CLINICAL RESEARCH / KLİNİK ÇALIŞMA

EFFECTS OF USING PROPOFOL OR SEVOFLURANE FOR MAINTENANCE OF ANESTHESIA ON POSTOPERATIVE METABOLIC STATE IN BARIATRIC SURGERY

BARİATRİK CERRAHİDE PROPOFOL VEYA SEVOFLURAN İLE YAPILAN ANESTEZİ İDAMESİNİN POSTOPERATİF METABOLİK DURUM ÜZERİNE ETKİLERİ

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SUMMARY

Objective: *Surgical method and anesthesia have variable effects on postoperative metabolic state of the obese patients. In the current study, we investigated metabolic consequences of maintenance of anesthesia with intravenous propofol infusion or inhaled sevoflurane in obese patients.*

Method: *Data of 140 patients who underwent laparoscopic sleeve gastrectomy in reverse trendelenburg position were reviewed for the study. The first group consisted of patients receiving total intravenous anesthesia for maintenance and the second group included patients receiving inhalation anesthesia with sevoflurane. Remifentanil was the additional agent used for maintenance in both groups. Demographic data, pre and postoperative laboratory values, duration of operation and intraoperative fluid management were recorded for two study groups.*

Results: *Patients in Group propofol received higher intraoperative fluid replacement. Postoperative AST and ALT values were greater than preoperative values in both groups (p=0.0001). Postoperative $PaCO_2$ values were greater than preoperative values but remained within physiological limits in both groups (p=0.0001). Compared to preoperative values, propofol group had greater postoperative CK and LDH and lower pH and HCO_3 values (p=0.0001). Postoperative ALT elevation was more severe in sevoflurane group versus propofol group but reductions in pH and HCO_3 were more significant in propofol group.*

Conclusion: *Anesthesia has clear postoperative metabolic consequences in bariatric surgery. It should be kept in mind that propofol infusion induces overt metabolic acidosis and sevoflurane can result in elevated liver enzymes and although these increases remain in physiological limits, care should be taken when choosing drugs for patients who can not compensate such adverse effects.*

KEY WORDS: *Obesity, Propofol, Sevoflurane, Metabolism, Blood Gas*

ÖZET

Amaç: *Cerrahi yöntem ve anestezinin obez hastaların postoperatif metabolik durumu üzerine değişen derecelerde etkisi mevcuttur. Bu çalışma ile intravenöz propofol infüzyonu ya da inhaler sevofluranla anestezi idamesinin obez hastalardaki metabolik sonuçlarını araştırdık.*

Yöntem: *Ters trendelenburg pozisyonunda laparoskopik sleeve gastrektomi yöntemiyle yapılan 140 hastanın verileri çalışmaya dahil edildi. Birinci gruba idamede total intravenöz anestezi alanlar, ikinci gruba sevofluranla inhalasyon anestezisi alanlar dahil edildi. Her iki grupta da idamedeki ek ajan remifentanil idi. Her iki gruptaki hastaların demografik verileri, preoperatif ve postoperatif laboratuar incelemeleri, cerrahi süreleri, intraoperatif sıvı yönetimleri kaydedildi.*

Bulgular: *Hastaların demografik verileri, cerrahi süreleri açısından gruplar arası farklılık tespit edilmedi. Propofol alan grupta daha çok mayi ihtiyacı olduğu tespit edildi. Her iki grupta da postoperatif AST, ALT değerleri preoperatif ölçümlerden yüksekti (p<0.001). AKG'da her iki gruptada postoperatif $PaCO_2$ değeri preoperatif değerden yüksekti ama yine de fizyolojik sınırlardaydı (p<0.001). Sevofluran grubunda kan gazıyla ilgili başka anlamlı değişiklik saptanmadı. Propofol alan grupta postoperatif CK, LDH düzeyleri preoperatif dönemden daha yüksekti ve pH, HCO_3 değerleri daha düşüktü (p<0.001). Gruplar arası farklılığa bakıldığında sevofluran grubundaki postoperatif ALT yüksekliği propofol grubundan daha şiddetli iken; pH ve HCO_3 düşüşü propofol grubunda daha şiddetli idi.*

