

Effects of Different Anesthetic Techniques on Serum Leptin, C-reactive Protein, and Cortisol Concentrations in Anorectal Surgery

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Aim To compare the effects of intratracheal general anesthesia (ITGA) and regional (saddle block) anesthesia on leptin, C-reactive protein (CRP), and cortisol blood concentrations during anorectal surgery.

Methods Fifty-eight patients suffering from hemorrhoidal disease, pilonidal sinus, anal fissure, or anal fistula were included in the study. Patients were randomly assigned into one of the two groups (n = 29). Patients in one group received ITGA. After thiopental and fentanyl induction, vecuronium was used as a muscle relaxant. Anesthesia was maintained with sevoflurane. In the other group we applied saddle block, injecting hyperbaric bupivacaine into the subarachnoid space, through the L3-L4 intervertebral space, in the sitting position. Blood samples were collected for leptin, CRP, and cortisol analysis before the induction of anesthesia at 3 and 24 hours postoperatively.

Results Preoperative leptin, CRP, and cortisol concentrations were comparable between the groups. There was no significant difference in postoperative levels of leptin and CRP in both groups. Although not significant, leptin and CRP concentrations were lower in the saddle block group at three hours postoperatively (mean \pm SD, 6.95 ± 8.59 and 6.02 ± 12.25 , respectively) than in the ITGA group (mean \pm SD, 9.04 ± 9.89 and 8.40 ± 15.75 , respectively). During early postoperative period, cortisol increased slightly in the ITGA group and remained at similar level in the saddle block group, but later decreased in both groups. Cortisol levels in the saddle block group were significantly lower than in the ITGA group at 3 hours postoperatively (343.7 ± 329.6 vs 611.4 ± 569.8 ; $P = 0.034$).

Conclusion Saddle block, a regional anesthetic technique, may attenuate stress response in patients undergoing anorectal surgery, by blocking afferent neural input during early postoperative period.

Stress response to surgery is characterized by neurohumoral, immunologic, and metabolic alterations (1). Surgery-related metabolic and endocrine derangements lead to adverse effects, including increased oxygen consumption, catabolism, and impaired immune function. These derangements have been associated with poor postoperative course and clinical outcome (2,3).

Leptin is a cytokine-like molecule and is secreted in proportion to the adipose tissue mass. Leptin is structurally similar to the granulocyte colony-stimulating factor (G-CSF), which stimulates the synthesis of the acute phase proteins (APPs). It has been suggested that leptin may be involved in the acute stress response after surgery, regulating the hypothalamic-pituitary-adrenal (HPA) axis. Leptin has a slower time course of the adrenal-suppressive effect in contrast to its effect on hypothalamus (4-7). Testosterone and catecholamine inhibit leptin secretion while insulin and cortisol stimulate leptin secretion by adiposities. Leptin shows a circadian rhythmicity, with a nocturnal rise. Temporal relationship was showed between circadian variation of serum levels of leptin and cortisol, with cortisol peak following leptin peak (8).

Cortisol has an inhibitory role on APP response in a chronic setting and stimulatory effect in an acute setting. After an acute injury, there is first a physiological increase in cortisol, followed by leptin and APPs increase (9,10). C-reactive protein (CRP) is one of the main APPs. A significant correlation between leptin and CRP levels indicates that leptin co-stimulates APPs synthesis during the acute phase response following an inflammatory stimulus (6).

Stress response to surgery is affected by several factors, including the type of surgery (eg, laparoscopy vs laparotomy) and anesthesia, magnitude of surgical injury, duration of operation, and the degree of postoperative pain. Anesthetic technique may modulate the extent of this response. Research has been conducted to find a "stress-free anesthetic technique" in order to lim-

it neuroendocrine, inflammatory, and immune responses (1). Attenuation of the endocrine-metabolic response may reduce the frequency of postoperative complications (11,12).

In this study, we chose a minor surgery, ie, non-malignant anorectal surgery, to evaluate anesthesia effects on stress response. We aimed to compare the effects of two different anesthetic techniques (ITGA and saddle block) on leptin, CRP, and cortisol response to anorectal surgery.

