Impact of opoid free anesthesia on glycemia: a randomized controlled trial

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Abstract

Background: **General anesthesia induces frequently hyperglycemia. This is associated with an increased risk of morbidity and mortality in patients undergoing surgery. The type of anesthesia used may affect the severity of the peri-operative hyperglycemia.**
Methods: **Patients undergoing an elective primary laparoscopic bariatric surgery at AZ Sint-Jan Brugge between February 2022 and March 2022 were randomized between opioid-free anesthesia (OFA) and opioid anesthesia (OA) after ethical approval. Any patient with diabetes type 1, diabetes type 2, having glucose intolerance at the time of surgery, or during pregnancy were excluded from the study. Dexmedetomidine, lidocaine, ketamine, and magnesium were used for the OFA, while sufentanil was given in the OA. No intravenously steroids were administered to protect the peritoneum nor as antiemetic prophylaxis. The increase in blood glucose level at 180' was assessed as the primary outcome. A first measurement was taken just before the anesthesia induction (T0), followed by a measurement every hour (T60', T120', and T180'). As secondary endpoints, the total dose of opioids given in the first 24 hours and the postoperative pain using the VAS (visual analog scale) score were measured. Additionally, postoperative nausea and vomiting (PONV), duration of surgery, and surgical and/or anesthetic complications were recorded.**
Results: **A total of 43 patients underwent an elective primary laparoscopic bariatric surgery. 22 patients received OFA and 20 patients received OA and were analyzed. One patient from the OA group withdrew written consent. 2 patients from the OFA group were lost to follow up having therefore 19 in the OA and 20 in the OFA for analysis. There were no significant differences between the two groups regarding age, BMI, gender, duration of surgery, and pre-induction glycemia. The glycemia level increased in both groups but increased significantly higher in the OA group at 180 minutes (Mann-Whitney test p = 0.027). OFA was associated with lower VAS scores postoperative (OFA: 3(2-4) vs OA: 4(4-5,5)) and a reduced need for postoperative opioids (OFA: 4.9(2,4-7,2) mg versus OA: 10,4(8,4-12,7) mg).**
Conclusion: **This research suggest that the use of opioid-free anesthesia causes a smaller increase in glycemia during elective laparoscopic bariatric surgery compared to opioid anesthesia. Furthermore, patients undergoing OFA showed higher levels of postoperative comfort, demonstrated through the lower postoperative VAS scores and the reduced need for postoperative opioids.**

Keywords: **Opioid-free anesthesia, Laparoscopic bariatric surgery, Surgical stress, Hyperglycemia, VAS score, postoperative nausea and vomiting.**

Ethics Committee approval and informed consent: Ethics approval was granted on February 10, 2022 by the Ethics Committee of AZ St. Jan Brugge Oostende AV (Ruddershove 10, 8000 Bruges). The chair of this committee is dr. L. Vanopdenbosch. The study registration number is B0492021000033 and its reference is 2958. A written informed consent was obtained from all subjects. Inclusion of patients started on 15/02/2022 and ended on 31/03/2022.

Introduction

Hyperglycemia associated with surgery under general anesthesia is probably caused by surgical stress[1]. Hyperglycemia is associated with an increased risk for surgical morbidity and mortality in patients undergoing major surgery[2].The type of anesthesia may affect the severity of the perioperative hyperglycemia[1]. The primary goal of this study is to measure the impact of two types of anesthesia, opioid anesthesia (OA) and opioid-free anesthesia (OFA), on the increase of the peri-operative glycemia in patients undergoing elective primary laparoscopic bariatric surgery. The secondary goal is to compare the postoperative pain and postoperative nausea and vomiting (PONV) in both groups and look for a possible association with hyperglycemia.

