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Case Report

The Early Detection and Managements of Euglycemic Diabetic Ketoacidosis Based on a Rapid Response System: Two Case Reports

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Abstract

With increase in the use of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus, the incidence of perioperative euglycemic diabetic ketoacidosis has been on the rise. The diagnosis of perioperative euglycemic DKA is a conundrum for physicians due to the absence of hyperglycemia and other perioperative complications should be excluded. Here, we report two cases of euglycemic DKA after surgery in patients who had been diagnosed T2DM and taken SGLT2 inhibitors. In our cases, the patients were initially detected by the screening of the rapid response system in our hospital using modified early warning score, which enabled the diagnosis and management of euglycemic DKA promptly done.

Keywords: Complications; Diabetic ketoacidosis; Euglycemic; Rapid response systems; Sodium-glucose cotransporter 2 inhibitors; Surgery

Abbreviations

DKA: Diabetic Ketoacidosis; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; CRRT: Continuous Renal Replacement Therapy; ICU: Intensive Care Unit

Introduction

Diabetic Ketoacidosis (DKA), a life-threatening metabolic emergency, is not rare in hospital; despite it is a preventable complication. DKA is caused by a decrease in effective circulating insulin associated with elevations in counter-regulatory hormones in Type 1 Diabetes Mellitus (T1DM). However, euglycemic DKA can be developed in T2DM. The diagnosis of euglycemic DKA is based on the triad of ketonemia, acidosis, and only moderately elevated blood glucose level (less than 250 mg/dl or 14 mmol/L). The relatively low blood glucose may delay diagnosis and treatment of euglycemic DKA, causing poor prognosis and increased mortality.

Here, we report two cases of euglycemic DKA after surgery in patients who had taken SGLT2 inhibitors after the diagnosis of T2DM. Those patients were detected by the computerized screening system of our hospital, and they were fully recovered in several days after the rapid and proper management by our professional response team.

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Case Presentation

Case 1

A 52-year-old female patient (height; 153 cm and weight; 57 kg) was admitted to our hospital for surgery after a diagnosis of early gastric cancer (clinical stage T1N0M0) during medical check-up. She had been diagnosed with T2DM a month prior to the admission and had been administered 5 mg of empagliflozin and 500 mg of metformin twice daily. The blood glucose level measured at admission was 328 mg/dl, and the HbA1c was 13.5%, which suggest her blood glucose level had been poorly controlled. The administration of oral hypoglycemic agents had been discontinued 24 hours before surgery, and the infusion of intravenous Regular Insulin (RI) was initiated. After the infusion of RI, her blood glucose level was maintained euglycemic (110 mg/dl-180 mg/dl) for 8 hours before surgery. Total laparoscopic distal gastrectomy was performed without any special event.

On the third day after surgery, RI administration was discontinued, and medication of previous OHA (empagliflozin 5 mg and metformin 500 mg) was resumed. However, on the next day, the patient complained an abdominal discomfort and indigestion, and she was unable to eat meals. On the fifth day after surgery, the patient complained a sudden dyspnea and chest pain. Her vital signs were checked; Blood Pressure (BP) 183/109 mmHg, Heart Rate (HR) 121 bpm/min, Respiratory Rate (RR) 30/min, and Saturation of Percutaneous Oxygen (SpO_2) 100%. At the time, her Modified Early Warning Score (MEWS) was 5, and it was detected by our screening system.

When the rapid response team arrived, nitroglycerin was administered sublingually, cardiac enzyme labs were taken, and Electrocardiogram (ECG) was performed under the first impression of acute coronary syndrome. In addition, chest computed tomography was arranged to evaluate a pulmonary embolism. Her ECG showed sinus tachycardia (HR 121 bpm) without any ST-segment elevation, and no regional wall motion abnormality was observed by portable

ultrasound. As the patient became drowsy, she was transferred to the Intensive Care Unit (ICU), and mechanical ventilation was initiated. Arterial Blood Gas Analysis (ABGA) showed high anion gap metabolic acidosis with pH 6.9, pCO_2 16.6 mmHg, HCO3- 5.4 mmol/L, and serum anion gap 20.9 mmol/L. At that time, blood glucose level was 231 mg/dl.

