 percent) had serum potassium lower than 2.5 mmol/L. Insulin infusion was not withdrawn in either subgroup. This could cause even more severity of hypokalemia due to shifting of potassium into intracellular compartment, which might pose a risk of serious cardiac arrhythmia. However no serious cardiac arrhythmia was observed. Hypernatremia and overshoot alkalosis were found in 24.5 percent and 4.1

percent respectively due to excessive administration of sodium bicarbonate. Mean initial volume of saline infusion was 2.82 ± 2.35 liters in 4.45 ± 2.45 hours. Hypoglycemia and recurrent DKA/HHS due to out-of-protocol treatment occurred at the frequencies 12.2 percent and 2 percent respectively. Cerebral edema, a rare complication from DM in pediatric and young adult patients, occurred in a 16-year-old patient with T1DM due to delayed diagnosis from other hospital. Improper management by using adult DKA treatment protocol, which should be applied only in patients over 20 years of age, and rapid decline of plasma glucose level as a result of intravenous insulin infusion were also likely the causes of cerebral edema in this patient. She was in deep coma and responded dramatically after mannitol infusion.

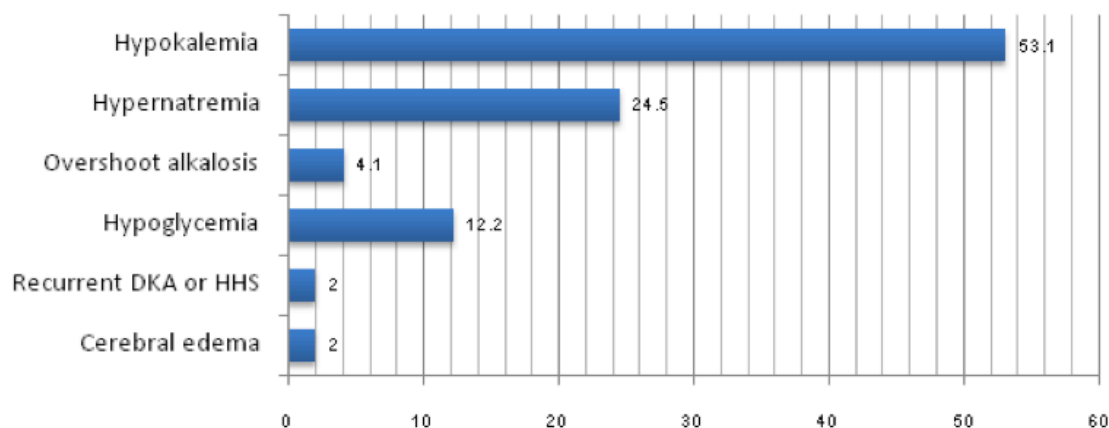


Figure 3 Treatment complications (%)

For subgroup analysis, incidence of hypokalemia was not different between DKA and HHS patient, $p=0.16$. Hypernatremia was more common in HHS than DKA, $p<0.01$. The more volume loss of free water in HHS compared with DKA might be a contributing factor in development of this complication. Hypoglycemia was more common in HHS than DKA as well ($p\text{-value} < 0.01$).

Death occurred in 6 patients with hyperglycemic crisis, giving a mortality rate of 12.24 percent, (3 cases from severe pneumonia, 1 case each from gram-negative septicemia, massive UGIH and severe acute pancreatitis) (Figure 4). Syndrome specific mortality was

5.56 percent and 36.36 percent in DKA and HHS respectively. Of the 4 patients who expired from infection, community-acquired lobar pneumonia at left lower lung field was found in 1 case, hospital-acquired lobar pneumonia at left tower lung field in 2 cases and septic shock from *Burkholderiapseudomallei* on the fifth day of hospitalization in one case. The result of sputum and blood cultures of the patient with community-acquired lobar pneumonia was negative. Of the two cases with hospital-acquired pneumonia, ESBL-producing *Klebsiella pneumonia* was the etiologic organism. Delayed treatment with proper antibiotics was responsible for the case with septic shock.

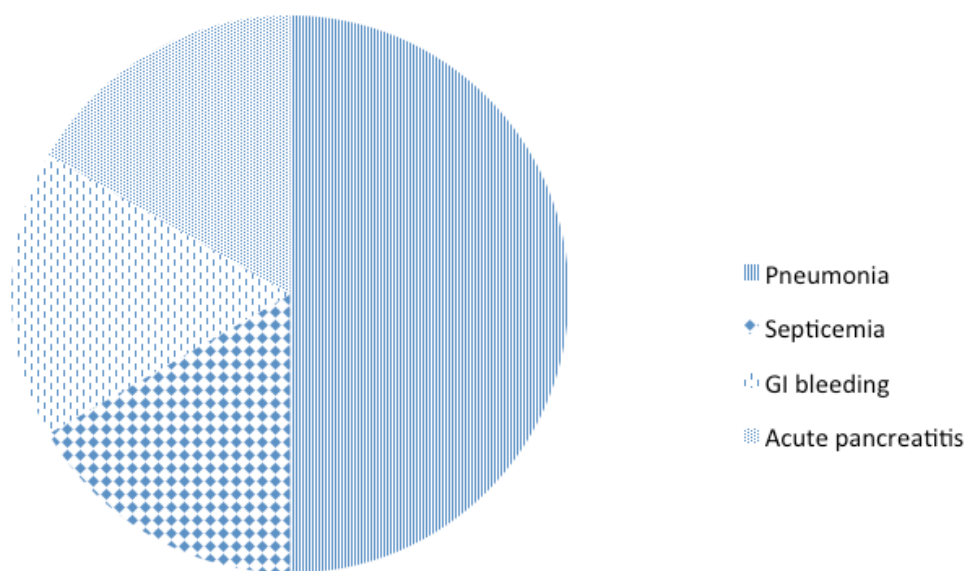


Figure 4 Mortality in hyperglycemic crisis

Discussions

Previous retrospective study⁴ showed that incidence of DKA, HHS and mixed DKA/HHS were 27 percent, 48 percent and 25 percent respectively, with overall mean age being 53.6 ± 3.3 years (35.9 ± 4.3 years in DKA, 64.5 ± 3.9 years in HHS) and female to male ratio of 1.1:1.