Participants and methods

Setting

Fifty-eight patients with American Society of Anesthesiologists physical status classification (ASA) I-II (13) scheduled for anorectal surgery were enrolled in the study after obtaining Local Hospital Ethics Committee approval and informed consent from the patients. Anorectal surgery was performed under intratracheal general anesthesia (ITGA) or regional (spinal anesthesia, saddle block) anesthesia. According to medical considerations, only patients who had no contraindication for general and regional anesthesia and were operated on between 9:00 AM and 11:00 AM were included. Patients with congestive heart failure, diabetes mellitus, thyroid, pituitary, adrenal, kidney, liver or metabolic disease, steroid therapy, hypotension, hypertension, hormone replacement therapy, malignancy, signs of infection or inflammation, pregnancy, malnutrition, and drugs or alcohol abuse were excluded. Patients who rejected the anesthetic technique scheduled according to randomization were excluded as well.

Anesthetic and surgical techniques

All patients fasted overnight and received diazepam 10 mg and atropine 0.5 mg intramuscularly (IM) for premedication 1 hour before surgery.

Patients were systematically assigned into one of the two groups. After enrolment into the

study, patients were assigned consecutive numbers. The patients numbered with odd numbers received ITGA and the patients numbered with even numbers received saddle block. In the ITGA group, anesthesia was induced with thiopental (5-7mg/kg) and fentanyl (1 µg/kg) intravenously (IV). Vecuronium bromide 0.1 mg/kg IV was administered to facilitate tracheal intubation and 50% nitrous oxide in oxygen with 2% sevoflurane (end-tidal concentration 1.9%-2.1%) was used for maintenance. The flow of anesthetic gas mixture was 4 L/min during the surgery. At the end of the surgery, residual muscle relaxation was antagonized using neostigmine (0.04 mg/kg) with atropine.

In the saddle block group, after a 500 mL fluid bolus, patients were placed in the sitting position and a 25-gauge spinal needle was inserted through the L3-4 intervertebral space. Hyperbaric bupivacaine 0.5% 2 mL was injected into the subarachnoid space and the patients were maintained in the sitting position for 3 to 5 minutes, to provide saddle block with T10 sensory level. Motor block was assessed using the Bromage scale (13) (0 – no motor block, 1 – able to flex knees, but not the hips, 2 – unable to flex knees, but no problems with ankle movement, 3 – no movement possible in the lower extremities).

Each group consisted of 29 patients. The patients with unsuccessful saddle block were excluded from the study. These patients were operated on under general anesthesia.

Intraoperative monitoring included heart rate, non-invasive arterial blood pressure, and pulse oximetry using Datex monitor (Datex Ohmeda Cardiocap/5 Louisville, CO, USA). Normal saline and 5% dextrose were given IV at a rate of 4-6 mL/kg/h peroperatively until oral intake. Oral intake was started approximately at 4 hours after surgery in all patients.

Hypertension and hypotension were defined as a 25% increase or decrease, respectively, from baseline systolic blood pressure. Bradycardia was defined as a heart rate below 55 beats/min.

Severity of postoperative pain was assessed by a visual analog scale (VAS, 10-cm horizontal line labeled “no pain” at one end and “worst pain imaginable” on the other end). Metamizol 1 g IM was applied every 8 hours routinely for postoperative pain management during postoperative 24-48 hours. The first dose of analgesic was administered 2 hours after surgery. If analgesia was unsatisfactory (VAS>3 cm), supplementary analgesia was provided by meperidine 1 mg/kg IM. The total amount of supplemental analgesics administered was recorded. Patients were usually discharged on the second postoperative day.

All patients had an enema night before the operation and another one in the morning of surgical intervention.

