CLINICS

CLINICAL SCIENCE

General anesthesia type does not influence serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in video laparoscopic bariatric surgery

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OBJECTIVES: Video laparoscopic bariatric surgery is the preferred surgical technique for treating morbid obesity. However, pneumoperitoneum can pose risks to the kidneys by causing a decrease in renal blood flow. Furthermore, as in other surgical procedures, laparoscopic bariatric surgery triggers an acute inflammatory response. Neutrophil gelatinase-associated lipocalin is an early and accurate biomarker of renal injury, as well as of the inflammatory response. Anesthetic drugs could offer some protection for the kidneys and could attenuate the acute inflammatory response from surgical trauma. The objective of this study was to compare the effects of two types of anesthetics, propofol and sevoflurane, on the serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in laparoscopic bariatric surgery.

METHODS: Sixty-four patients scheduled for laparoscopic bariatric surgery were randomized into two anesthesia groups and were administered either total intravenous anesthesia (propofol) or inhalation anesthesia (sevoflurane). In the perioperative period, blood samples were collected at three time points (before anesthesia, 6 hours after pneumoperitoneum and 24 hours after pneumoperitoneum) and urine output was measured for 24 hours. Acute kidney injuries were evaluated by examining both the clinical and laboratory parameters during the postoperative period. The differences between the groups were compared using non-parametric tests. ReBEC (http://www.ensaiosclinicos.gov.br/rg/recruiting/): RBR-8wt2fy

RESULTS: None of the patients developed an acute kidney injury during the study and no significant differences were found between the serum neutrophil gelatinase-associated lipocalin levels of the groups during the perioperative period.

CONCLUSION: The choice of anesthetic drug, either propofol or sevoflurane, did not affect the serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in laparoscopic bariatric surgery.

KEYWORDS: Morbid Obesity; NGAL; Bariatric Surgery; Acute Kidney Injury; Anesthesia.

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INTRODUCTION

The worldwide rates of surgical procedures for weight control have been increasing to address the recent obesity epidemic (1). Currently, video laparoscopic bariatric surgery (VLBS) is considered the best surgical technique for morbidly obese individuals who have health complications associated with excess body fat (2). Despite the proven benefits of VLBS, these procedures, like any other surgery, can produce a pattern of systemic inflammatory responses. VLBS also carries an inherent risk of pneumoperitoneum to the kidneys due to elevated intra-abdominal pressure, which reduces cortical capillary blood flow by increasing renal vascular resistance. Consequently, the glomerular filtration rate (GFR) is decreased and transient oliguria occurs (3). Rhabdomyolysis, which is also associated with bariatric surgery, is another cause of kidney injury, but it appears to be less problematic in VLBS than in open surgery (4). Acute kidney failure, which presents as a major elevation in creatinine levels with oliguria, is not a common

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complication of VLBS when proper preventive measures are followed during the perioperative period (4). However, traditional laboratory markers, such as urea and creatinine, are not sufficiently sensitive to detect subclinical acute kidney injuries in this population (5).

Neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa glycoprotein in the lipocalin family (6) is produced by the epithelia of the kidneys, lungs, colon, liver, adipose tissue and inflammatory cells. The most well-known functions of NGAL are iron transport (7), apoptosis regulation (8), infection control (9), structural development (10) and renal recuperation (11). Clinical interest in NGAL is related to the sensitivity and speed with which it is elevated in the serum and urine after acute tubular injury, enabling the diagnosis of renal damage within 2 hours of the injurious event. In comparison, the elevation of other traditional markers, such as creatinine, can be delayed by up to 48 hours after an acute kidney injury (5). Various other causes of organ stress are also associated with NGAL elevation, which can be mediated by pro-inflammatory cytokines (12) and is considered a marker of a systemic inflammatory response (13).

General anesthesia, commonly used in procedures such as VLBS, can have protective effects on the renal system during the intraoperative period. Though different mechanisms, both propofol (14) and sevoflurane (15) have appeared to reduce renal injury in clinical-surgical and experimental injury models. Various markers are measured serially to monitor kidney injury during the perioperative period, but many of these markers are delayed, or they have sensitivity limitations. The purpose of the present study was to compare the effects of two anesthetics, propofol (TIVA) and sevoflurane (SEVO), on serum NGAL levels over a 24-hour perioperative period in obese patients undergoing VLBS.

