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Sitagliptin for prevention of stress hyperglycemia in patients without diabetes undergoing general surgery: a pilot randomized study.

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Abstract

Aim: We investigated if a dipeptidyl peptidase-4 inhibitor, sitagliptin, can prevent perioperative stress hyperglycemia in patients without prior history of diabetes mellitus undergoing general surgery.

Methods: This prospective, double-blind pilot trial, randomized general surgery patients to receive sitagliptin (n=44) or placebo (n=36) once daily, starting one day prior to surgery and continued during the hospital stay. The primary outcome was the occurrence of stress hyperglycemia, defined by blood glucose (BG) >140 mg/dL and >180 mg/dL after surgery. Secondary outcomes included: length-of-stay, ICU transfers, hypoglycemia, and hospital complications.

Results: BG >140 mg/dL was present in 44(55%) of subjects following surgery. There were no differences in the rates of stress hyperglycemia between treatment with placebo and sitagliptin (56% vs 55%, p=0.93). BG>180 mg/dL was observed in 19% and 11% of patients treated with placebo and sitagliptin, respectively, p=0.36. Treatment with placebo and sitagliptin resulted in similar postoperative BG (148.9±29.4 mg/dL vs. 146.9±35.2 mg/dL, p=0.73). There were no differences in length-of-stay (4 vs 3 days, p=0.84), ICU transfer (3% vs 5%, p=1.00), hypoglycemia <70 mg/dL (6% vs 11%, p=0.45), complications (14% vs 18%, p=0.76).

Conclusion: In this pilot trial, treatment with sitagliptin during the perioperative period did not prevent stress hyperglycemia or complications in individuals without diabetes undergoing general surgery.

Keywords

Stress hyperglycemia; hospital complications; perioperative management; DPP4-inhibitors

1. Introduction

Several observational and randomized controlled trials have reported that hyperglycemia is an independent risk factor for hospital complications, longer hospital stay, increased rates of infection and mortality compared to patients with normoglycemia.^{1–3} Approximately 30% of patients without prior history of diabetes undergoing non-cardiac surgery develop stress hyperglycemia, usually occurring by 72 hours postoperatively.^{4–7} In such patients, stress hyperglycemia is associated with worse outcomes compared to patients without diabetes maintaining normoglycemia, and similar rates of complications compared to those with pre-existing diabetes.^{1,8,9}

The current standard of care from national medical associations is to treat stress hyperglycemia with intravenous insulin in the ICU or with subcutaneous insulin regimens in non-ICU settings.^{4,6} Although effective, intensive insulin therapy is costly and requires significant nursing resources, and is associated with ~20–30% risk of hypoglycemia.^{10,11} Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral glucose lowering agents that reduce breakdown of endogenous glucagon-like peptide-1 (GLP-1) stimulating insulin secretion in a glucose-dependent manner.¹² Recent studies have demonstrated that DPP-4 inhibitors are effective in improving glycemic control with low-risk of hypoglycemia in general medicine and surgical hospitalized patients with type 2 diabetes mellitus (DM).^{13,14} Thus, the present study aimed to determine whether use of a DPP-4 inhibitor, sitagliptin, initiated before surgery and continued during the hospital stay could reduce the risk of developing postoperative stress hyperglycemia in patients without prior history of diabetes undergoing general non-cardiac surgery.

2. Materials and Methods:

2.1. Study Design and Subjects

This randomized placebo-controlled double-blind trial ([ClinicalTrials.gov](https://clinicaltrials.gov)) was designed to evaluate feasibility and obtain preliminary estimates on the effect of sitagliptin in preventing stress hyperglycemia during the perioperative period. We enrolled patients without a history of diabetes undergoing general non-cardiac surgery. Patients were recruited from Emory University Hospital and Grady Memorial Hospital in Atlanta, Georgia between April 2016 and March 2017. The Institutional Review Board at Emory University approved this study.

Patients were included if they were between the ages of 18 and 80 years old, had no prior history of DM [based on ICD-10 diagnoses and confirmed by hemoglobin A1c (HbA1c) of <6.5% and without preoperative hyperglycemia (fasting BG < 126 mg/dL or random BG < 140 mg/dL)]. We excluded patients expected to require post-operative intensive care unit (ICU) admission, or those planned to be kept on strict NPO following surgery (unable to take study medication). Only subjects requiring general anesthesia for their surgery were enrolled in the study. Additional exclusion criteria included patients undergoing cardiac surgery, and/or those with severely impaired renal function (GFR <30 ml/min/1.73 m²), clinically significant hepatic failure, pancreatic, or gallbladder disease, surgery for gastrointestinal obstruction, ileus or potential need for gastric suction, pre-operative treatment with glucocorticoids (equivalent to prednisone > 5 mg/day), pregnancy or inability

to consent for any reason. Anesthesiologists were asked to avoid steroids for perioperative nausea prophylaxis and use alternative therapies whenever possible.

