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Blood Glucose Variation in Non-diabetic Patients Undergoing Intraabdominal Surgery

Chananya Potisuk, Kornchanok Kromcharee, Wacharin Sindhvananda
Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Background: Perioperative hyperglycemia in non-diabetes (non-DM) has been reported as much as 30%. Glycemic variability (GV) becomes a better predictive index of complications than hyperglycemia. High GV in non-DM was associated with more severity of complications than diabetes. There has been no study of GV in non-diabetes undergoing intraabdominal surgery.

Objectives: To evaluate 1) incidence of hyperglycemia/hypoglycemia 2) perioperative GV and 3) risk factors of high GV

Methods: A prospective observational study was performed after IRB approval. Adult non-diabetic patients undergoing intraabdominal surgery were recruited. Predicted operation time (<2 h) and planned sole regional anesthesia were excluded. Selection criteria of non-DM were defined. Blood glucose (BG) was monitored by POCT every hour. Controls of BG were tight or non-tight controls as appropriate. GV was calculated in the form of SD. Descriptive statistics and Mantel-Haenszel odds ratio were used.

Results: Final patients of 120 were retained for analysis. The 1st and 2nd most common types of surgery were hollow viscus organ (50.83%) and solid organ (36.57%). Surgical techniques was open (81.33%) and laparoscopic (16.67%) approaches. Combined continuous epidural with general anesthesia (CEA-GA) was performed (67.5%). Hyperglycemia (>180 mg/dL) and hypoglycemia (<60 mg/dL) were 15% and 5%, respectively. Patients with hyperglycemia of 15/18 (12.5%) received BG control. Hyperglycemia began during the 2nd operative hour and mostly occurred in the 3rd hour. 44% of patients exhibited perioperative high GV. Solid organ surgery was a significant risk factor (OR = 2.25).

Conclusion: Hyperglycemia, high GV and hypoglycemia can occur in non-DM undergoing intraabdominal surgery.

Keywords: Glycemic variability, hyperglycemia, Non-diabetes

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Background

Surgery-related sympathetic stimulation leads to neurohormonal derangement and catabolic state.[1,2] Based on this fact, hyperglycemia could possibly occur perioperatively in spite of non-diabetes. In the past, perioperative hyperglycemia was found in non-diabetes as much as 30%.[3] Also, Frisch A et al. demonstrated intraoperative blood glucose (BG) significantly increases in 30-40% of patients in spite of non-cardiac surgery.[4]

Hyperglycemia is highly related to postoperative complications.[5] Perioperative hyperglycemia in non-diabetic patients (non-DM) was demonstrated to be more associated with severity of infection, myocardial ischemia and higher mortality than that of DM.[6-8] Since intraoperative surgery has been less invasive in current practice, it is not certain whether hyperglycemia remains to be a concern or not.

It is important that glycemic variability (GV) is an associated factor of postoperative complications because fluctuation of BG leads to endothelial injury.[9,10] However, GV in non-DM undergoing intraabdominal surgery has not been investigated.

This study was aimed to evaluate in non-DM patients undergoing intraabdominal surgery: 1) incidence of

Correspondence to: Wacharin Sindhvananda, MD., E-mail: wacharins@hotmail.com
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hyperglycemia/hypoglycemia, 2) glycemic variability and 3) factors associated with high GV.

Methods

This study was a prospective observational study approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB. 576/60) and registered with Thaiclinicaltrial.gov (TCTR 20191104002).

Setting

This study was a single-site study at King Chulalongkorn Memorial Hospital. Patients were recruited between October 2017 and September 2019.

Participants

All adult (>20 years) non-diabetic patients admitted to undergoing elective intraabdominal surgery comprised the study group. Non-diabetes were selected by no history of diagnosed DM in the past, fasting blood sugar (FBS) <126 mg/dL, or random blood sugar (RBS) <200 mg/dL.[11]

Exclusion criteria were: 1) predicted time of operation was <2 hours, 2) regional anesthesia was planned to be a sole anesthetic technique and 3) previous history of cerebrovascular accident (CVA).

All recruited patients gave informed consent after being informed of details of the study.

Surgery and anesthesia

Surgical techniques were chosen to be open or laparoscopic surgery by surgeons. Anesthesia was performed as standard routine management. General anesthesia (GA) was inducted with propofol 2-3 mg/kg or etomidate 0.2-0.3 mg/kg. Anesthesia level was maintained with 50-70% nitrous oxide in oxygen, 1-2 MAC of sevoflurane or isoflurane to keep expired end-tidal anesthetic gas of 0.7-1.3 MAC, fentanyl 1-2 mcg/kg, and cisatracurium 0.15-0.2 mg/kg for loading then 0.02 mg/kg every 45-60 minutes. Combined continuous epidural anesthesia with general anesthesia (CEA-GA) was allowed to be administered if there are no contraindications. Local anesthetic for CEA was 0.125-0.25% bupivacaine.