METHODS

This study was approved by the Committee of Research Ethics of the São Rafael Hospital (HSR) in Salvador, Bahia, Brazil, in accordance with the national standards of ethics on human experimentation, as well as the Helsinki Declaration of 1975 and it was also registered at ReBEC (http://www.ensaiosclinicos.gov.br/rg/recruiting/): RBR-8wt2fy. Informed consent was obtained from 64 morbidly obese patients who were scheduled to undergo VLBS between October 2010 and July 2011. The surgical indications followed the current recommendations of the Brazilian Society of Metabolic and Bariatric Surgery (individuals who are incapable of losing weight with recognized clinical treatments and have either a body mass index (BMI)>40 kg/m^2 or>35 kg/m^2 with obesity-related illnesses). The following medical conditions were considered the exclusion criteria for the study: chronic obstructive pulmonary disease, congestive heart failure, cancer, chronic steroid use and a GFR <60 mL/min (as estimated by the Cockcroft-Gault equation (16) using lean body weight for the calculation (17)). The gastric bypass technique was used in all of the patients. Two teams of surgeons performed the procedures.

The patients were randomly placed into either the TIVA or SEVO group. Both groups received 5 mg of midazolam as premedication.

Induction of general anesthesia was accomplished with propofol plus fentanyl in both groups; the SEVO group received a propofol dose of 1 mg/kg (real body weight) and the TIVA group received a propofol dose calculated by a target controlled infusion pump. Fentanyl (5 mcg/kg; ideal body weight) was used in both groups.

Maintenance of general anesthesia was assured using a combination of sevoflurane plus remifentanil in the SEVO group or of propofol plus remifentanil in the TIVA group. For the SEVO group, sevoflurane was administered throughout the surgery at a dose of between 1.4% and 3% of the expiratory gas concentration. For the TIVA group, the target controlled propofol infusion was at an estimated 3 to 5 mcg/mL blood concentration. Both groups received a continuous, target-controlled remifentanil infusion (at an estimated 3 to 6 ng/mL blood concentration, according to clinical necessity).

Morphine (100 mcg/kg of ideal body weight), dipyrone (2000 mg) and ondansetron (8 mg) were administered intravenously 30 minutes before the expected termination of surgery for postoperative analgesia and nausea prevention (both groups).

Neuromuscular blocking agents were the same in both groups and a succinylcholine dose of 1 mg/kg (ideal body weight) was used to induce patients with expected difficult airways. Also, cisatracurium was employed during the procedure.

Perioperative hydration was provided identically to both groups. A 0.9% NaCl solution was administered as an infusion of 18 mL/kg (ideal body weight) for the first hour, 14 mL/kg (ideal body weight) for the second and third hours and 10 mL/kg (ideal body weight) for subsequent hours. Blood samples for measuring creatinine and NGAL were collected at three time points: M0, immediately before anesthesia induction; M1, 6 hours after pneumoperitoneum was established; and M2, 24 hours after pneumoperitoneum. Creatinine was measured by an automated chromatographic technique immediately after the blood sample was collected. NGAL was measured by the enzyme-linked immunosorbent assay (ELISA) technique (NGAL rapid ELISA kit; BioPorto, Gentofte, Denmark), which was retrospectively conducted on serum stored at -80℃. The patients underwent bladder catheterization after anesthesia was induced to measure 24 hours of urine output. The GFR at the M1 and M2 time points was calculated by the Cockcroft-Gault equation, using lean body weight (17). Blood pressure levels were measured every five minutes via a non-invasive method (oscillometry) and the average mean arterial pressure was calculated at the following time points relative to surgery: before anesthesia induction, after tracheal intubation, during pneumoperitoneum, after pneumoperitoneum deflation and after tracheal extubation. The intra-abdominal pressure during pneumoperitoneum was limited to 14 cm H_2O in all of the patients. Capillary blood glucose was monitored (*Accu-Chek*, Roche Diagnostics GmbH Sandhofer Strasse 116 D-68305 Mannheim, Germany) before anesthesia induction and then every hour during surgery.

Statistical analysis

The sample size was calculated using estimates in the literature regarding the mean and standard deviation for NGAL levels in obese patients. To achieve power of 80% with a 5% significance level and a difference of 33% in mean NGAL serum levels, the sample size was estimated as 30 patients per

Table 1 - Demographic data according to the anesthesia type (32 patients in each group).