2.2 Enrollment and Randomization

Patients were enrolled and randomized at least one day prior to surgery during either their preoperative clinic visit or inpatient stay while awaiting surgery. Patients were randomly assigned (1:1) to treatment with sitagliptin or placebo. The research pharmacists at Grady and Emory University Hospitals received computer generated randomization tables that were generated by block randomization without stratification. The research pharmacists coordinated randomization and dispensed medication at each institution. A total of 97 were approached for eligibility and, 96 were randomized. Of those, 80 patients who underwent surgery, received the study drug or placebo and had at least one post operative blood glucose check were included in the final data analysis (see Figure).

2.3 Study Procedures

Patients were treated with sitagliptin or placebo once daily starting the day prior to surgery. Sitagliptin is rapidly absorbed reaching peak levels within 4 hours¹² and efficacy in inhibiting DPP-4 activity by 24 hours.¹⁵ Initiation of the study medication one day before surgery ensured maximal potential efficacy in preventing postoperative stress hyperglycemia. The investigators, study coordinators, and medical providers remained blinded to the treatment given. Those with normal renal function received 100 milligrams (mg) once daily. For those with estimated glomerular filtration rate (eGFR) $< 50 \text{ ml/min/1.73 m}^2$, the dose of sitagliptin was reduced to 50 mg per day. Although no subjects were enrolled in the trial if they had a GFR $< 30 \text{ ml/min/1.73 m}^2$, those developing an eGFR $< 30 \text{ ml/min/1.73 m}^2$ after study enrollment received an adjusted sitagliptin dose of 25 mg daily. Medication administration was managed by the investigational drug pharmacy. Patient demographics, baseline HbA1c, American Society of Anesthesiology (ASA) preoperative classification score, and BG measurement were obtained prior to surgery. Following surgery, individuals were monitored with point of care BG testing (POC) before meals and at bedtime for those who were eating and every six hours for patients who were not eating. All subjects were scheduled to have POC testing 4 times daily. However, all 4 checks were not completed on days when patients were off of the floor as well as on days of surgery and discharge days. Patients were monitored for postoperative complications, length of stay and hypoglycemia. Corrective (sliding scale) insulin therapy was started following a first episode of BG $> 180 \text{ mg/dL}$ following standard hospital protocol.

2.4 Outcomes

The primary study outcome was difference in percentage of patients developing stress hyperglycemia (BG $> 140 \text{ mg/dL}$ and $> 180 \text{ mg/dL}$) during the postoperative period. Secondary endpoints included length of hospital stay (LOS), need for intensive care unit (ICU) transfer and hypoglycemia (< 70 and $< 54 \text{ mg/dL}$), need for insulin therapy, and hospital complications. Complications recorded included gastrointestinal symptoms or distress (nausea, vomiting, abdominal pain, ileus), acute kidney injury (AKI), defined by an increase of $> 0.5 \text{ mg/dL}$ from baseline in serum creatinine, re-operative intervention, and acute coronary syndrome.

2.5 Statistical Analysis

No previous data is available on the role of DPP-4 inhibitors on the prevention of hyperglycemia in patients without diabetes. A power calculation was not feasible; therefore, we conducted a pilot trial with a convenience sample of 80 subjects. We compared clinical characteristics and outcomes, such as mean hospital BG, percentage of patients developing stress hyperglycemia between treatment groups and between patients with or without pre-diabetes. Nonparametric Wilcoxon tests or Kruskal-Wallis tests were used to compare continuous variables between different groups. For discrete variables, Chi-square tests or Fisher exact tests were used. The data were generally presented as mean $\pm$ SD for continuous variables and count (percentage) for discrete variables. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using SAS (version 9.3).

3. Results

A total of 80 patients were included in the analysis. Baseline characteristics of the study groups are shown in Table 1. A total of 36 patients received placebo and 44 received sitagliptin. There were no significant differences in sex, age, weight, race, body mass index (BMI) or American Society of Anesthesiologists (ASA) score between groups (Table 1). There were no differences in HbA1c or preoperative BG between sitagliptin and placebo groups at baseline (Table 2). The primary surgery types included were orthopedic, genitourinary, gynecologic and neurologic. All patients had their surgery performed under general anesthesia. Nine patients in the placebo group and six patients in the sitagliptin group received one dose of dexamethasone treatment one time prior to surgery for nausea prophylaxis. One patient in the placebo group received a five-day hydrocortisone taper starting at 100 mg for bronchospasm following surgery.