Blood glucose monitor

Capillary blood was used for intraoperative POCT of BG (using Dextrostrix, Accucheck Performa®). POCT of BG (POCT-BG) was performed every hour until the end of surgery. Postoperative POCT-BG was performed once at PACU and again on the first postoperative day.

Control of hyperglycemia

Institutional BG control protocol is to keep BG range at 140-180 mg/dL and to choose between two modes of BG control (tight and non-tight control). For non-tight control, the protocol recommends regular insulin (RI) bolus 5-10 units once POCT-BG = 180-250 mg/dL and RI bolus 10-15 units once POCT-BG >250 mg/dL. For tight control, the protocol recommends starting RI infusion 1 unit/h once POCT-BG = 180-200 mg/dL, 2 units/h once POCT-BG = 201-250 mg/dL, and 3 units/h once POCT-BG = 251-300 mg/dL with RI bolus 5-10 units.

At the start of treatment, a mode of BG control and dose adjustment were chosen as appropriate by in-charge anesthesiologists.

Management of hypoglycemia

Patients were treated with 50% glucose intravenously either 10 ml for POCT-BG 50-60 mg/dL or 20 ml for POCT-BG <50 mg/dL.

Fluid and electrolytes management

Either acetar or saline was the fundamental fluid replacement. Infusion of 5% dextrose in saline with rate of 40-60 ml/h was started along with administration of RI.

Serum potassium was monitored in all patients who received RI infusion. Blood sampling was done after 1 h of RI administration and every 4-6 hours if RI was continuously infused.

Outcome Variables

Hyperglycemia was defined once intraoperative POCT-BG showed >180 mg/dL. Hypoglycemia was defined once intraoperative POCT-BG showed <60 mg/dL.

GV is defined as fluctuation in blood glucose level.[10] Standard deviation (SD) is a measure of GV. SD is an appropriate measure in case of normal-to-high BG values.[12] Perioperative SD in this study was calculated from a formula of standard deviation using POCT-BG at pre-induction, 1st, 2nd, 3rd, 4th hour and 1st postoperative day. SD>30 mg/dL indicated a significant high GV due to the association with higher morbidity than normal GV.[13]

Bias

Selection of patients who exhibited high normal values of FBS or RBS might tentatively be diabetes. Measurement bias might occurred in GV since all GV measuremets derive from calculations based on specific formula.

Study size

Based on Frisch A' study[4], the incidence of perioperative hyperglycemia in non-DM undergoing non-cardiac surgery was 30-40%. The incidence of 35% of population was used for sample size calculation. The incidence of perioperative hyperglycemia in non-DM for less invasive surgery in current practice is assumed to be lower. The incidence of hyperglycemia in the study group was assumed to be 20-25%. The incidence of 22% was used for calculation. The calculated sample size was 97.

Statistical analysis

All data were analysed using the SPSS software. Demographic data, underlying diseases and types of operation were recorded. Baseline data were expressed as numbers, percentage, mean, and 95% confidence interval.

The outcome data (BG and SD) were expressed using the mean and 95% confidence interval according to time periods. Events of hyperglycemia (>180 mg/dL), hypoglycemia (<60 mg/dL) and BG control were demonstrated by percentage. Mantel-Haenszel odds ratio (OR) was applied for univariate factors (age, operation time, type of surgery, surgical approach and type of anesthesia). Adjusted odds ratio was later analyzed for significant univariate factors. A probability value (p-value) less than 0.05 was considered statistically significant.

Results

Initial recruitment consisted of 444 adult non-DM patients scheduled for intraabdominal surgery. Exclusion criteria were: 1) less-than-2-hour predicted duration of operation (n=229), 2) planned sole regional anesthesia (n=88), 3) history of CVA (n=1), 4) participation refusal (n=3), and 5) after-study exclusion (incomplete data record and the less-than-2-hour exact operation time, n=3). Finally, a total of 120 patients was retained for analysis. Flow of patient recruitment is depicted in Figure 1.