Additional laboratory results and images showed no evidence of acute vascular event or infection. Subsequently, both urine and serum tests were found positive for ketone bodies; the patient was diagnosed with diabetic ketoacidosis and treatments were started accordingly. Despite of sufficient resuscitation including massive volume replacement, RI infusion, correction of acidosis and electrolytes, and use of vasopressors, acidosis (pH <7.2) and hypotension (mean BP<65 mmHg) persisted. Therefore, Continuous Renal Replacement Therapy (CRRT) was initiated. On the next day, vital signs were stabilized, and metabolic acidosis was also corrected. With continuous RI infusion, blood glucose levels were well controlled at 200 mg/dl or lower.

On the 3rd day after ICU admission, the patient was transferred to the general ward, and linagliptin (dipeptidyl peptidase-4 inhibitor) and metformin were given instead of re-administration of empagliflozin. On the 13th day after surgery, the patient discharged without any complication.

Case 2

A 71-year-old female patient (height; 152 cm and weight; 58 kg) was admitted to our hospital for a surgical removal of left buccal mucosal cancer. She had been diagnosed with T2DM about 30 years ago and had been administered 10 mg of dapagliflozin once a day, and 4 mg of glimepiride and 50 mg/850 mg of sitagliptin/metformin twice daily. The blood glucose level measured at admission was 301 mg/dl, and the HbA1c was 8.5%. She had taken the medications until a day before surgery, and RI was not administered before surgery, since her blood glucose level was maintained 138 mg/dl-177 mg/dl.

The surgical excision of buccal tumor and reconstruction was successfully done without any complication, even though it took a long surgical time of 625 min and anesthesia time of 720 min, respectively. The patient was transferred to the ICU in the sedated state. Blood glucose level was controlled by repetitive blood sugar tests and RI infusion during and after surgery. On the next day, extubation was performed and she was transferred to general ward, and nasogastric tube feeding was initiated on the second day after surgery.

On the third day after surgery, the patient complained poor oral intake and dizziness, and the total amount of feeding in two meals was only 100 cc. In addition, she complained a mild dyspnea and chest discomfort, therefore her vital signs were checked; BP 149/85 mmHg, HR 85 bpm/min, RR 18/min, and SpO_2 96%. Since her symptoms were not threatening and vital signs were stable, her primary doctor closely observed her if there were any change in her status and routine labs were taken. However, when laboratory results were reported, serum total CO_2 was 6 mmHg.

When the rapid response team visited the patient, they found her blood glucose level was 242 mg/dl. In addition, Venous Blood Gas Analysis (VBGA) and urine analysis were taken to rule out DKA. High anion gap metabolic acidosis with pH 7.06, pCO_2 20.8 mmHg, HCO_3 7.8 mmol/L, and serum anion gap 23.7 mmol/L were observed in VBGA. At the time, her symptoms got worse and vital signs became unstable; BP 118/56 mmHg, HR 80-147 bpm/min, RR 22 /min, SpO_2 99%, and Body Temperature (BT) 37.6°C. She became drowsy, so that she only could response to verbal commands by shaking her.

She was transferred to the ICU, and her ECG rhythms showed atrial fibrillation with irregular HR 120 bpm/min -180 bpm/min. Bed-side echocardiography was performed, and a newly developed regional wall motion abnormality was observed. Since, ketone bodies were found positive in her urine and blood test, we concluded DKA as a final diagnosis. As the correction of acidosis had failed despite of sufficient hydration, infusion of bicarbonate, and additional RI bolus injection, CRRT was initiated. On the third day after CRRT applied, the patient was fully recovered from DKA, and CRRT was discontinued.

Coronary angiography was done to rule out acute coronary syndrome due to irregular heartbeat, echocardiographic abnormalities, and elevated Troponin I up to 33.17 ng/ml. The coronary angiography showed no evidence of acute infarct, but she was diagnosed chronic 3-vessels coronary artery disease and stress-induced cardiomyopathy with reduced ejection fraction (46%). The patient kept insulin therapy instead of restarting OHA until her oral intake improves and blood glucose level becomes stable.