Perioperative glycemic control is shown in Table 2. The peak postoperative BG was 148.9 ± 29.4 mg/dL in the placebo group and 146.9 ± 35.2 mg/dL in the sitagliptin group ($p=0.73$). Average postoperative BG during hospitalization was 111.8 ± 16.9 mg/dL for the placebo group and 109.3 ± 12.7 mg/dL for the sitagliptin treated group ($p=0.65$). There were no significant differences in the rates of stress hyperglycemia with at least one BG >140 mg/dL between treatment groups (placebo: 56% vs. sitagliptin: 55%, $p=0.93$). There were no day to day differences in glycemic control between treatment groups ($p>0.05$ for days 1–5) (Figure 2). Only one patient who was in the sitagliptin group was treated with insulin in the hospital following a second episode of hyperglycemia with BG >180 mg/dL. Although patients in the sitagliptin group had higher rate of mild hypoglycemia (BG <70 mg/dL), this difference was not statistically significant, (placebo: 6% vs. sitagliptin: 11%, $p=0.45$). No patients in the study developed clinically significant hypoglycemia with BG <54 mg/dL.

Hospital complications are reported in Table 3. There were no significant differences in rates of complications among the treatment groups (14% vs 18%, $p=0.76$). There were no differences in rates of gastrointestinal complications including ileus, nausea, vomiting, abdominal pain or diarrhea. One patient in the sitagliptin group developed transient chest pain. No EKG changes were noted and the patient did not develop acute coronary syndrome. Of the serious adverse events, one patient in the placebo group developed acute bronchospasm following surgery attributed to anesthesia medication requiring transfer to the

intensive care unit and treated with a hydrocortisone taper. One patient in the sitagliptin group had pulmonary embolism following surgery.

To explore if pre-operative dysglycemia influenced the risk of stress hyperglycemia, we performed a subgroup analysis stratified by pre-diabetes status. The 74 patients who had HbA1c values available were stratified based on HbA1c in the normal range <5.7% compared to HbA1c in pre-diabetes range between 5.7% and 6.4%. Overall, patients with pre-diabetes tended to develop stress hyperglycemia with BG >140 mg/dL (76% vs 51%, $p=0.09$) with higher peak post-operative BG of 143.2 ± 31.1 mg/dL vs 166.5 ± 30.2 mg/dL, $p=0.006$ as compared to patients without pre-diabetes. When stratified by treatment group, among patients with pre-diabetes, there were no significant differences in rates of stress hyperglycemia for BG >140 mg/dL: placebo-67% vs sitagliptin-88%, $p=0.58$; or > 180 mg/dL (placebo-44% vs. sitagliptin-25%, $p=0.62$).

4. Discussion:

This pilot study investigated whether stress hyperglycemia can be prevented with the use of a DPP-4 inhibitor in patients without a prior history of diabetes undergoing general non-cardiac surgery. We report that sitagliptin treatment, given one day before surgery and daily during the hospital stay, did not reduce the frequency of stress hyperglycemia compared to placebo. In addition, we observed no differences in hospital LOS, frequency of hypoglycemia, hospital complications or need for insulin use between treatment groups.

There is no consensus regarding what BG level defines stress hyperglycemia. Observational studies have reported that over 30–40% of general medicine and surgery patients and up to 80% of those undergoing cardiac surgery^{16–18} have elevated BG ranging between >140 mg/dL.^{1,9,19} Large cohort studies have identified stress hyperglycemia and DM as an independent risk factors for poor outcomes after surgery as compared to patients with normoglycemia, specifically with increased incidence of perioperative mortality,^{20,21} deep sternal wound infection,²² renal failure,¹⁸ perioperative stroke,^{23,24} longer hospital stays,^{20,24} and higher health care resource utilization.^{25–27} In patients undergoing non-cardiac general surgery, both diabetes and stress hyperglycemia are associated with up to four-fold increase in complications and over a two-fold increase in death compared to patients with normoglycemia.^{2,28,29} In addition, some studies have reported that the development of stress hyperglycemia in patients without prior history of DM is associated with worse clinical outcomes than patients with a known history of DM.¹