Demographic data and types of operation are shown in Table 1. Types of operation were gynecological, urological, solid organ, and hollow viscus organ surgeries. Hollow viscus organ is defined as operating on either esophagus, stomach, intestine or colorectum. Solid organ surgery is defined as operating on either pancreas, hepatobiliary organ or adrenal gland. Regarding surgical techniques, they are open (98/120, 81.67%) and laparoscopic surgery (22/120, 18.33%). Combined CEA with GA was the most common anesthetic technique (67.5%).

Six patients (5%) who exhibited hypoglycemia (BG <60 mg/dL) since pre-induction period had hypoglycemic event decreased after starting the operation. No episode of hypoglycemia was found after the second hour of operation. Also, no episode of hypoglycemia occurred in patients who received RI (Table 2).

In this study, Hyperglycemia (8.3%) mostly occurred in the 3rd operative hour. 18 out of 120 patients (15%) experienced episodes of hyperglycemia, but only 15 (12.5%) received RI for BG control. Hyperglycemia occurred in patients who received BG control approximately 25-50% and in patients who had no BG control about 2-3%. Variation of BG from the beginning of operation to the first postoperative day was depicted in Table 2. BG controls were 3/15 (20%) of tight control with RI infusion and 12/15 (80%) of non-tight control with RI bolus.

Perioperative mean SD of total patients was 29.25 mg/dL. A high value of mean SD (47.04 mg/dL) occurred in patients who received BG control. There were 53/120 (44.1%) patients who had SD >30 mg/dL. Univariate analysis for odds ratio of high GV are presented in Table 3. Solid organ surgery was a significant risk factor in high GV. OR of solid organ surgery was adjusted with age, duration of operation, CEA-GA and laparoscopic surgery. The adjusted OR was 2.24, 2.25, 2.40, and 2.31, respectively. Odds ratios of urological (OR=0.70) and hollow viscus organ surgery (OR=0.51) along with CEA-GA (OR=0.88) were <1.0 but not statistically significant.

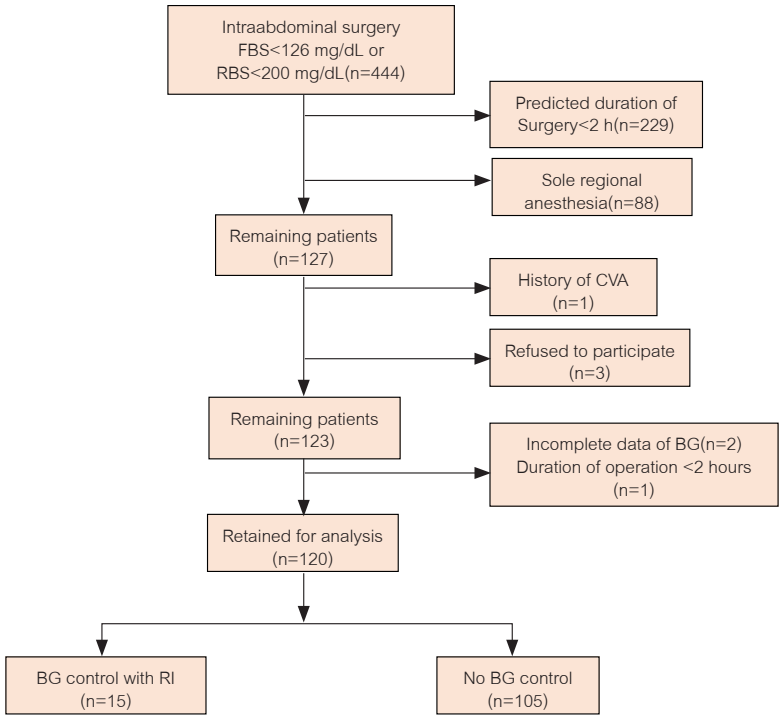

Figure 1 Flow chart of patient recruitment

Table 1 Demographic data, type of surgery and anesthetic technique.