Sonuç: *Obezite cerrahisinde anestezinin postoperatif metabolik sonuçları olduğu aşikardır. Propofol infüzyonunun belirgin metabolik asidoz yaptığı, sevofluranın da fizyolojik kompansasyon sınırlarının içinde de olsa karaciğer enzim yüksekliği yapabildiği bilinmeli ve bu etkileri kompanse edemeyecek hastalarda ilaç seçimlerine dikkat edilmelidir.*

ANAHTAR KELİMELER: *Obezite, Propofol, Sevofluran, Metabolizma, Kan Gazı*

Çıkar çatışması/*Conflict of Interest*: Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir./ *Authors do not report any conflict of interest.*
Geliş tarihi/*Received*: 12/10/2016 Kabul tarihi/*Accepted*: 01/04/2017

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INTRODUCTION

According to the World Health Organization (WHO), obesity which is defined as the accumulation of excess body fat, has become a global health problem in epidemic proportions. Data show that there are approximately 1.5 billion obese patients worldwide (1). In line with this data, there is an increased incidence of obese patients presenting for surgery. Based on the definitions established by the WHO, a body mass index of 30 kg m^{-2} or above is defined as Class I obesity, a BMI of 35 kg m^{-2} or above is Class II obesity and a BMI of 40 kg m^{-2} or above is Class III obesity (morbid obesity) (2). In these patients, comorbidities associated with obesity including hypertension, diabetes mellitus, dislipidemia, coronary artery disease, stroke, and obstructive sleep apnea syndrome necessitate treatment of obesity. Surgical treatments have emerged for the obese population due to ineffective pharmacological therapy and dietary interventions. Patients with a BMI greater than 40 kg/m^2 or patients with a severe obesity related comorbidity and a BMI greater than 35 kg m^{-2} are considered to require surgical intervention (2). As a result, anesthesiologists encounter more and more morbidly obese patients with comorbidities. Metabolic condition of the patients is not the sole concern for anesthesiologist during obesity surgery also known as bariatric surgery. Other problems that the anesthesiologist has to cope with include difficult airway anatomy, variable drug metabolism, physiological effects of pneumoperitoneum during laparoscopic surgeries and positioning of the patient (3). Currently, there is no consensus on the optimal anesthetic method to be used for bariatric surgery. In particular, few studies exist in literature on the maintenance of anesthesia. In the present study, we aimed to investigate the effects of differential anesthetic methods used for these surgeries which are associated with changes in abdominal organ perfusion as well as variations in pulmonary physiology due to both patient position and laparoscopy, leading to altered acute metabolic outcomes. For this purpose, we examined the effects of selected intravenous or inhaler anesthetic methods on hepatic and renal functions and blood gases postoperatively. The study was based on the comparison between propofol (the most commonly used intravenous agent for total intravenous anesthesia) and sevoflurane (considered as the safest agent for inhalation anesthesia) with respect to their effects.

MATERIAL AND METHOD

After obtaining approval from the local Ethics Committee of our hospital, this retrospective study included patients who underwent laparoscopic sleeve gastrectomy operation in the last 3 years. Patient data were retrieved from both medical files and electronic patient registry. Study patients were divided into two groups based on the type of general anesthesia they have received. The first group consisted of patients receiving total intravenous anesthesia (Group TIVA) and patients receiving inhalation anesthesia formed the second group (Group IA). Total intravenous anesthesia group included only those patients who received maintenance anesthesia with propofol and remifentanil infusion, whereas inhalation anesthesia group consisted of patients receiving only sevoflurane, air mixture and remifentanil infusion. In addition to demographic data, perioperative laboratory values were recorded for all study population. Data recorded included age, gender, actual body weight, height, existing comorbidities, duration of operation, amounts of fluids given intraoperatively and laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), urea, creatine kinase (CK), muscle band of creatine kinase (CK-MB), lactate dehydrogenase (LDH), arterial blood gases (ABG) when available. Current biochemical data of patients were recorded both preoperatively and postoperatively. Body mass index (BMI) values were estimated from these data. For the intraoperative period, all anesthetic drugs and intravenous fluids administered, duration and type of surgery, surgical complications if any and monitoring techniques were recorded for each patient.