Opioid Anesthesia

Opioids are still one of the major drug classes used for general anesthesia. Opioids being the strongest analgesics available, are essential in the treatment of pain during the peri-operative period. Additionally, they provide balanced anesthesia with less hemodynamic instability[3]. Despite the effectiveness of these drugs, they are associated with numerous side effects with varying severity: respiratory depression; a short moment of muscular stiffness and weak pharyngeal musculature (hence obstructive breathing problems); somnolence; dizziness; nausea and vomiting; constipation; itching and; urinary retention. Other side effects of opioid use are hyperalgesia and opioid tolerance[4]. Complete suppression of hormonal and metabolic stress responses by opioids cannot be guaranteed suggesting a reason for hyperglycemia[5].

Opioid Free Anesthesia

Opioid-free anesthesia is a technique where opioids are avoided in the intraoperative period reducing the opioid requirements in the postoperative period with a reduction in the opioidrelated side effects and a lowering of the post-operative pain scores (Visual Analogue Scale, VAS score)[6,7]. OFA in bariatric surgery is associated with a lower rate of complications, shorter LOS (length of hospital stay), and reduced postoperative opioid use[8,9].

Stress Response – Hyperglycaemia

Surgery evokes a series of hormonal and metabolic changes commonly referred to as the stress response. In general, there is an enhanced secretion of catabolic hormones such as catecholamines, glucocorticoids (cortisol), and pituitary hormones, whereas anabolic hormones, such as insulin and testosterone are suppressed[10-12]. In addition, the failure of the negative feedback mechanism ensures that the concentration of cortisol remains persistently high. This mobilization of energy sources prepares the individual for its new circumstance, valuable when fight or flight is necessary but, dangerous for a weak body[10]. Insulin is an anabolic hormone that is usually secreted in response to hyperglycemia, promoting glucose utilization and glycogen synthesis. The failure of the body to secrete insulin in response to stress is partly caused by the inhibition of the β-cells in the pancreas by the α2-adrenergic inhibitory effects of catecholamines. 'Insulin resistance' by target cells occurs later due to a defect in the insulin receptor and intracellular signaling pathway. Thus, the peri-operative period is characterized by a state of functional insulin deficiency. Furthermore, glucose utilization is impaired, known as an 'anti-insulin effect'[11]. The responses summarized above suggest that surgical stress could cause hyperglycemia[12].

Diabetes

Kotagal et al[13] found that surgical patients without diabetes (NDM) have an increased risk of adverse events linked to hyperglycemia than patients with diabetes (DM). A dose-response relationship was demonstrated. One of the mechanisms to explain this 'diabetes paradox' is that equal levels of hyperglycemia indicate higher levels of surgical stress in NDM patients than in DM patients[13].

The above findings lead us to question, if opioid-free anesthesia could lessen the increase in glycemia during elective laparoscopic bariatric surgery when compared to opioid anesthesia, using sufentanil, in non-diabetic patients.

Methods

This study (BUN B0492021000033 and Int. Nr.: 2958) was approved by the Ethics Committee of AZ Sint-Jan (Ruddershove 10, 8000 Brugge) on 10/02/2022 by Dr. Vanopdenbosch. We calculated the sample size to be 20 patients in each group with a power of 90% and a significance level of 0,05%. A written patient informed consent was received from each participant in this prospective, randomized controlled single-blinded trial. Patients > 18 years of age, who were undergoing an elective primary laparoscopic bariatric Roux & Y surgery were enrolled.

Exclusion criteria for this study included patients with diabetes type 1 or diabetes type 2 (IV or anti-diabetic medication), having glucose intolerance at the time of surgery or during pregnancy, ASA IV patients, patients with an addiction to opioids

or chronic opioid use, patients with allergy or contraindications to any of the drugs included for anesthesia, patients with major cardiovascular, pulmonary, liver or renal insufficiency before surgery, patients planned for postoperative intensive care admission, and patients with a contra-indication for general anesthesia with intubation and mechanical ventilation.