Baseline data	Total (n=120)	No BG control (n=105)	BG control (n=15)
Age (Year)*	59.37 [56.9-61.9] (21,102)	58.55 [55.5-61.6] (21,102)	61.83 [54.2-69.4] (43,84)
Male gender; n (%)	59 (49.1%)	51 (48.6%)	8 (53.3%)
Fasting blood sugar (mg/dL)*	93.64 [91.5-96.6] (47, 123)	92.90 [91.0-94.8] (47, 122)	99.10 [92.8-105.1] (85, 123)
BMI (kg/m^2)*	23.20 [22.4-24.1] (15.2,45.3)	23.31 [22.5-24.9] (15.2,42.2)	24.46 [20.5-28.8] (18.1,45.3)
Hypertension; n (%)	51 (42.5%)	43 (40.9%)	8 (53.3%)
Renal insufficiency (Cr>1 mg/dL); n (%)	12 (10.0%)	10 (9.5%)	2 (13.3%)
Duration of operation (min)	370.18 [340.3-420.1] (120,1020)	370.72 [335.3-406.1] (120,1020)	365.81 [268.1-463.5] (217,760)
Anesthesia: CEA-GA; n (%)	81 (67.50%)	71 (67.6%)	10 (66.7%)
Gynecological surgery; n (%)	4 (3.33%)	4 (3.8%)	0 (0%)
Solid organ surgery; n (%)	44 (36.57%)	35 (33.3%)	9 (60.0%)
Hollow viscus organ surgery; n (%)	61 (50.83%)	57 (54.3%)	4 (26.7%)
Urology surgery; n (%)	11 (9.17%)	9 (8.6%)	2 (13.3%)

*Values are mean, [95% confidence interval], and (min, max). Cr = Creatinine.

Table 2 BG by time period, events of hyperglycemia/hypoglycemia and perioperative SD.

Events	Total (n=120)	No BG control (n=105)	BG control (n=15)
Hypoglycemia (<60 mg/dL)			
Pre-induction (n,%)	6 (5%)	6 (5.7%)	0
At 1st hour (n,%)	2 (1.7%)	2 (1.9%)	0
At 2nd hour (n,%)	1 (0.8%)	1 (0.9%)	0
Hyperglycemia (>180 mg/dL)			
At 2nd hour (n,%)	8 (6.7%)	3 (2.9%)	5 (33.3%)
At 3rd hour (n,%)	10 (8.3%)	2 (1.9%)	8 (53.3%)
At 4th hour (n,%)	8 (6.7%)	2 (1.9%)	6 (40%)
At postoperative 1st day	7 (5.8%)	3 (2.9%)	4 (25%)
Blood glucose*			
At 1st hour	112.61 [101.1-122.6] (51, 183)	107.20 [102.0-112.1] (51, 180)	130.21 [114.1-146.2] (73, 183)
At 2nd hour	124.68 [112.6-137.4] (59, 267)	124.05 [119.1-129.0] (59, 200)	162.53 [139.2-187.5] (84, 267)
At 3rd hour	135.84 [124.6-150.5] (65, 288)	128.39 [123.1-124.0] (65, 192)	173.80 [147.8-199.7] (105, 288)
At 4th hour	137.48 [122.1-149.6] (65, 234)	129.98 [124.7-135.1] (65,192)	174.57 [153.9-196.6] (74, 234)
Postoperative blood glucose*			
At 1st day	133.39 [123.5-144.2] (67, 197)	136.30 [130.9-142.3] (86, 206)	155.60 [130.9-179.9] (67, 217)
Glycemic variability*			
Perioperative SD (mg/dL)	29.25 [27.5-31.5] (8.8, 69.1)	26.71 [24.6-28.2] (8.8, 62.2)	47.04 [40.7-53.4] (29.9, 69.1)

*Values are mean, [95%confidence interval] and (min, max).

Table 3 Odds ratios of SD>30 mg/dL.

	Odd ratio	95% CI
Age>65 Y	1.23	0.58-2.61
Operation time>240 min	1.16	0.51-2.61
Gynecological surgery	1.27	0.17-1.26
Urological surgery	0.70	0.19-2.53
Solid organ surgery	2.25*	1.05-4.81
Hollow viscus organ surgery	0.51	0.24-1.06
Laparoscopic surgery	1.67	0.61-4.53
CEA-GA	0.88	0.41-1.9

*= p-value <0.05

Discussion

For the case of non-DM patients, surgical-induced hyperglycemia can occur. The present study also demonstrated intraoperative hyperglycemia in non-DM patients undergoing intraabdominal surgery. The incidence of hyperglycemia in this study was 15%, which was lower than previous reports.[3,7,14] The explanation might be less-invasive surgical technique in current practice. However, it should be noted that increases in intraoperative BG was severe. We found the highest BG of 288 mg/dL occurring in the 3rd hour in operation. Furthermore, hyperglycemia existed until postoperative period. Therefore, BG monitoring should be routinely performed in spite of no history of diabetes.