Patients categorized as ASA Class 3 and who has severe cardiopulmonary, hepatic or renal disease were excluded. Patients with serious surgical (eg. iatrogenic trauma, massive hemorrhage) or anesthesia-related complications (severe bronchospasm, intraoperative unstable hemodynamic data) and those who required further follow-up at intensive care unit postoperatively were also excluded.

Study data were analyzed using SPSS 20.0 software package. Descriptive statistics (mean, standard deviation, minimum, maximum) were provided for data from both groups.

Analyses of preoperative and postoperative biochemical data were performed with matched pairs significance test for normally distributed data or with Wilcoxon test for non-normally distributed data. Student's t-test was used for comparison of study groups for parametric values.

RESULTS

Following retrospective review of patients, data for 140 patients undergoing laparoscopic sleeve gastrectomy

meeting the inclusion criteria were included in the study. Sixty five patients were identified as receiving total intravenous anesthesia and 75 had received inhalation anesthesia. General demographic data, duration of surgery and details of intraoperative fluids given by the anesthesiologist are shown in Table I. As seen from the table, there were no statistically significant differences between groups in demographic data.

Table I. Patient characteristics according to the groups

	Group TIVA (n=65)	GroupIA (n=75)	p
Gender(F/M) (n)	56/9	62/13	>0.05
Age (year)	42.8±11.3	38.3±10.3	>0.05
Weight (kg)	124.7±21.5	124.7±17.2	>0.05
Height (cm)	162.8±8.25	161.8±9.7	>0.05
BMI (kg m^{-2})	47.0±8.2	47.2±6.1	>0.05
Surgery Time (dk)	168.0±69.5	162.0±47.6	>0.05
FluidTherapy (mL)*	2565±1135	2088±801	0.004

Values are defined as mean±standard deviation
BMI; Body Mass Index
* Intraoperative amount of kristalloid replacement

In Group TIVA, there were 22 patients with hypertension, 5 patients with coronary artery disease, 8 patients with diabetes mellitus, 2 patients with asthma and 2 patients with obstructive sleep apnea syndrome. Group IA consisted of 10 patients with hypertension, 6 patients with coronary artery disease, 12 patients with diabetes mellitus, 1 patient with asthma and 5 patients with obstructive sleep apnea syndrome

Bispectral Index (BIS) monitoring was present in all patients receiving TIVA. The mean amount of propofol consumed by TIVA patients was 1719.5±769.0 mg. Based on the body weight and mean duration of surgery of study patients, estimated propofol consumption was 5.2±2.0 mg kg^{-1} per hour.

Analysis of intraoperative fluid quantities showed that TIVA group required a greater amount of crystalloid fluids (p=0.004). Additionally, 15 patients from Group TIVA and 7 patients from Group IA needed colloidal fluids.

Tables II and III show the analytical results of blood samples obtained from patients. Preoperative values and postoperative day 1 values of patients were analyzed. Statistically significant elevations were observed in postoperative AST and ALT values in both groups (p<0.001). While postoperative creatinine values were not significantly different from baseline, urea values were reduced in both groups. The reduction in urea values was statistically significant only in Group IA. Multiple available arterial blood gas analyses (ABG) of patients were assessed. The first post-induction ABG value was included in the analysis as the preoperative