Submucosal hemorrhoidectomy was chosen as surgical technique for patients with hemorrhoidal disease. Limberg fasciocutaneous flap was performed in patients with pilonidal sinus. A closed suction drain was routinely placed in the wound in all of the patients. Lateral internal sphincterotomy was performed for all of the patients with anal fissure. Excision of the fissure was included to surgery in some chronic anal fissure patients. Fistulectomy or fistulotomy were performed in patients with anal fistula (14).

Blood samples and analysis

Three consecutive venous blood samples were collected peripherally, in tubes with ethylenediamine tetra-acetic acid (EDTA) before induction of anesthesia (baseline, sample 1), at 3 (sample 2), and 24 hours (sample 3), postoperatively. After being centrifuged, plasma was stored at -20°C until assayed. Leptin was measured by micro enzyme-linked immunosorbent assay method (ELISA) with Biosource kits, using µQuant micro plate reader (Biotek, Nivelles, Belgium). CRP levels were assayed by immunoturbidimetric method with Roche kits, using modular analytics P module (Roche Diagnostics, Mannheim, Germany). Cortisol levels were determined by electrochemiluminescence immu-

noassay method with Roche kits, using E-170 analyzer (Roche Diagnostics, Mannheim, Germany). The sensitivity, dynamic range, and accuracy of these tests were the following: 0.36, 1.56-100, and 4.6% for leptin; 0.425, 1-280, and 4.61% for CRP; and 8, 1-1750, and 2.8% for cortisol.

The total protein concentrations of blood samples were measured and the levels of leptin, CRP, and cortisol were corrected using the changes in the total protein concentrations, to minimize the effect of hemodilution on the test results postoperatively.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences for Windows, version 11.0 (SPSS Inc., Chicago, IL; USA). Demographic data and the levels of leptin, CRP, and cortisol between the groups were compared with *t* tests. The changes within the groups were analyzed using repeated measures of ANOVA and paired *t* tests. Pearson correlation analysis was used to examine the relation between serum concentration of leptin (sample 1) and body mass index (BMI). Statistical significance was considered at $P < 0.05$. Data were presented as mean \pm SD.

Results

There was no difference between groups in patient characteristics and surgical data (Table 1).

Table 1. Patient characteristics and surgical data (mean \pm SD)*

	Group		P
	ITGA	saddle block	
Gender (M/F)	18/11	16/13	0.790 [†]
Age (y)	34.7 \pm 13.8	33.5 \pm 11.5	0.717 [†]
BMI (kg/m ²)	26.8 \pm 4.7	25.9 \pm 3.4	0.462 [†]
Surgery time (min)	60.2 \pm 22.4	66.1 \pm 23.5	0.336 [†]
Disease (No. of patients):			0.945 [†]
hemorrhoid	13	12	
pilonidal sinus	9	10	
anal fissure	4	3	
anal fistula	3	4	

*Abbreviations: ITGA – intratracheal general anesthesia; BMI – body mass index; SD – standard deviation.

[†] χ^2 test.

[‡]*t* test.

Preoperative concentrations of leptin, CRP, and cortisol in two groups were comparable (Table 2).

When postoperative concentrations were compared, there was no significant difference between the groups, except for cortisol (Table 2). Cortisol increased slightly during early postoperative period and then decreased after 24 hours postoperatively in the ITGA group. In the saddle block group, cortisol remained at a similar level at 3 hours postoperatively, but decreased later. Cortisol concentrations in the ITGA group were higher than in the saddle block group at 3 hours after surgery ($P = 0.034$), (Table 2).

Table 2. Leptin, CRP, and cortisol concentrations (mean \pm SD) during general or saddle block anesthesia*

Sample [†]		Group		P [‡]
		ITGA	saddle block	
Leptin (ng/mL)	1	7.62 \pm 7.02	5.88 \pm 5.71	0.306
	2	9.04 \pm 9.89	6.95 \pm 8.59	0.395
	3	17.99 \pm 20.08	11.43 \pm 11.43	0.133
	P [§]	0.004	0.005	
CRP (mg/L)	1	6.64 \pm 12.92	5.26 \pm 11.18	0.666
	2	8.40 \pm 15.75	6.02 \pm 12.25	0.524
	3	15.08 \pm 14.36	18.06 \pm 21.01	0.531
	P [§]	0.048	0.003	
Cortisol (nmol/L)	1	456.7 \pm 278.2	383.6 \pm 172.4	0.234
	2	611.4 \pm 569.8	343.7 \pm 329.6	0.034
	3	340.7 \pm 168.6	297.9 \pm 151.3	0.314
	P [§]	0.075	0.033	

*Abbreviations: ITGA – intratracheal general anesthesia; CRP – C-reactive protein; SD – standard deviation.