Despite the association between stress hyperglycemia and increased rates of hospital complications, few studies have reported on best treatment strategies in non-ICU settings.⁹ Most patients with stress hyperglycemia are treated with insulin by sliding scale or basal insulin, which is associated with increased rates of hypoglycemia. Thus, we investigated whether hyperglycemia could be avoided after surgery, thereby facilitating glycemic management and preventing potential complications. In this study, we used sitagliptin as it has recently been shown to improve glycemic control in hospitalized patients with type 2 diabetes with hyperglycemia.^{13,14} In two recent studies, sitagliptin with or without glargine insulin resulted in similar glycemic control in medical and surgical patients compared to

basal bolus regimen.^{14,30} Similar to our results, a recent pilot study by Brackbill *et al*, showed sitagliptin therapy in patients with DM following cardiac surgery resulted in non significant differences in glycemic control compared to insulin therapy.³¹

The causes of stress hyperglycemia are complex involving increased levels of counter-regulatory hormones (glucagon, growth hormone, catecholamines), oxidative stress and circulating inflammatory cytokines.^{32–34} These metabolic derangements result in insulin resistance with impaired glucose uptake by skeletal muscle and failure of insulin to suppress hepatic gluconeogenesis thus propagating hyperglycemia.^{32,35} It is not known if hyperglycemia represents a simple marker of acute stress and inflammation, or if it has direct impact on the development of complications, impaired immune function³⁶ and thrombogenic effect.^{37,38} Sitagliptin and other DPP-4 inhibitors act by reducing the breakdown of native GLP-1 in a glucose-dependant manner, thus potentiating its effects in increasing insulin release and reduced glucagon secretion.¹² It is possible that DPP-4 inhibitors are not potent enough in increasing native GLP-1 or that other mechanisms play a more significant role in the pathogenesis of stress hyperglycemia including inflammation and insulin resistance.^{34,39} Future prospective studies of stress hyperglycemia may include measures of counter-regulatory hormones and inflammatory markers to assess the potential impact of interventions on these intermediaries.

We acknowledge several limitations to this study. We included a selective cohort of subjects without history of hyperglycemia before surgery excluding those expected to require ICU care or unable to eat following surgery. Overall, the sample population was composed of relatively healthy young and non-obese adults who may have a lower risk of developing hyperglycemia than older and more ill individuals. The study also excluded patients with evidence of dysglycemia based on pre-operative BG and those who were planned for ICU care following surgery potentially lowering the acuity of the cases and reducing the overall risk of hyperglycemia. Similarly, because the study drug was started one day prior to surgery, patients who required immediate operation following admission could not be enrolled in the trial. We also did not have a BMI cut off for enrollment and average BMI of the study population was 28.0 Kg/m². It is possible that inclusion of a more obese individuals, those undergoing higher acuity surgery, requiring steroid therapy and with abnormal pre-operative BG would have resulted in higher rates of hyperglycemia. POC testing may have also failed to capture all episodes of stress hyperglycemia, especially in the immediate perioperative period. Future studies of interventions in stress hyperglycemia may implement continuous glucose monitoring during and after surgery to improve monitoring in the immediate perioperative period.

5. Conclusion:

In summary, the results of this pilot study suggest that the use of sitagliptin, given one day before surgery and continued during the hospital stay, although safe, did not reduce the development of stress hyperglycemia in patients without a history of diabetes undergoing general surgery.

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Figure 1: Study Enrollment Flowsheet

Figure 2: Mean Daily Blood Glucose

Mean daily BG per treatment group. Pre-operative and immediate post-operative 3 BGs reported.

Table 1:**Patient Demographics**

<i>Variable</i>	Placebo (N=36)	Sitagliptin (N=44)	<i>P-value</i>
Sex, n (%)			0.54
Female	18 (50%)	19 (43%)	
Male	18 (50%)	25 (57%)	
Age	45.9 ± 14.5	51.1 ± 12.8	0.10
Race, n (%)			0.83
Black	26 (72%)	32 (73%)	
White	8 (22%)	11 (25%)	
Other	2 (6%)	1 (2%)	
Surgery Type, n (%)			0.44
Orthopedic	6 (17%)	11 (25%)	
Genitourinary	9 (25%)	14 (32%)	
Gastrointestinal	3 (8%)	3 (7%)	
Gynecologic	7 (19%)	3 (7%)	
Neurologic	4 (11%)	5 (11%)	
OMFS [∞]	4 (11%)	1 (2%)	
Thoracic	2 (6%)	2 (5%)	
Burn/Wound	1 (3%)	4 (9%)	
Vascular	0 (0%)	1 (2%)	
Weight, Kg	80.5 ± 22.7	81.7 ± 18.5	0.46
Body Mass Index, Kg/m ² (mean±SD)	27.9 ± 8.1	28.3 ± 6.0	0.30
ASA [*] Status, n (%) ^α			0.94
1	4 (13%)	4 (10%)	
2	17 (57%)	22 (56%)	
3	9 (30%)	13 (33%)	
Glucocorticoid use, n (%)	10 (28%)	6 (14%)	0.16

Continuous variable reported as mean± standard deviation

^{*} ASA Status: American Society of Anesthesiology Physical Status Classification

[∞] Oral Maxillofacial Surgery

^α Inconsistency between total population and population summed for individual variables was due to missing information.