Methods of intraoperative BG control are tight and non-tight control. For cardiac surgery, tight control with RI infusion has been recommended.[15] However, in case of non-DM, risk-benefit of tight control with RI infusion remains questionable. Additionally, BG monitoring is mandatory to be more frequent in case of tight control with RI infusion. Based on our findings, BG control with RI bolus (80%) was preferred by anesthesiologists. The results also show that 25-50% of patients who received BG control remained hyperglycemia and 2-3% of patients who did not received BG control also experienced hyperglycemia. These findings implied that BG control in case of non-DM was tentatively ineffective.

Regarding the 3 out of 18 patients who had hyperglycemia but did not receive any methods of BG control, possible explanations as to why they did not are offered as follow. First, the treatment was deemed unnecessary by anesthesiologists because their BG level was less than 200 mg/dL, which is acceptable in non-DM patients. Second, awareness or fear of hypoglycemia in non-diabetes is a more pressing concern. Since our results did not show any occurrences of hypoglycemic episodes after treatment with RI, such awareness or fear should not be heightened as the overriding concern in order to strike a balance in how patients are monitored.

Of note, 5% of hypoglycemia was mostly found before induction of anesthesia. The lowest BG was 51 mg/dL and the patient's BG remained low untill the 2nd hour of operation. An explanation might be nothing per oral after midnight. Moreover, dextrose-free intravascular fluid is normally used as the first priority because it is believed that BG would increase after skin incision. Since hypoglycemia can lead to CVA and death, routine BG monitoring before induction of anesthesia should be mandatory in non-diabetes.

GV is an index that is highly associated with microvascular complications. In other words, GV is a better indicator of complications than hyperglycemia.[12] SD is the simple standard measure of GV.[16,17] SD>30 mg/dL was revealed to be a morbid risk in diabetes.[13] A prior study indicated that a high GV caused more severity of cardiac complications in non-diabetes than diabetes.[18] Our study demonstrates perioperative SD being as high as 69.1 mg/dL in non-diabetes. Therefore, high BG in non-diabetes undergoing non-cardiac surgery should be intensely controlled.

We assumed that types of operation might be associated with an increase in the level of fluctuation of GV. Solid organs, such as hepatobiliary organs, pancreas and adrenal gland, are related to glucose metabolic derangement.[19-21] According to our study, intraabdominal solid organ surgery was found to be a significant risk (adjusted OR=2.23-2.40). Thus, it is recommended that close monitoring of BG as well as intensive BG control in intraabdominal solid organ surgery should be considered.

It is our intention to include surgeries that can use general anesthesia as a sole anesthetic technique since general anesthesia did not directly suppress sympathetic activation at adrenal gland. Theoretically speaking, CEA might be better at preventing stress-induced hyperglycemia than sole GA. Combined CEA-GA was used up to 67.5% in this study resulting in OR of this to be <1, which means CEA might prevent an increase in the level of fluctuation of GV. However, this finding is not statistically significant. In other words, CEA is not beneficial for the reduction of glycemic variation in non-DM.

This study was a preliminary study. It is noteworthy that our study specifically targeted surgery of extended duration to reveal intraoperative glycemic condition in non-DM because extended duration (>2 h) of surgery cause intense inflammation that might be related to significant BG changes. Moreover, it seems to be unreasonable to perform POCT-BG in patients undergoing a short duration of surgery without indications (such as DM and receiving BG control).

Another important finding of this study is that glycemic variability was not related to the size of skin incision. An intraabdominal surgery was the focus of our study since it was such a common type of surgery in practice. Moreover, it is observed in our study that laparoscopic surgery, which is assumed to be less-invasive surgery, tentatively leads to more glycemic fluctuation than open laparotomy. Finally, this study also demonstrated occurrences of hyperglycemia of 15%, but high GV of 44%. It can be speculated that hyperglycemia was partially associated with high GV.

Study limitations include: 1) no examination of HbA1c so that it might cause selection bias, 2) too small events of hyperglycemia to unsuitably identify risks of hyperglycemia, 3) too small events of both hypoglycemia and hyperglycemia to unsuitably analyze their risks to high GV, 4) different modes of BG control and small group of patients who received BG control causing some outcome bias, and 5) due to the fact that sole regional anesthesia could be used as a sole technique in most of gynecological surgeries, which limits the generalization of the results.

Conclusion

Incidence of hyperglycemia was 15% in non-DM patients undergoing intraabdominal surgery. Hyperglycemia occurred from the 2nd operative hour to, mostly, 3rd operative hour. 44% of patients had high GV. Solid organ surgery was a significant risk factor of high GV (OR = 2.25).

Conflicts of interest

The authors certify that there are no conflicts of interests. All financial supports were from Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University.

All authors certify that all parts of the present research work has been corporately processed by the authors without copying any part from elsewhere.

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