

A Retrospective Analysis of the Incidence, Outcome and Factors Associated with the Occurrence of Euglycemic Ketoacidosis in Diabetic Patients on Sodium Glucose Co-Transporter – 2 Inhibitors Undergoing Cardiac Surgery

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ABSTRACT

Introduction: SGLT2i is a new class of drugs used for type 2 diabetes. SGLT2i are known to cause EuKA in the perioperative period. Euglycemic ketoacidosis (EuKA) can cause life-threatening metabolic acidosis in the perioperative setting. Though the event rate of SGLT2i associated diabetic ketoacidosis in nonoperative setting is low, incidence among peri-operative patients can be very high and remains unknown.

Aim: The aim of this study was to find the incidence, analyze outcome, and establish correlation between risk factors and EuKA in cardiac surgical patients on SGLT2i.

Materials and Methods: This is a retrospective study analyzing 24 cardiac surgical patients who were on SGLT2i for type 2 diabetes mellitus. Data collection included age, sex, BMI, preoperative HbA1C, albumin, creatinine, type of SGLT2i and timing of stopping before surgery, insulin administration in the immediate pre-operative period; use of CPB, GI infusion and inotropes in the intraoperative period; blood ketone, duration of ventilation, hydration status and length of postoperative stay in postoperative period. Patients were diagnosed to have EuKA if any one of the serially measured postoperative ketone values was more than 0.6 mmol/L (ketone positive). The collected data were used to find an association between the risk factors and the occurrence of EuKA.

Results: Of the 24 patients, 17 patients developed EuKA. (70.8%). 10 of the 17 EuKA in our study required preoperative Insulin for diabetic control whereas none in the ketone negative patients required insulin. This was statistically significant ($P = 0.019$). Association of other factors to EuKA were not statistically significant.

Conclusion: Though the event rate of SGLT2i associated Diabetic ketoacidosis in nonoperative setting is low, (17), the occurrence of EUKA in cardiac surgical patients on SGLT2i in our study was 70.8% (17 out of 24 patients). Patients who require insulin in addition to other oral hypoglycemic drugs for immediate preoperative glycemic control are at risk for the development of SGLT2 inhibitor-induced EuKA postoperatively. Missing the diagnosis of EuKA is fatal in these patients. We couldn't make a diagnosis in our first patient whom we lost. Since it was diagnosed in all our study patients by measuring serial ketone values, there was no mortality and insignificant morbidity. Cessation of SGLT2i before surgery, expectant watch for blood ketones, and treatment with GI infusion reduce morbidity and mortality in cardiac surgical patients.

Keywords: EuKA, GI infusion, Glucose insulin infusion, SGLT2i

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INTRODUCTION

Sodium-glucose co-transporter inhibitors (SGLT2i) such as empagliflozin and dapagliflozin are the newest class of oral hypoglycemic agents in the armamentarium for the treatment of type 2 diabetes mellitus. The American Diabetes Association and American Association of Clinical Endocrinologists (AACE) recommend the use of SGLT2i as either adjuvant therapy with metformin, first-line therapy for those who are intolerant to metformin, or in combination with insulin therapy.^[1]

Euglycemic ketoacidosis (EuKA) can be a serious complication of treatment with SGLT2i and can cause life-threatening metabolic acidosis in the perioperative setting. Though the event rate of SGLT2i associated Diabetic ketoacidosis in nonoperative setting is low, incidence among peri-operative patients can be very high and yet to be analyzed. The occurrence of EUKA in cardiac surgical patients on SGLT2i in our study was 70.8% (17 out of 24 patients). The precise mechanism by which SGLT2 inhibitors induce EuKA is not fully understood. A possible explanation is that SGLT2 inhibitors lower serum glucose levels through the inhibition of glucose reabsorption in the kidneys, leading to decreased insulin release and increased glucagon secretion by the pancreatic cells, both of which stimulate the production of ketones via the beta-oxidation of free fatty acids in the liver. SGLT2 inhibitors also directly stimulate glucagon release from the pancreas, which feeds back to more ketone production.^[2]

The SGLT2 inhibitor's spectrum of use is increasing because of its proven benefits like Glycemic control,^[3-9] reducing Blood Pressure,^[3-8,10] reduction in body weight,^[3-10] reduction in HbA1c,^[3,5] reduce all cause and cardiovascular death in patients with HFrEF^[11,12] (Heart Failure with reduced Ejection Fraction), cardiovascular benefits,^[12,13] increase HDL cholesterol,^[10] improve renal outcomes,^[11,12] and renoprotective effects.^[14,15]

Aim

This study aimed to find the incidence, analyze outcome, and establish a correlation between risk factors and EuKA in cardiac surgical patients on SGLT2i.