Table II. Biochemical values according to the groups

		Preoperative	Postoperative	p
Group TIVA	**AST (U L^{-1})**	24.3±12.6	77.0±87.0	**p<0.001**
	ALT (U L^{-1})	28.5±24.0	67.9±60.1	**p<0.001**
	Creatinine (mg dL^{-1})	0.80±0.17	0.80±0.16	0.426
	Urea (mg dL^{-1})	26.6±8.0	25.2±9.4	0.268
	CK (IU L^{-1})	78.7±17.6	167.7±88.0	**p<0.001**
	LDH (U L^{-1})	212.0±39.5	316.0±164.0	**p<0.001**
Group IA	**AST (U L^{-1})**	24.9±12.9	109.9±119.3	**p<0.001**
	ALT (U L^{-1})	31.7±24.6	106.9±111.5	**p<0.001**
	Creatinine (mg dL^{-1})	0.73±0.13	0.76±0.18	0.079
	Urea (mg dL^{-1})	29.2±10.2	24.7±9.7	**p<0.001**

Values are defined as mean±standard deviation
ALT; alanine aminotransferase, AST; aspartate aminotransferase, CK; creatine kinase, CK-MB; muscle band of creatine kinase, LDH; lactate dehydrogenase

Table III. Arterial blood gas analyses according to the groups

		Preoperative	Postoperative	p
Group TIVA	**pH**	7.396±0.044	7.328±0.057	**p<0.001**
	pO_2	119.79±34.65	125.46±28.76	0.064
	pCO_2	36.29±4.34	39.83±5.1	**p<0.001**
	HCO_3	21.96±1.85	20.65±2.03	**p<0.001**
Group IA	**pH**	7.396±0.37	7.404±0.034	0.370
	pO_2	117.94±41.19	119.24±20.27	0.555
	pCO_2	35.02±3.63	39.1±4.87	**p<0.001**
	HCO_3	21.41±1.69	21.8±1.67	0.067

Values are defined as mean±standard deviation

value and the last ABG obtained before extubation was considered as the postoperative value. For Group IA, no difference was found between preoperative and postoperative pH values but Group TIVA showed a significant decline postoperatively. In both groups, postoperative ABG analyses demonstrated greater PaO_2 values versus baseline but statistical significance was not observed in either group. Statistically significant elevations were found in postoperative $PaCO_2$ values in both groups ($p<0.001$) with no difference between groups. For postoperative HCO_3 values, Group IA did not show significant changes versus preoperative values but a statistically significant decline was seen in postoperative HCO_3 values of Group TIVA.

Statistical analyses for the preoperative versus postoperative differences between groups in ABG and biochemical values showed between-group differences in AST, PaO_2 and pCO_2 values. While the increase in ALT values was significantly greater in Group IA ($p<0.01$), the decline in pH and HCO_3 values were significantly more severe in Group TIVA ($p<0.001$).

Examination of analytical results for CK and LDH revealed that these parameters were studied only for 17 patients in Group IA and 55 patients in Group TIVA. Thus, a comparison could not be done between groups for these parameters. When preoperative and postoperative values of Group TIVA were reviewed, statistically significant increases were found in CK (preop: 78.7±17.6 IU L^{-1}, postop: 167.7±88.0 IU L^{-1}) and LDH (preop: 212.0±39.5 IU L^{-1}, postop: 316.0±164.0 IU L^{-1}) values ($p<0.001$).

For induction of anesthesia, thiopental sodium was administered to 17 patients from Group TIVA and 13 patients from Group IA and propofol was given to all of the remaining patients.