Discussion

DKA is an acute life-threatening metabolic emergency, diagnosed with the triad of hyperglycemia (serum glucose >250 mg/dl or 14 mmol/L), metabolic acidosis, and ketonemia. DKA, caused by a decrease in insulin and elevations in counter-regulatory hormones, usually occurs in T1DM patients. However, other factors like infection, surgery, fasting and acute vascular events can also evoke DKA in T2DM patients [1].

Euglycemic DKA, defined as mild hyperglycemia (serum glucose <250 mg/dl or 14 mmol/L), is uncommon. In addition to their lower incidence, atypical presentations of euglycemic DKA make it difficult to be diagnosed. The delay in diagnosis and treatment of DKA leads to poor prognosis and high mortality. In euglycemic DKA, carbohydrate deficit is a major cause, while insulin deficit or resistance is a relatively minor and secondary cause [2]. The incidence of euglycemic DKA in peri-operative period increases due to surgical stress, volume depletion, reduced oral intake and inadequate insulin therapy [3].

The use of SGLT2 inhibitors has been increased since they have protective effects against cardiovascular events, slow chronic kidney disease progression, lower body weight and BP [4]. However, there has been a steady increase in the published reports on DKA with the growing use of SGLT2 inhibitors [2].

We reported two cases of euglycemic DKA after surgery in patients who had been administered SGLT2 inhibitors. At the time they were detected, their serum glucose levels were 231 mg/dl and 242 mg/dl, respectively. In addition, both patients were exposed to several risk factors of euglycemic DKA: surgery, medication history of SGLT2 inhibitors, and prolonged fasting.

Symptoms of DKA are various and atypical including fast and short breath, headache, lethargy, nausea, and vomiting. Those are common symptoms in post-operative patients due to other causes such as post-operative pain, poor oral intake, analgesics-related complication, and more seriously, peri-operative respiratory distress or vascular events. Therefore, the direct diagnoses of DKA by their symptoms are difficult. In principle, the diagnosis of DKA should be a diagnosis of exclusion [3].

RRS, a safety net to identify antecedents of the adverse events and to respond in a timely manner, was first implemented in Korea in 2008, and it has been developed in over 15 medical centers in 2019 and continues to expand [5]. In the two cases we reported, the patients were detected by the RRS in our hospital, which uses MEWS criteria for evaluation; unexplained hypotension (systolic BP<80 mmHg), bradycardia (HR<40 bpm/min) or tachycardia (HR>140 bpm/min), acute airway distress (RR<8/min or RR>30/min), acute hypoxia (SpO_2<85% or pO_2<55 mmHg), acute hypercapnia (pCO_2>50 mmHg), severe metabolic acidosis (pH<7.3 or total CO_2<12 mmHg), and sudden mental change including seizure. Each sign or symptom scores 1 respectively, and the total score with 5 or higher is automatically detected by the screening system.

Those two events occurred in recent two years, and both patients were managed by the same rapid response team members. In the first case, the patient was detected due to her unstable vital signs and symptoms, and several examinations and procedures should have been taken before they concluded the final diagnosis was euglycemic DKA. On the other hand, the second patient was detected by her abnormal laboratory findings; serum total CO_2 was 6 mmHg. The experience of the first case contributed to the second patient's managements faster and more efficient. In addition, both patients were detected and managed before proceeding to cardiopulmonary arrest.

According to a systemic review and meta-analysis by Maharaj et al. [6] RRS were associated with a reduction in hospital mortality and cardiopulmonary arrest. The automated screening system of RRS enables a prompt detection of patient at risk since it reduces the delay while notifying the patient's status by calls. In addition, in RRS, direct managements by professionals are possible so that any intervention by the other person could be excluded.

Euglycemic DKA can be developed as a peri-operative complication in T2DM patients with risk factors such as prolonged fasting and the use of SGLT2 inhibitors. Due to its rarity, physicians who are not familiar with euglycemic DKA have difficulty with having the impression of euglycemic DKA by their ambiguous symptoms and signs. Even though the definitive diagnosis of euglycemic DKA is dependent on the typical lab findings, other causes of higher anion gap acidosis should be excluded first. In addition, it takes a procedural time to prove ketonemia in urine or blood, and no significant hyperglycemia can be missed. Considering euglycemic DKA is a medical emergency, immediate and appropriate managements by RRS make a significant contribution to patient's prognosis.

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