MATERIALS AND METHODS

This retrospective study included 24 patients, all ≥ 18 years of age who underwent cardiac surgery at our institution between October 2018 and November 2020. All these 24 Patients were receiving SGLT2 inhibitors for type 2 diabetes mellitus. This study was approved by the

Institutional Ethics Committee without the need for informed consent, on the condition that the subject's identities be removed before analysis due to this study being a retrospective one. The demographics, preoperative, intraoperative, and postoperative data were collected from the medical records.

The following data were collected:

Preoperative

1. Age, sex, BMI
2. HbA1C
3. Serum albumin
4. Serum creatinine
5. Type of SGLT2i and time of stopping in the preoperative period
6. Insulin administration in the immediate preoperative period.

Intraoperative

1. Use of CPB
2. Use of Glucose insulin infusion
3. Use of inotropes.

Postoperative

1. Blood ketone values
2. Duration of mechanical ventilation
3. Hydration status
4. Length of ICU stay.

In all the 24 patients, blood ketone was tested every fourth hourly in the immediate postoperative period, and 6th hourly or 8th hourly depending on the level of ketone. After 2 days, testing for ketone was stopped if two consecutive ketone values were negative. Patients were diagnosed to have EuKA if any one of the postoperative ketone values was more than 0.6 mmol/L (ketone positive).^[16] This was our hospital lab control value. The collected data was used to find an association between the risk factors and the occurrence of EuKA.

Data analysis

Levene's test was used for age, BMI, preop creatine, preop albumin, HbA1C to compare between both the groups (ketone positive and negative).

Mann-Whitney *U* test was used for duration of ventilation, fluid balance.

Pearson's 'Chi-square test' and logistic regression was used to find any association between the risk factors and the occurrence of EuKA.

RESULTS

Occurrence

Of the 24 patients, 17 patients had EuKA (ketone positive) (70.8%) [Table 1].

Patient characteristics

Of the total 24 patients, 20 were men and 4 were women. Of the 20 male patients, 14 turned positive for ketone and 6 were negative. Of the four female patients, three were positive for ketone and one was negative. There was no statistically significant difference between sex of the patients and occurrence of EuKA ($P = 0.841$).

Mean age in ketone positive group was 62.5 ± 8.80 vs 57.7 ± 9.74 in the negative group. A value of $P = 0.255$ indicates that the differences are not significant.

BMI was 24.9 ± 4.75 in ketone positive patients vs. 27.8 ± 3.4 in the negative group.

Statistically the difference is not significant ($P = 0.165$).

Diabetic control and anti-diabetic medications in the preoperative period

The mean HbA1C in ketone positive patients was 8.95 ± 1.80 and 9.98 ± 2.45 in the ketone negative group. The difference in the HbA1C is not significant ($P = 0.266$).

Of the 17 positive patients, 10 patients needed insulin in the immediate preop period along with other oral hypoglycemic drugs for glycemic control and 7 patients needed only OHA; however, all the seven negative patients were only on OHA other than SGLT2 inhibitors. This difference was statistically significant ($P = 0.019$). [Table 2].

Preoperative factors

The mean of serum albumin was 3.64 ± 0.54 in the ketone positive group vs 3.71 ± 0.24 in the negative group ($P = 0.757$, statically not significant).

The serum creatinine was 0.96 ± 0.24 in the ketone positive vs. 0.88 ± 0.21 in the negative group ($P = 0.464$, statically not significant).

Perioperative handling of SGLT2 inhibitors

Of the 17 ketone positive patients 6 were on dapagliflozin and 11 were on empagliflozin, whereas in the negative group 2 were on dapagliflozin and 5 were on Empagliflozin [Table 2] ($P = 0.751$, statically not significant).

In all 24 patients SGLT2i was stopped, but the timing of cessation was different.

Table 1: Results - original

Characteristics	Number (%)
Sex	
Male	20 (83.3)
Female	4 (16.7)
Insulin Pre op	
Insulin + OHA	10 (41.7)
Other OHA	14 (58.3)
CPB	
On CPB	9 (37.5)
Off CBP	15 (62.5)
Inotropes	
≤ 1	15 (62.5)
≥ 2	9 (37.5)
SGL2T	
Dapagliflozin	8 (33.3)
Empagliflozin	16 (66.7)
GI Infusion	
Delayed	9 (37.5)
At induction	15 (62.5)
Ketone	
Positive	17 (70.8)
Negative	7 (29.2)
ICU Stay	
Delayed	8 (33.3)
Not delayed	16 (66.7)

Table 2: Comparison of clinical factors between ketone positive and negative: - original