DISCUSSION

Based on the results of our study, sevoflurane was found to be associated with more severe elevations in liver enzymes when used for maintenance of anesthesia, whereas propofol caused more severe metabolic acidosis. A multifactorial analysis should be considered when examining acute metabolic effects following bariatric surgery. In order to increase the reliability of the present study, we included a uniform surgical technique (laparoscopic sleeve gastrectomy) and a uniform surgical position (reverse trendelenburg position). In bariatric surgery, major factors which have metabolic effects are pneumoperitoneum, systemic carbondioxide (CO_2) absorption and reverse trendelenburg position (3). In fact, absorbed CO_2 is removed by the lungs due to its high solubility and rapid membrane penetration. However, respiratory acidosis ensues when adequate ventilation cannot be achieved, resulting in reduced pH and bicarbonate levels and increased $PaCO_2$ (4). As hypercapnia and acidosis may lead to pulmonary vasoconstriction, tachycardia and myocardial depression, close monitoring should be conducted intraoperatively for end-tidal carbondioxide ($ETCO_2$) or $PaCO_2$ (4). In our clinic, $ETCO_2$ follow-up is a part of routine anesthesia monitoring which allows timely intervention to correct hypercarbia in obese patients. No cases of severe hypercarbia out of normal limits were identified in any of the study patients. Postoperative mean $PaCO_2$ value was approximately 39 mmHg in both groups which was significantly greater versus mean preoperative value; however, there was no between group difference and this led us to explain this elevation by minimal abdominal CO_2 absorption. Other systemic effects of pneumoperitoneum occur due to increased intraabdominal pressure. As with non-obese patients, intraabdominal

pressure should not exceed 15 mmHg during laparoscopy in obese patients (3). Cardiac outcomes of increased intraabdominal pressure (<15 mm Hg) mainly include tachycardia, increased central venous pressure and minimal changes in cardiac output (5,-7). These changes usually remain within physiological compensatory limits. However, a severe fall in venous return and hypotension may occur due to inferior vena cava compression when intraabdominal pressures exceed 15 mmHg (8). Additionally, it should be kept in mind that the reverse trendelenburg position may contribute negatively to adverse cardiac effects in bariatric surgery, leading to reduced venous return, increased peripheral vascular resistance and eventually decreased cardiac output (9). One of the major limitations of our study is the absence of intraoperative intraabdominal pressure follow-up data.

An additional adverse effect of an intraabdominal pressure of 15 mm Hg is reduced portal venous blood flow as demonstrated in both human and animal studies (10). Resulting hepatic hypoperfusion manifests itself as elevated liver enzymes (11). Following laparoscopy, transient elevations in hepatic enzyme levels by nearly six fold were reported which tended to return to baseline 3 days after the operation (12). In the present study, postoperative increases were also observed in liver enzymes in both groups with mean values that were 3-4 fold greater than baseline. However, ALT increase was greater in the group receiving sevoflurane compared to the other group. Three fold or greater elevations in hepatic enzymes should suggest acute hepatocyte damage and close monitoring is advised. Reasons for postoperatively increased liver enzyme levels include intraoperative hepatic injury, general anesthetics, and reduced portal blood flow due to pneumoperitoneum (3). Our study excluded patients with hepatic injury and since both study groups were exposed to pneumoperitoneum, it can be said that sevoflurane caused more severe hepatic enzyme elevations. This is particularly important for morbidly obese patients who usually have serious preoperative hepatic disorders. Steatohepatitis which is highly prevalent (56-84%) in obese individuals is an example of the high risk hepatic conditions (13, 14).

In a clinical trial which explored the effects of propofol and sevoflurane used for maintenance of anesthesia on hepatic enzymes (AST, ALT) in nonabdominal elective surgeries, the authors did not find any preoperative versus postoperative differences or between group differences (15). In a study investigating the effects of sevoflurane used for elective orthopedic surgeries longer than 10 hours, normal postoperative creatinine and creatinine clearance were found with transient minimal increases in ALT and glutathione S-transferase (GST) levels (16). GST, one of the many hepatic conjugation enzymes is considered as a reliable indicator of hepatocellular integrity (17). In studies examining liver injury with sevoflurane, GST values were either unchanged or transiently elevated within the first hours and were not life threatening (18,19). Variable results have been reported by studies that examined hepatocellular damage with propofol by looking at GST and there is a general consensus that propofol may increase GST level in a dose dependent manner or may not affect it at all and subclinical effects might occur with doses used in humans (20-22). Thus, it should be borne in mind that these two agents have certain effects on the cells, albeit at a subclinical level and such effects may be important in patients with underlying comorbidities (eg, morbid obesity).