Once patients were enrolled in the study, randomization was performed by closed envelopes handed out by the secretary of Anesthesia using an excel randomization generator. Patients were randomized to one of the two groups. Patients in group 1 (OFA,n 20) received opioid-free anesthesia using dexmedetomidine in a loading dose of 0,25 mcg/kg before incision followed by a continuous infusion of 0,1 mcg/kg/h during surgery; Lidocaine in a loading dose of 1 mg/kg before incision followed by a continuous infusion of 1 mg/kg/h during surgery; Esketamine in a loading dose of 25 mg before incision followed by a continuous infusion of 0,05 mg/kg/h during surgery. All the above adapted up to a 50% increase or decrease at the discretion of the attending anesthesiologist. Furthermore, a loading dose of 2,5 gr Magnesium was given to every OFA patient. Patients in group 2 (OA, n = 19) received opioid anesthesia using Sufentanil in a loading dose of 15- 25 mcg Sufentanil before incision, followed by additional 5-10 mcg Sufentanil at the discretion of the attending anesthesiologist. All doses are calculated on the Janmahasatian's estimation of 'Lean Body Weight' (LBW)[14].

Deep clinical neuromuscular blockade (NMB) with a Post Tetanic Count (PTC) of less than 5 was provided by a rocuronium infusion (0,3 – 0,4 mg/kg/h) in both groups. For induction patients received propofol (1-2,5 mg/kg) followed by sevoflurane that was given as hypnotic maintaining the bispectral index monitor (BIS) level between 40 and 60.

For both groups, the same protocol for postoperative analgesia was used, consisting of paracetamol 2gr loading dose followed by 1gr/6 hours, diclofenac 150 mg loading dose followed by 75mg/12h for the first postoperative day only, and clonidine 75 mcg/12h. Piritramide was used as rescue medication in the post-anesthesia care unit (PACU), and Oxynorm 10mg/4h on the ward. Volume controlled ventilation with a 6ml/kg tidal volume was used to achieve endtidal carbon dioxide of 40-50 mmHg by adjusting respiratory rates first and tidal volume second. Both groups received a Plasmalyte infusion at 100-200ml/h (or 2ml/kg/h). During the perioperative period, no patient received any infusion containing glucose. Neither did they receive any steroid for peritoneal protection nor antiemesis. This was to avoid their known impact on glycemia.

The patient, surgeon, and physicians/nurses following the patient in the PACU and ward were blinded to allocation. The attending anesthesiologist and the nurses (intra-operative) were not blinded.

Pain scores were measured on the PACU every 30 minutes and the maximum value was used for statistics. If the postoperative VAS score of pain was greater than 5 in the PACU, Piritramide 5 mg was given intravenously and repeated after 15 minutes until pain-free. For the VAS score, we used a straight horizontal line where the ends were defined as the extreme limits of pain, orientated from the left (worst) to the right (best).

The following demographic data were retrieved: age, gender, total body weight, height, and ASA classification.

Data Collection

All patients underwent an elective laparoscopic gastric bypass Roux & Y surgery[15].

The blood glucose level (BGL) was measured in both groups using a electronic blood glucose meter (Accu-Chek Inform II), by a single drop of capillary blood, at the time of admission in the operation theater (T0), and at 60, 120, and 180 minutes after induction of anesthesia (T60',T120', T180').

The following data were also recorded: the maximum visual analog scale (VAS); the total dosage of opioids used postoperatively; the existence of PONV in the PACU; and the duration of surgery.

Opioid usage was converted to total iv morphine equivalents as follows: 1 mg IV morphine = 1 mg IV or subcutaneous piritramide; 10 mg IV tramadol or; 2 mg sublingual oxycodone[16].

Statistical Analysis

Patient groups were demographically compared for age, gender, BMI, ASA and referenceglycemia (Mann-Whitney, two unpaired groups with a continuous, score or binomial outcome) with $p > 0,05$. (see Table I) Patient groups were compared for the increase in glycemia at T180' (being the primary endpoint), for the maximum VAS score on the PACU, the total dose of opioids given postoperative on the PACU, incidence of PONV, and duration of surgery. These clinical outcome parameters are expressed median and interquartile range, and were either analyzed using the Mann-Whitney test or expressed as numbers and analyzed using the ChiSquare test. The correlation between change in glycemia and duration of surgery, VAS

score, and PONV is analyzed. Statistics were performed using the statistical package Wizard ver 1.9.49 created by Miller.