The majority of patients (88 percent) had type-2 diabetes. Our study results were similar to this retrospective study in terms of overall mean age and gender distribution. However, the percentage (73.5 percent) and mean age (45.97 ± 17.29 years) of our DKA subgroup were significantly higher.

As shown in table 1, 26.5 percent of study population presenting with hyperglycemic crisis at the time of admission were newly diagnosed diabetic cases. This is consistent with the previous study.^{5,6} Due to inadequate knowledge about the classic symptoms of diabetes (polydipsia, polyurea, polyphagia and weight loss), most of them had never been screened for diabetes before development of the crisis. They should be educated about the classic symptoms, and if present, they might be on high alert and early screened for diabetes to prevent this serious complication.

The two most common hyperglycemic crises are DKA and HHS. DKA occurrence is more frequent in T1DM whereas HHS in T2DM. Our study result showed that approximately two-thirds of the patients with DKA were over 30 years of age, not thin in body build

and had no precipitating factors. This finding was also found in other literatures in the term of ketosis-prone diabetes.⁷⁻¹⁵ Unfortunately, in our hospital, we cannot perform a blood check for antibodies to β -cell or HLA typing. Further studies of this subgroup are necessary to definitely specify diabetic type.

Infection, especially in respiratory and urinary tracts, were the most important precipitating causes of hyperglycemic crisis. This is in consistence with the two previous studies of Yan et al and Lin et al.^{16,17} The second most common and preventable cause of hyperglycemic crisis was the self-discontinuation from medication. These were similarly noted in many previous studies.^{4,6,16,17,18,19} It is necessary that patients and their community are educated about diabetes including sick-day care and the symptoms of hyperglycemic crisis, in order that they can have earlier medical care.

Hypokalemia, a preventable condition, was found in half of patients during treatment of hyperglycemic crisis. This was due to inadequate potassium supplement. About half of the hypokalemic patients had serum levels lower than 3.3 mmol/L. This could result in serious cardiac arrhythmia. Insulin infusion should be temporarily stopped to prevent further intracellular shift of potassium. Although no occurrence of serious cardiac arrhythmia was observed in this study, treatment of hyperglycemic crisis should adhere to DKA/HHS protocol to ensure adequate potassium supplement.

Hypernatremia was found in 12 cases (24.49 percent). Of these, one-third occurred as a result of excessive administration of sodium bicarbonate and the remainder as a result of prolonged saline infusion without proper switching to lower sodium-containing solution. Although no serious neurological impairment was noted, adhering to the treatment protocol was necessary in order to be free from this preventable complication.

Hypoglycemia is another one of common complications during treatment of hyperglycemic crisis. It developed in 6 cases (12.2 percent) due to excessive insulin infusion that should have been reduced to 0.05 unit/kg when plasma glucose level decreased lower than 200 mg/dL. If glucose-free fluid is not switched to another one with glucose when plasma glucose is already lower than 200 mg/mL, it will subsequently become even lower. This may lead to too early withdrawal of insulin infusion by the attending physician, resulting in recurrence of DKA. This event occurred in one patient in this study. Treatment should follow ADA guideline to prevent hypoglycemia and recurrent DKA/HHS.

Cerebral edema, a rare complication, may lead to significant morbidity and mortality.^{20,21} There was one case in this study, involving a 16-year-old patient with T1DM. Her DKA was treated in other hospital using adult treatment guideline before being transferred. The adult treatment guideline should be applied only in patients aged over 20 years.

Recovery from this complication is uncommon. However she had an amazing recovery after mannitol infusion.

The mortality from hyperglycemic crisis has been dramatically reduced in subsequent years, after the discovery of insulin and improvement of protocol treatment, with overall mortality between 0.67 to 17.7 percent.^{4,6,11,17,18,22} In our study, the overall mortality rate was 12.24 percent. Syndrome specific mortality was 5.56 percent in DKA and 36.36 percent in HHS. Six patients died and three of them died from severe hospital acquired *Klebsiella pneumoniae*. This organism has been found to be a leading causative pathogen among Taiwan diabetic patients.^{23,24} Melioidosis has increased prevalence in diabetes patient^{25,26,27} and we also found that one case in our study had melioidosis septicemia and later developed refractory shock. This patient expired despite appropriate antibiotic administration. Therefore, melioidosis must be included in differential diagnosis in any diabetic patients presenting with fever suggestive of infection, particularly those who live in the high prevalent area such as in north-eastern part of Thailand.

Conclusions

This study showed that hyperglycemic crisis had serious complication with high morbidity and mortality. It caused a huge loss of medical resource as well. Infection and self-discontinuation from medication were

the two most common precipitating causes. Patient education, being on high alert to DM and undergoing screening for this disease, particularly when they have classic symptoms of DM, are important strategy for prevention of this critical illness. Adherence to DKA/HHS treatment protocol is necessary for prevention of arrhythmia-prone hypokalemia.

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