[†]Sample 1 – before induction of anesthesia; Sample 2 – at 3 h postoperatively; Sample 3 – at 24 h postoperatively.

[‡]*t* test.

[§]Difference among the three measurements within a group. Repeated measures of ANOVA.

Leptin concentrations increased postoperatively in both groups. The levels at 24 hours after operation (sample 3) were significantly higher than the levels at 3 hours after operation (sample 2) and baseline levels (sample 1) in both groups ($P = 0.016$, $P = 0.003$, in the ITGA group; and $P = 0.004$, $P = 0.001$ in the saddle block group, respectively) (Table 2). However, there was no significant difference between general and regional anesthesia ($P = 0.306$ for sample 1, $P = 0.395$ for sample 2, and $P = 0.133$ for sample 3).

C-reactive protein displayed a pattern resembling leptin. Its levels were increased after surgery in both groups. In the ITGA group, levels of

the sample 3 were significantly higher than levels of the sample 1 ($P=0.031$). In the saddle block group, the differences between sample 3 and sample 1, and sample 3 and sample 2 were significant ($P=0.001$) (Table 2).

A positive correlation was found between serum concentration of leptin (sample 1) and body mass index ($r=0.391$, $P=0.036$ in the ITGA group, and $r=0.401$, $P=0.033$ in the saddle block group, respectively).

There were no statistically significant differences in mean VAS pain scores at 3 and 24 hours postoperatively and postoperative total analgesic requirements between two groups.

No complete motor blockage was seen in patients undergoing saddle block. The Bromage score was usually score-1 and duration of the saddle block was 2 hours.

Hypothermia was not seen in any of the patients. No patient received a blood transfusion. Perioperative hypotension developed in 3 patients in the ITGA group and 7 patients in the saddle block group. Hypotension was treated first by fluid loading and second by administering ephedrine IV. Ephedrine requirements were similar in both groups. Heart rate values of the patients were within normal values during the operation. Severe bradycardia and hypertension were not observed in any of the patients.

Discussion

When tissue damage occurs, mediators that trigger stress response are secreted from the tissue. In large tissue damage, stress response may arise without any neuronal transmission, whereas in minor damage transmission is a predominant mechanism. We found lower perioperative cortisol levels in patients receiving regional anesthesia (the saddle block group) than in those under general anesthesia, as previously described (15). Cortisol concentrations at 3 hours after surgery in the saddle block group were lower than in the ITGA group. It is known that blocking affer-

ent and efferent pathways in the sympathetic and the somatic nervous system suppresses the neuroendocrine activation during surgery (11). This difference may be attributed to blocking afferent sensory nerve stimuli arising from the operating area and early postoperative pain relief with spinal anesthesia (saddle block). However, during major and upper abdominal surgery less inhibition and measurable benefit on clinical outcome is observed, due to insufficient afferent somatic and sympathetic block (3,16). Delogu et al (17) demonstrated that reduced immunoendocrine response to surgical trauma was mainly dependent on surgical technique, but there was still little information on the direct effects of anesthesia on this response. Our study was conducted in patients undergoing non-malignant anorectal surgery to minimize the effects of surgical trauma on stress response. The difference in early postoperative VAS scores was not significant and cortisol levels decreased at 24 hours postoperatively in both groups.

Hemodilution is a factor affecting the circulating levels of cytokines, but it was thought that our data were not affected by hemodilution because there were no large fluid shifts due to blood loss and replacement in anorectal surgery. In our previous study, hemodilution related to fluid therapy in spinal anesthesia disappeared 24 hours after surgery (18) and the corrections were made measuring total protein concentrations to minimize the effect of hemodilution on the test results at 3 hours postoperatively.