Results

Patient characteristics

A total of 43 patients underwent an elective primary laparoscopic bariatric surgery at AZ Sint Jan Brugge from February 2022 to March 2022. One patient from the OA group did not get the study intervention and one withdrew written consent and two patients from the OFA group were lost to follow-up (see flow diagram) Demographic and clinical characteristics of the OFA (n = 20) and OA (n = 19) groups analyzed are shown in Table I. No significant difference between both groups was found.

Clinical Outcomes

The clinical outcomes of both groups are shown in Table II. The glycemia levels of both groups are shown in boxplots in figures 1 and 2. The increase in glycemia at 180 minutes, being the primary endpoint, was significantly higher in the OA group (Mann-Whitney test p=0,027).

The maximum VAS score on the PACU was lower in the OFA group (3(2-4)) compared to the

OA group (4(4-5,5)) while the amount of postoperative opioids used was lower in the OFA (OA: 10,4(8,4-12,7) mg versus OFA: 4.9(2,4-7,2) mg). There were no significant differences between both groups for surgery duration and the incidence of postoperative nausea and vomiting. No major complications were noted during hospitalization.

No correlation was found with the following outcomes: total opioid consumption (Kolmogorov – Smirnov 0,96), surgery duration (Kolmogorov – Smirnov 0,93), and maximum VAS score on the PACU (Kolmogorov – Smirnov 0.99).

Discussion

The glycemia did change in both groups, presumably due to surgical stress. The OFA group had a significantly lower increase in glycemia, supporting our hypothesis of a possible better suppression of the metabolic stress. Opioid consumption was, as shown already in other OFA studies, lower for an even lower VAS score, emphasizing the value of OFA[6]. Though PONV was frequently lower in OFA, it was not statistically significant as the patient groups were too small, and no PONV gradation was recorded. No other measured factors besides OFA could be associated with the glycemia rise suggesting a better surgical stress suppression.

Surgical stress can result in decreased insulin sensitivity and subsequent hyperglycemia. This relationship is relative to the magnitude of the surgical procedure[1]. Previous studies indicate that peri-operative hyperglycemia is associated with an increased risk of morbidity and mortality. Studies

Table I. — Patient characteristics .

Characteristic	OA	OFA	P-value
Age (years)*	34 (22-45)	37 (27-52)	0.443[a]
Gender (n)	6	8	0.584[b]
Pre-operative glycemia (mg/dl)*	91 (77-98.5)	93 (86-100)	0.411[a]
BMI (kg/m^2)*	39 (37-41)	38 (35-41)	0.603[a]
ASA physical status class*	2 (2-3)	2 (2-3)	0.648[b]

[a]Mann-Whitney; [b]Chi-Square Test; OA, opioid anaesthesia; OFA, opioid-free anaesthesia; PONV, postoperative nausea and vomiting; VAS, visual analogue scale. *Median (Interquartile range).

Table II. — Clinical Outcomes.

Outcome	OA	OFA	P-value
Change in glycemia at 180 min(mg/dl)*	54,9 (37.5-70)	38.5 (31.8-46.3)	**0.027**[a]
Maximum postoperative VAS*	4 (4-5.5)	3 (2-4)	**< 0.001**[a]
Duration of surgery (min)*	97 (90-104.5)	98.5 (87-103)	0.86[a]
PONV (n)	9	5	0.179[b]
Total morfine equivalents postoperatively (mg)*	10.4 (8.4-12.7)	4.9 (2.4-7.2)	**0.001**[a]
Intraoperative Sufentanil (OA) (mcg)*	25.3 (22.9-27.8)	0	-
Dexmedetomidine (OFA) (mcg)*	0	53.1 (47.9-58.3)	-

Statistically significant P-values are indicated in bold.
[a]Mann-Whitney; [b]Chi-Square Test; OA, opioid anaesthesia; OFA, opioid-free anaesthesia; PONV, postoperative nausea and vomiting; VAS, visual analogue scale. *Median (Interquartile range).