	KETONE		P
	Positive	Negative	
Age	62.5±8.80	57.7±9.74	0.255
BMI	24.9±4.75	27.8±3.40	0.165
Sex			
Male	14 (82.4)	6 (85.7)	0.841
Female	3 (17.6)	1 (14.3)	
Creatinine Preop	0.96±0.24	0.88±0.21	0.464
Albumin Preop	3.64±0.54	3.71±0.24	0.757
HbA1c	8.95±1.80	9.98±2.45	0.266
SGLT2 i			
Dapagliflozin	6 (35.3)	2 (28.6)	0.751
Empagliflozin	11 (64.7)	5 (71.4)	
Stopping SGLT2 i			
>72 hrs	5 (29.4)	4 (57.2)	1.627
48-72 hrs	8 (47.1)	2 (28.5)	
<48 hrs	4 (23.5)	1 (14.3)	
Insulin Preop			
Insulin + OHA	10 (58.8)	0	0.019
Other OHA	7 (41.2)	7 (100)	
CPB			
On CBP	7 (41.2)	2 (28.6)	0.562
Off CBP	10 (58.8)	5 (71.4)	
GI infusion			
Delayed	7 (41.2)	2 (28.6)	0.336
At induction	10 (58.8)	5 (71.4)	
Inotropes			
≤ 1	11	4	0.121
≥ 2	6	3	
Duration of ventilation	9.00 (5.50, 13.0)	6.50 (5.00, 8.50)	0.234
Fluid balance	529 (91.5, 1149)	797 (498, 844)	0.664
ICU stay			
Delayed	7 (41.2)	1 (14.3)	0.204
Not delayed	10 (58.8)	6 (85.7)	

Of the 17 ketone positive patients 5 patients stopped SGLT2 more than 72 h prior to surgery, 8 patients stopped

between 48 and 72 h and 4 patients less than 48 h of surgery; whereas 4 patients stopped SGLT2 more than 72 h prior to surgery, 2 patients between 48 and 72 h and 1 patient stopped less than 48 h prior to surgery in the negative group ($P = 1.627$, statically not significant).

Cardiopulmonary bypass and EuKA

Of the 17 ketone positive patients, in 7 patients cardiac surgery was performed on CPB and 10 had OPCAB surgery; whereas in the ketone negative group, surgery was performed on CPB only in 2 patients and 5 patients had OPCAB surgery ($P = 0.562$, statically not significant).

Perioperative insulin management

Of the 17 ketone positive patients intraoperative glucose insulin infusion was started at induction in 10 patients and 7 patients received infusion in the postoperative period; whereas 5 patients in the negative group received GI infusion at induction and 2 patients in the postoperative period ($P = 0.336$, statically not significant). Glucose insulin infusion was started electively as a preventive measure to suppress ketogenesis even before ketone positive values [Table 2].

Perioperative inotropic support

Of the ketone positive patients 11 patients required ≤ 1 inotrope and 6 patients required ≥ 2 inotropes; whereas in the ketone negative patients 4 required ≤ 1 inotrope and 3 patients required ≥ 2 inotropes in the perioperative period ($P = 0.121$, statically not significant).

Outcomes

Of the ketone positive patients 7 patients (7/17) had a delayed discharge from ICU; whereas in the ketone negative group 1 patient (1/7) had a delayed discharge from ICU ($P = 0.204$, statically not significant).

The mean duration of ventilation in the ketone positive patients was 9.8 h; whereas it was 7.2 h in the ketone negative group. [Table 2] ($P = 0.234$, statically not significant).

DISCUSSION

EuKA is an uncommon complication associated with the use of SGLT2i use in type 2 diabetic patients. SGLT2 inhibitors are thought to lower production of insulin and increase the glucagon secretion, which promotes a shift of glucose to fat metabolism and stimulating ketogenesis resulting in EuKA.^[17]

The event rate of SGLT2i-associated Diabetic Keto Acidosis in a predominant non-operative setting is

estimated to be between 1.8 and 4.9 cases per 1000 patient years.^[18]

But the incidence within perioperative patients remains unknown. The occurrence of EuKA in cardiac surgical patients on SGLT2i in our study was 70.8% (17 out of 24 patients). Thiruvengkatarajan *et al.*,^[18] in their systematic review of 47 perioperative surgical cases which included 7 cardiac surgical patients, found the occurrence of EuKA to be 89%. In the data analysis from the Food and Drug Administration Adverse Event Reporting System (FAERS) in which 51 (three surgical and 48 non-surgical) confirmed cases of SGLT2i-related DKA analyzed from the FAERS data, 29 (71%) were proved EuKA.^[18]

Patients with EuKA can have symptoms such as nausea, vomiting, and tachypnea. Although these nonspecific postoperative findings are common they will have anion gap metabolic acidosis ($\text{pH} < 7.3$, anion gap $> 12 \text{ mmol}\cdot\text{L}^{-1}$) with lower than anticipated serum glucose levels ($< 250 \text{ mg/dl}$). However, serum and urine ketones will confirm the diagnose of EuKA. The EuKA positive patients in our study had ketonemia with serum ketones $> 0.6 \text{ mmol/L}$.