Table 2:

Perioperative Glycemic Control

Variable	Placebo (N=36)	Sitagliptin (N=44)	P-value
Admission HbA1c, % mg/dL (mean±SD) *	5.5 ±0.4	5.4 ± 0.4	0.07
Subjects by Pre-DM status **			0.40
Without Pre-DM, n (%)	22 (71)	35 (81)	
With Pre-DM, n (%)	9 (29)	8 (19)	
Admission BG (mg/dL)	98.5 ± 20.0	107.6 ± 25.3	0.09
Randomization BG, mg/dL (mean±SD)	90.1 ± 17.2	94.7 ± 15.6	0.07
Pre-operative BG, mg/dL	93.9 ± 15.2	94.8 ± 15.3	0.76
Immediate Post-operative BG, mg/dL	126.5 ± 27.4	123.9 ± 27.9	0.81
Peak post-operative BG, mg/dL	148.9 ± 29.4	146.9 ± 35.2	0.73
Peak post-operative BG in subjects without Pre-DM, mg/dL	144.0 ±23.3	144.6 ±35.0	0.74
Peak post-operative BG in subjects with Pre-DM, mg/dL	168.6 ±34.5	165.3 ±25.3	0.92
Average Postoperative Hospitalization BG, mg/dL	111.8 ± 16.9	109.3 ± 12.7	0.65
Patients with at least 1 BG> 140 mg/dL, n (%)	20 (56%)	24 (55%)	0.93
Patients with at least 1 BG> 180 mg/dL, n (%)	7 (19%)	5 (11%)	0.36
Patients with 1 or more BG < 70 mg/dL, n (%)	2 (6%)	5 (11%)	0.45
Patients with 1 or more BG < 54 mg/dL, n (%)	0 (0%)	0 (0%)	
Average POC checks per patient	2.6 ± 0.8	2.5 ± 0.7	0.73

Continuous variables reported as mean± standard deviation

* HbA1c values were not available for 5 patients in the placebo arm and 1 patient in the sitagliptin arm.

** Without pre-DM defined by HbA1c < 5.7%; With Pre-DM defined by HbA1c ≥ 5.7, <6.5,

Table 3:**Complications**

Variable	Placebo (N=36)	Sitagliptin (N=44)	P-value
Composite Complications, n (%)	5 (14%)	8 (18%)	0.76
Gastrointestinal, n (%)	1 (3%)	4 (9%)	0.37
Ileus, n (%)	1 (3%)	2 (5%)	1.00
Nausea, n (%)	0 (0%)	1 (2%)	1.00
Vomiting, n (%)	0 (0%)	2 (5%)	0.50
Diarrhea, n (%)	0 (0%)	1 (2%)	1.00
Abdominal Pain, n (%)	1 (3%)	1 (2%)	1.00
AKI [*] , n (%)	1 (3%)	1 (2%)	1.00
Chest pain, n (%)	0 (0%)	1 (2%)	1.00
Thrombosis, n (%)	1 (3%)	0 (0%)	0.45
Pulmonary Embolism, n (%)	0 (0%)	1 (2%)	1.00
Bronchospasm, n (%)	1 (3%)	0 (0%)	0.45
Re-intervention, n (%)	1 (3%)	2 (5%)	1.00
Other, No. (%) ^a	1 (3%)	0 (0%)	0.45
Postoperative ICU, n (%)	1 (3%)	2 (5%)	1.00
ICU length of stay, days, Median (Q1,Q3)	2.0 (2.0,2.0)	1.5 (1.0,2.0)	0.48
Total LOS, days (Median,Q1,Q3) ^β	3.5 (2.0,6.0)	3.0 (2.0,7.0)	0.84

^{*} AKI: acute kidney injury with rise in creatinine by 38 μmol/L from baseline, ICU: Intensive Care Unit, LOS: Length of Stay

^a Other: tachycardia and anemia (same patient)

^β Q1,Q3: Interquartile range 1–3