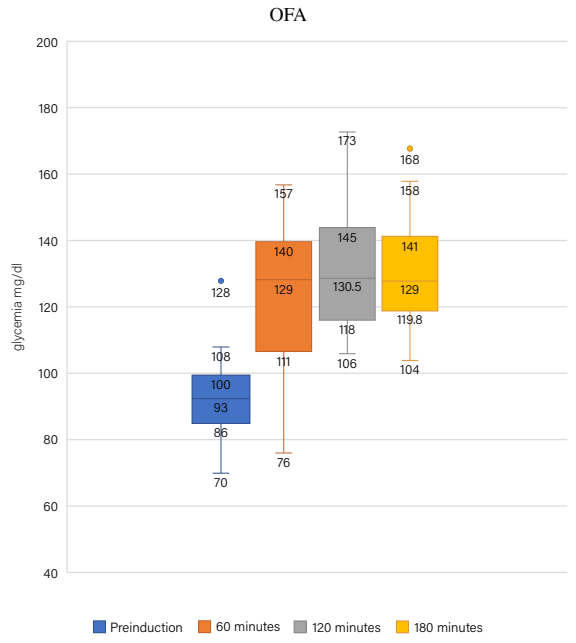

Fig. 1 — OFA
Time-related blood glucose concentrations in the OFA group.

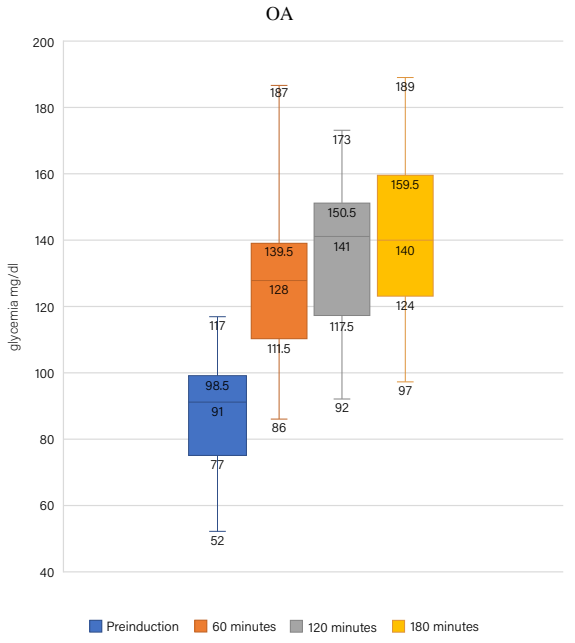

Fig. 2 — OA
Time-related blood glucose concentrations in the OFA group.

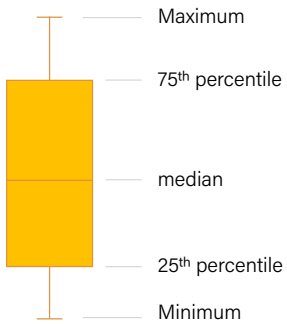

Fig. 3 — Legend of the boxplot.

that investigated outcomes of hyperglycemia concluded that non-diabetic patients were at greater risk for poorer outcomes than diabetic patients[15,16]. The fact that patients without a history of diabetes experience poorer outcomes and higher mortality when they have the same glucose level as that of patients with a known history of diabetes, suggests a lack of adaptation to acute hyperglycemia or a stronger stress reaction[17]. Surgical stress can be measured by many other parameters; we have taken only hyperglycemia into account. Moreover, hyperglycemia can have many other confounders independent of surgical stress. An attempt to minimize these is made by limiting NPO orders to 6 hours before surgery and prohibiting carbohydrate liquids to 2 hours before surgery.

Despite the limited sample size, this randomized controlled trial has shown a sufficient difference in the primary investigative subject, the lower rate of glycemic increase in the OFA group. The difference in glycemia between both groups might not be clinically relevant, and the hyperglycemia level reached may still be acceptable, therefore, not always requiring insulin therapy; however, it is a sign of better metabolic stress suppression.

We did not plan to treat hyperglycemia with insulin, as following the glycemia in nondiabetic patients is not a routine procedure. The maximum glycemia levels in both groups were 189 mg/dl (OA) vs 173mg/dl (OFA), making further discussion of this point necessary.