Goldenberg *et al.*,^[19] recommend cessations of SGLT2 inhibitors 3 days (5 half-lives) before surgery. Pace *et al.*^[20] recommend that SGLT2 inhibitors be held at least 5 days preoperatively. FDA^[21] recommends Canagliflozin, dapagliflozin, and empagliflozin to be discontinued 3 days before scheduled surgery, and ertugliflozin should be stopped at least 4 days before surgery.

Of the 9 patients in whom SGLT2i was discontinued > 72 h before surgery, 5 were in EuKA positive group and 4 were in the ketone negative group, and this was not statistically significant [Table 2].

Though we are certain that taking SGLT2 in cardiac surgical factors is a risk factor for the occurrence of EUKA, stopping the drug for < 48 h, 48–72 h or > 72 h didn't make a difference. So we understand from our statistics that timing of cessation of the drug has a minor or no influence on the occurrence of EuKA. Further evaluation is needed in this context since this conclusion was not statistically significant.

Missing the diagnosis of EuKA is fatal in these patients. We could not make a diagnosis in our first patient whom we lost. All patients who receive SGLT2 inhibitors until surgery should be tested for blood ketones if EuKA is suspected, regardless of the blood glucose level.^[16,22,23]

In our study, we tested for blood ketones every fourth hourly in the immediate post-operative period, and to 6th hourly or 8th hourly depending on the level of ketone. After 2 days, we stopped if two consecutive ketone values were negative. We labeled the patient had ketoacidosis, if at least one value is more than or equal to 0.6 mmol/L.^[16]

There are case reports of EuKA occurring in patients on SGLT2i undergoing cardiac surgery on Cardio Pulmonary Bypass^[2] (CPB) and hence CPB could be implicated as a precipitating factor for the development of EuKA. But in our study no such correlation was observed. Of the 17 positive patients, only 7 patients had the surgery on CPB and in 10 patients CPB was not used.

Surgery is a triggering factor for the development of EuKA in patients on SGLT2i. It is recommended that prophylactic low dose of long-acting insulin be started after cessation of oral agents to mitigate the risk of developing EuKA in at-risk populations. 10 of the 17 EuKA in our study required preoperative Insulin for diabetic control whereas none in the EuKA negative patients required. This was statistically significant ($P = 0.019$). Thus, on the basis of our observation, patients who require insulin in addition to other oral hypoglycemic drugs for immediate preoperative glycemic control are at risk for the development of SGLT2 inhibitor-induced EuKA postoperatively. This is supported by the evidence - Goldenberg *et al.*,^[19] patients with insulin-treated type 2 diabetes are at risk for DKA.

In a case series reported by Aaron Lau *et al.*,^[24] after insulin and dextrose infusions were initiated, rapid resolution of metabolic abnormalities occurred.

If blood ketones are positive (>0.6 mmol/L) during acute illness, a supplemental bolus of insulin is recommended every 2–4 h to reduce ketosis, along with an oral source of carbohydrate.^[19]

Glucose insulin infusion is recommended in the treatment of DKA when the blood glucose level falls below 250 mg/dL to suppress ketogenesis while preventing hypoglycemia. We observed that starting Insulin glucose infusion before the development of ketoacidosis both at induction of anesthesia in 10 patients and in seven patients in the postoperative period did not prevent the development of EuKA.

Perioperative complications in the cardiac surgical patients can impact patient-centered outcomes, increasing mortality and morbidity. EuKA patients in our study had clinically significant but statistically insignificant prolongation

of mechanical ventilation and delay in discharge from intensive care. The mean duration of ventilation in the ketone-positive patients was 9.8 h whereas it was 7.2 h in the ketone-negative group. Of the positive patients, seven patients (7/17) had a delayed discharge from ICU as compared to only one patient (1/7) in the ketone negative group. There was no perioperative mortality in diabetic, cardiac surgical patients on SGLT2i in spite of the high incidence of EuKA. This probably was due to awareness and vigilance for the development of ketoacidosis, early diagnosis, and management of the complication.

CONCLUSION

We found a very high incidence of euglycemic diabetic ketoacidosis in cardiac surgical patients on SGLT2i, though not associated with increased mortality. Patients who required insulin in the preoperative period for diabetic control had a correlation for the development of EuKA.

Based on our experience and review of the literature, we suggest the following for patients on SGLT2 inhibitors coming for cardiac surgery. Cessation of SGLT2 inhibitors at least 3 days before in elective surgeries or as early as possible in emergency surgeries, checking for ketones in periodic intervals, initiation of GI infusion electively intraoperatively and postoperatively.

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Conflicts of interest

There are no conflicts of interest.

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