Anesthetic technique with high dose opioid and isoflurane blunted intraoperative surgical stress response in cardiac operations (7,19,20). In this study, low dose opioid (fentanyl 1 $\mu\text{g}/\text{kg}$, IV) and sevoflurane were used in general anesthesia group, and anorectal surgery has been accepted as less stressful surgery than cardiac surgery. Marana et al (1) found that, when compared with isoflurane, sevoflurane increased stress response to laparoscopic surgery by decreasing cortisol release. Contrary to this, in our patients receiving

sevoflurane, cortisol levels increased at early post-operative period.

Excessive cortisol levels may delay wound healing, leading to immune suppression and infection. In this study, wound healing was not affected because the rise in cortisol levels lasted for a short period. We did not observe leptin's inhibitory effect on cortisol secretion (21). Although raised, leptin levels may not have been high enough to suppress cortisol secretion.

Patients undergoing surgery late in the morning or in the afternoon were excluded from the study to avoid the confounding effect of diurnal variation. In spite of the increase in leptin secretion caused by glucocorticoids, the role of glucocorticoids in leptin diurnal rhythm, with nocturnal rise and loss of diurnal variation detected under fasting conditions, was not essential but a modulatory one. It was possible for insulin to be involved in the control of circadian variation of leptin secretion (8,22).

The increase in leptin was explained by the increase in hormones related to surgical stress (insulin and cortisol). Leptin could play a role in regulation of energy expenditure in surgical stress (8,23). Our patients did not receive oral intake perioperatively, but received 5% dextrose. Oral intake started at 4 hours postoperatively. Although not as effective as oral intake, IV glucose administration also stimulates insulin secretion (24). Glucose infusion may reverse the decrease in leptin levels induced by fasting, in spite of receiving much less glucose. Short time food restriction does not seem to affect leptin expression (5).

Kain et al (7) found that leptin decreased 2 hours and was elevated 24 hours after surgery. They explained that one of the reasons of the initial decrease was peroperative fasting. No decrease during early postoperative period was seen in our study. This discrepancy may be explained with sampling times. We measured leptin levels at 3 hours instead at 2 hours after surgery. The increase in leptin at 24 hours postoperatively is consistent with our and other previous studies

(7,23). Leptin levels increased after surgery but this increase was found statistically significant in patients undergoing spinal anesthesia (25).

In this study, leptin levels correlated directly with BMI, resembling previous studies because plasma leptin concentration usually reflected the total amount of fat in the body (8,26).

Significant increase in CRP was observed after 24 hours in patients undergoing abdominal hysterectomy (27) and elective cardiac surgery (28), but after 48 hours in patients undergoing cholecystectomy (9). Our CRP results are consistent with the previous studies (2,3). CRP significantly increased after surgery in both groups regardless of the anesthetic modality.

Cortisol concentrations of the patients undergoing saddle block were significantly lower than those of the patients undergoing general anesthesia. Beside that, lower increase was observed in CRP and leptin concentrations of the patients in the saddle block group at 3 hours after surgery, in spite of non-significant difference. Saddle block, a regional anesthetic technique, may attenuate stress response to surgery, blocking afferent neural input, especially during early post-operative period. Even though regional anesthetic techniques using local anesthetics are effective in blunting preoperative hormonal changes, hormone concentrations remain increased postoperatively and postoperative strategies were investigated for modulating the stress response (12,18). Yet different techniques of anesthesia have not been shown to affect clinical outcome, so studies with more sensitive methods should be carried out to reveal positive results about this issue.

In conclusion, although two different anesthetic techniques (ITGA and saddle) led to difference in cortisol levels at early postoperative period, with the difference disappearing 24 hours postoperatively. Further long-term studies related to the influences of anesthetic techniques on stress response in patients undergoing anesthesia are required to detect whether this condition is important in clinical setting.

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