We did not investigate any patients with diabetes and therefore cannot expand this result to this group at this time.

The study of Tuduri 2016, showed for the first time a new role of the central opioid system, specifically the mu opioid receptors (MOR), in the regulation of insulin secretion and glucose metabolism[18]. The study has indicated that opioid anesthetics exacerbate hyperglycemia by reducing insulin sensitivity and increasing the expression of gluconeogenic genes in the liver which could lead to a direct hyperglycemia effect[18]. This randomized controlled trial had larger variability and more extreme values in the OA group. It might have been interesting to analyze glycemia levels over a longer period, even up to the first 24 hours postoperative. It might have been interesting to follow the glycemia levels until normalization in both groups. Therefore this study can be seen as a pilot study in analyzing the metabolic effects of OA versus OFA anesthesia.

We did not measure other stress-related laboratory parameters to avoid taking extra blood samples. And we have to take into account that the measured blood glucose level may be disturbed by less accurate measurement.

Not only is it a single-institution study, there is also only one type of surgery observed. Major

abdominal and thoracic surgery taking longer than 3 hours could have induced more metabolic stress, and a higher glycemia level and might have shown a larger difference between OA and OFA.

It is more common for patients undergoing elective laparoscopic bariatric surgery to have prediabetes than other patient groups, but BMI and gender were comparable between both groups[19]. The objective of this research was to evaluate the benefit of opioid-free anesthesia (OFA) on the stress response (and more particularly, the blood glucose level) associated with surgery.

Additionally, the incidence of PONV and the amount of postoperative pain using the VAS score were measured. The purpose of giving anesthesia is to bring the patient into an unconscious state and avoid experiencing and remembering the surgical trauma. But more importantly, anesthesia should suppress the sympathetic and metabolic reactions of the body better known as surgical stress. Due to shorter-acting opioids, the anesthesiologist can safely increase the opioid dose intraoperative, thereby, attempting to reduce the body's reaction to surgical stress. However H. Kehlet stated there is no such thing as 'stress-free anesthesia', no technique is capable of effectively suppressing all aspects of the surgery response even with very high opioid doses or locoregional anesthesia[11]. Mulier et al[6] have shown that OFA can efficiently suppress the sympathetic system with even lower cortisol levels compared to opioid anesthesia and requires less post-operative opioid analgesics. Until now there is limited evidence of metabolic stress being insufficiently blocked by opioid anesthesia.

OFA may more effectively lower peri-operative stress but can induce more hypotension, bradycardia, prolonged sedation, or other side effects. OFA is based on the concept of multimodal anesthesia and multimodal analgesia. However, a combination of drugs of different classes, such as dexmedetomidine, lidocaine, clonidine, ketamine, magnesium, and if possible combined with locoregional anesthesia, reduces the need for opioids.

This multimodal approach reduces the dose of each component, decreases its side effects, and avoids long working sedation[20].

Mulier et al[8] suggest that OFA in bariatric surgery gives equal hemodynamic stability intraoperatively in comparison with OA if the dose of dexmedetomidine is kept below maximum 1 mcg/kg LBW during the entire procedure or adapted to each patient using a stress monitor. Looking at the exclusion criteria, it might have been better to use the glycated hemoglobin test to exclude patients with glucose intolerance. On the other hand, another limitation of this study could be the exclusion of any patient with diabetes type 1, diabetes type 2, or having glucose intolerance at the time of surgery, or during pregnancy. Therefore, no information can be extracted from this study regarding the influence of OFA on diabetic patients undergoing bariatric surgery.

Conclusion and further research

In summary, the peri-operative blood glucose levels were increased in both groups (OA and OFA) but increased significantly higher in the OA group. Patients in the OA group had a higher maximum VAS score in the PACU than patients in the OFA group, while the amount of postoperative opioids used was lower in the OFA. No correlation was found between change in total opioid consumption, glycemia, surgical duration, and maximum VAS score in the PACU. Our results underscore the need for further research in larger patient groups which should include diabetic patients. The next step should correlate lower glycemia levels with better outcomes.

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