VARIABLE	TOTAL INTRAVENOUS ANESTHESIA	SEVOFLURANE ANESTHESIA	*p*-VALUE
Age (years) [a c]	34 (28/45)	33 (28/39)	0.371
Weight (kg) [a c]	105 (94/125)	104 (97/120)	0.995
Body mass index (kg/m^2) [a c]	40 (38/42)	38 (37/43)	0.528
Sex (male) [b d]	7 (22%)	9 (28%)	0.774
Systemic arterial hypertension [b d]	17 (53%)	16 (50%)	0.802
Diabetes mellitus [b d]	14 (43%)	11 (34%)	0.442
GFR baseline (mL/min) [a c]	97 (81/119)	103 (82/108)	0.601
Duration of pneumoperitoneum (min) [a c]	135 (115/149)	130 (111/144)	0.523
Intra-abdominal pressure during pneumoperitoneum (mm Hg) [a c]	13.55 (13/14)	13.00 (13/14)	0.248

[a] The median value (1st and 3rd quartiles) is reported for the age, weight, BMI, GFR, duration of pneumoperitoneum and intra-abdominal pressure during pneumoperitoneum.
[b] The other variables are expressed as the absolute and relative frequencies.
[c] The Mann-Whitney test was used to compare the weight, age, BMI, duration of pneumoperitoneum and intra-abdominal pressure during pneumoperitoneum.
[d] Other variables were compared using the chi-square test and Fisher's exact test.

group. The means of the independent continuous variables were compared between the groups by the Mann-Whitney test and Wilcoxon's test was used to compare the dependent variables within the same group (at different time points). The chi-square test and Fisher's exact test were used to analyze the categorical variables. Differences with p-values <0.05 were considered significant.

RESULTS

Sixty-eight patients were initially considered candidates for participation in the study; however, 4 patients were excluded before the random selection stage because they refused to participate, or their surgeries were cancelled. Of the 64 patients who were randomly selected, all of them completed the study in two equally distributed groups of 32 individuals each.

There were no significant differences between the groups in terms of the anthropometric data, sex distribution, associated diseases, duration of pneumoperitoneum, baseline GFR or average intra-abdominal pressure (Table 1).

As shown in Table 2, the serum levels of NGAL were not influenced by the type of anesthesia that was used (TIVA *vs.* SEVO) at any of the analyzed time points. No changes in the NGAL levels were observed during the periods between M0 and M1, between M1 and M2 or between M0 and M2 in either the individual patients or in the groups when they were analyzed separately.

No difference was found in the occurrence of the ''risk of renal injury'' between the two anesthesia groups during the periods measured and no patients were classified as having ''renal injury'' using the RIFLE criteria (Table 3).

DISCUSSION

Morbidly obese patients present a perioperative risk for acute kidney injury due to various factors. The causes for the occurrence of acute kidney damage found in the literature included the following: the production of bioactive substances by adipose tissues (18); an increase in the intra-abdominal pressure due to visceral fat accumulation; and tubular damage induced by rhabdomyolysis during surgery (4). Temporary oliguria is also a well-documented complication of laparoscopy, particularly in morbidly obese patients (19). The primary factors causing kidney injury during laparoscopic procedures were abdominal insufflation pressure and the length of pneumoperitoneum exposure (20). A decrease in the cortical blood flow, as well as an increase in vascular resistance and transient ischemia, was commonly observed under experimental conditions, but these effects were usually associated with elevated insufflation pressure of the abdominal cavity (>15 mm Hg) (20) and they were typically reversible by ending the pneumoperitoneum (19).

In 15.6% of the patients at time point M1 and 1.6% of the patients at time point M2, we found temporary changes in the urine volume and serum creatinine levels that were sufficiently large to be classified as at ''risk'' using the RIFLE criteria; there was no significant difference between

Table 2 - The median neutrophil gelatinase-associated lipocalin levels (ng/mL) (1st and 3rd quartiles) before anesthesia, 6 hours after pneumoperitoneum and 24 hours after pneumoperitoneum in all of the patients, separated according to type of anesthesia, total intravenous or inhalation anesthesia sevoflurane.