There are few reported cases of acute hepatotoxicity associated with propofol in literature (23-25). While there is no common denominator in these case reports, some of the culprit mechanisms included an underlying genetic disorder or impaired fatty acid oxidation by propofol. Nevertheless, propofol is still considered as a safe anesthetic agent even in individuals with hepatic dysfunction. A small number of cases of sevoflurane related hepatotoxicity exist in literature and it is worth considering that one of these cases was fatal and occurred in a patient with no risk factors (26, 27). An animal study that compared volatile anesthetic agents with respect to their potential hepatotoxic effects reported that halothane was the most toxic and sevoflurane was relatively safer with minimal effects on the liver (28). In a case report of an acute hepatitis that developed following exposure to sevoflurane during surgery in a patient with recent Epstein-Barr virus (EBV) infection, the authors suggested that production of compound A by metabolism of sevoflurane, increased cytosolic free calcium and activation of free radical metabolizing enzymes could be involved (29). Increased cytosolic free calcium by volatile anesthetics leading to cell death was implicated as the main mechanism (26, 30).

Kidney is another major organ affected by increased intraabdominal pressure. Studies in obese and non-obese patients showed reduced urine output as a result of decreased renal cortical blood flow due to pneumoperitoneum (31, 32). An important limitation of our study is absence of sufficient data on intraoperative urine output. Unchanged or minimally reduced concentrations of urea and creatinine were reported in studies where an intraabdominal pressure of 15 mm Hg

was generally considered safe for renal functioning (3, 32). Our findings support these data. No significant changes were found in urea and creatinine postperatively in the group receiving propofol. While creatinine values were not significantly altered postoperatively in the sevoflurane group, urea values were reduced. We considered that these findings were related to pneumoperitoneum rather than the anesthetics themselves.

Rhabdomyolysis (defined as CK>1000 IU L^{-1}) is an additional metabolic concern during laparoscopic bariatric surgery. In bariatric surgery, major risk factors for rhabdomyolysis include exposure of large muscle groups to increased pressure, pneumoperitoneum and in particular, a BMI greater than 55 kg m^{-2} (33). Thus, close ABG monitoring is mandatory when using TIVA for bariatric surgery since propofol may induce a so-called propofol infusion syndrome (PRIS) through a unique mechanism involving interruption of mitochondrial electron transport chain, resulting in destruction of cells with a high energy demand and manifestations of rhabdomyolysis (34). In literature, administration of propofol at a rate greater than 4 mg kg^{-1} h^{-1} is generally considered as a risk factor for PRIS but this does not necessarily happen in every patient. In our study, average propofol consumption was 5.2 mg kg^{-1} h^{-1} under BIS monitoring. Although significant elevations were seen in CK levels in both study groups, the increases were not sufficiently high to be considered as rhabdomyolysis. However, propofol consumption was found to cause severe metabolic acidosis in TIVA group. While cardinal clinical features of propofol infusion syndrome (profound lactic acidosis, hypotension, cardiac suppression) were not observed, subclinical effects cannot be overlooked which may impair postoperative quality of life in individuals with morbidities who cannot compensate metabolic asidosis.

CONCLUSION

In general, laparoscopic sleeve gastrectomy with sevoflurane or propofol infusion may be considered safe with minimal postoperative metabolic changes in patients without severe comorbidities. However, we suggest that intraabdominal pressure, $ETCO_2$, urine output, ABG and renal and hepatic marker as well as CK and LDH should be closely monitored in order to promptly overcome metabolic consequences of bariatric surgery. Additionally, we believe that care should be exercised when using sevoflurane in patients with liver disease and propofol infusion should be carefully monitored in patients with pulmonary or renal disease who cannot compensate metabolic changes.

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