GROUP	BEFORE ANESTHESIA	6 HOURS AFTER THE BEGINNING OF SURGERY	24 HOURS AFTER THE BEGINNING OF SURGERY
Sevoflurane	29.0 (17.5/43.5)[a.e]	30.0 (21.5/69.5)[b.e]	24.5 (16.5/43.2)[c.e]
TIVA	31.0 (20.0/51.0)[a.f]	26.5 (18.7/51.2)[b.f]	22.0 (14.0/51.0)[c.f]
All patients	30.0 (19.0/46.25)[d]	29.0 (21.0/60.0)[d]	24.0 (15.0/47.0)[d]

[a] Comparison of the values in the SEVO *vs.* TIVA groups for M0, $p=0.376$.
[b] Comparison of the values in the SEVO *vs.* TIVA groups for M1, $p=0.309$.
[c] Comparison of the values in the SEVO *vs.* TIVA groups for M2, $p=0.917$.
[d] Comparison of the values in all of the patients across different periods: M1-M0, $p=0.227$; M2-M1, $p=0.533$; and M2-M0, $p=0.894$.
[e] Comparison of the values within the SEVO group across different periods: M1-M0, $p=0.083$; M2-M1, $p=0.913$; and M2-M0, $p=0.421$.
[f] Comparison of the values within the TIVA group across different periods: M1-M0, $p=0.914$; M2-M1, $p=0.715$; and M2-M0, $p=0.966$.

Table 3 - RIFLE criteria classifications by the type of anesthesia in M1 and M2.

	RIFLE 6 H - M1				RIFLE 24 H - M2			
TYPE OF ANESTHESIA	ZERO	RISK (R)	INJURY (I) OR GREATER	TOTAL	ZERO	RISK (R)	INJURY (I) OR GREATER	TOTAL
TIVA	27	5	0	32	31	0	0	31
SEVOFLURANE	27	5	0	32	31	1	0	32
TOTAL	54	10	0	64	62	1	0	63
Fisher's exact test TIVA *vs.* SEVO		$p = 1.00$				$p = 1.00$		

the types of anesthesia (Table 3). All of the individuals classified as at ''risk'' of renal injury using the RIFLE criteria at M1 had their classifications reversed to normal in M2. No patients were considered at risk according to the RIFLE classification at hospital discharge. Similarly, in a study by Ettinger et al. (4), the authors could not find any cases of acute tubular necrosis (creatinine elevation criteria) in 58 morbidly obese patients who underwent VLBS under similar conditions. We also observed that the serum NGAL levels were not significantly different at the three different time points at which they were measured over the 24 hours of the perioperative period (Table 2). Similarly, Micalli et al. (21) did not observe any changes in the urinary levels of N-acetyl-β-D-glucosaminidase, a urinary marker of renal injury, in patients who had undergone surgical laparoscopy. In our study, low intra-abdominal pressures were used during the surgical procedures (the pneumoperitoneum was limited to 14 mm Hg), which might have contributed to the absence of observable clinical damage to the renal system.

As seen in Table 2, the type of general anesthesia (TIVA *vs.* SEVO) did not influence the serum NGAL levels at any time during the evaluated perioperative period. Both propofol and sevoflurane are anti-inflammatory agents because they decrease the production of the nuclear transcription factor (NF-kB) (15,22), which is considered a transcriptional inducer of pro-inflammatory interleukins, such as interleukins 1 and 6 (23) and of NGAL itself (24). Through different mechanisms, both sevoflurane and propofol exert protective effects on the kidneys: propofol decreased the tissue damage caused by oxidative stress (25) and in renal ischemia models, sevoflurane provided pharmacological preconditioning (15,26). However, there has been no consensus in the literature regarding the more effective drug for kidney protection.

Although VLBS carries a risk of acute kidney injury, proper perioperative care greatly reduces its occurrence and traditional laboratory markers do not have sufficient accuracy to identify subclinical damage. NGAL is a sensitive, specific and early biomarker of acute kidney injury that has been tested under many clinical conditions and it allows for diagnosing renal damage within two hours of the injurious event (5). In our study, there were no significant differences in the perioperative blood levels of this highly accurate biomarker between groups using propofol or sevoflurane to maintain general anesthesia during VLBS.

The type of general anesthesia (TIVA *vs.* SEVO) did not influence serum NGAL levels during the perioperative period in VLBS. Therefore, with regard to the risk of acute kidney injury, both types of anesthesia were equally safe during this surgery.

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■ AUTHOR CONTRIBUTIONS

Fernandes AT and Módolo NS participated in the conception, data collection and analysis and manuscript writing. Ettinger J and Amaral F participated in the data collection and manuscript writing. Alves R and Ramalho MJ participated in the data collection and analysis and manuscript writing.

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