

# Effects of combined general anesthesia and thoracic epidural analgesia on cytokine response in patients undergoing laparoscopic cholecystectomy

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## Abstract

**Background:** Severe postoperative pain is not often experienced in laparoscopic cholecystectomy. Anesthesia, surgery, and pain are stressful and cause different reactions in neuro-immuno-endocrine systems. Many factors such as the pharmacological effect of the drugs used, as well as the type and depth of anesthesia, can affect these reactions.

**Objective:** The aim of this study was to evaluate the effect of the combination of general anesthesia and thoracic epidural analgesia (TEA) on cytokine reaction in laparoscopic cholecystectomy.

**Study Design:** Prospective, randomized clinical comparative study.

**Materials and Methods:** Sixty adult patients scheduled for elective laparoscopic cholecystectomy were divided into four groups. Group saline (Group S), group fentanyl (Group F), group bupivacaine (Group B), and group levobupivacaine (Group L) were infused with saline, saline and fentanyl, bupivacaine and fentanyl, and levobupivacaine and fentanyl, respectively, via epidural catheter before surgical incision.

**Results:** There were no differences among groups in the demographic features, heart rate, mean arterial pressure, and peripheral oxygen saturation values. Group L had lower visual analogue scale value compared to the other postoperative groups ( $P < 0.01$ ). In all groups, interleukin-6 (IL-6), IL-8, and IL-10 levels started to increase at 2 h and returned to the basal level at 24 h. IL levels increased in most of the epidural saline-administered group compared to other groups ( $P < 0.05$ ).

**Conclusion:** Combined general anesthesia and TEA provided pain control and hemodynamic stability more efficiently during the first 24 h of the intraoperative and postoperative period by suppressing cytokine levels. However, we determined that this effect was more obvious with the local anesthetic and opioid combination.


**Key words:** Bupivacaine, combined-general-epidural anesthesia, inflammatory cytokines, laparoscopic cholecystectomy, levobupivacaine

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## Introduction

Laparoscopic cholecystectomy has become increasingly common since the 1980 s. It has replaced the classic open cholecystectomy.<sup>[1]</sup> The laparoscopic approach causes less morbidity and mortality compared to open cholecystectomy. It also offers shorter lasting and less intense pain than open cholecystectomy. However, patients may experience significant abdominal disturbances and pain, particularly during the first 24 h postoperatively.<sup>[2-4]</sup> Researchers reported various causes of the pain following laparoscopy, such as ruptured blood vessels due to rapid distension of the peritoneum, traumatic traction on the nerves, release of inflammatory molecules, trauma to the abdominal wall, trauma when the gallbladder is removed from the abdomen, pneumoperitoneum created by utilizing CO<sub>2</sub>, high abdominal pressure, and CO<sub>2</sub> residue under the diaphragm (caused by stimulating the phrenic nerve or tension on the triangular and coronary ligaments due to sagging of the liver).<sup>[2-4]</sup> Anesthesia, surgery, fluid-electrolyte changes, hemorrhage, hypoxia, and pain can affect the neuro-immuno-endocrine systems. However, anesthetic agents, anesthesia type, and anesthesia duration influence this response.<sup>[5]</sup> Stress response to surgical trauma includes activation of the hypothalamic pituitary adrenal axis and release of inflammatory cytokines. Inflammatory cytokines, particularly interleukin-6 (IL-6) and IL-8, play an important role in this response.<sup>[6,7]</sup> Within 30–60 min after the start of surgery, IL-6 concentration increases and the change in concentration becomes significant after 2–4 h. Cytokine production reflects the degree of tissue trauma; thus, cytokine release is lowest with less invasive and traumatic procedures, for example, laparoscopic surgery. After surgery, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively. IL-8, release and activity is similar to IL-6. It does not provide hemodynamic instability, but it is a potent activator of neutrophils. IL-10 inhibits the release of IL-1 and tumor necrosis factor- $\alpha$  from the macrophages and monocytes. Inflammatory cytokines, IL-6, IL-8, and granulocyte-colony stimulating factor have been reported to be up-regulated after major abdominal surgery and during surgery.<sup>[6,7]</sup> We hypothesized that providing efficient analgesia in combination with general anesthesia could dampen stress response to surgical trauma and cause milder activation of the hypothalamic pituitary adrenal axis and release of inflammatory cytokines. To test this hypothesis, we investigated the effect of the combination of general anesthesia and thoracic epidural analgesia (TEA) on cytokine reaction, hemodynamic changes, and Visual Analog Scale (VAS) scores in patients undergoing laparoscopic cholecystectomy.

## Materials and Methods

The protocol of this study was approved by the Ethical Committee FUMF of Firat University (Ethical Committee

FUMF-06/06), Elazig, Turkey. Sixty adult patients scheduled for elective laparoscopic cholecystectomy (American Society of Anesthesiologists physical status I, II, and III) agreed to be included in this study. Patients who had coronary or peripheral artery disease, renal or hepatic failure, insulin-dependent diabetes mellitus, allergy to local anesthetics or opioids, active infection, thoracic vertebra anomaly, and abnormal coagulation test results were excluded from the study.

All patients received 0.5 mg atropine and 2.5 mg midazolam intramuscularly 45 min before the induction of anesthesia. Routine vital parameters (electrocardiogram, pulse oximetry, and noninvasive blood pressure) were monitored in the operating room. A 20 G of epidural catheter was inserted under local analgesia (2 ml of 2% lidocaine) at T9–10, immediately before the induction of general anesthesia. The position of the epidural catheter was tested with 3 ml of 2% lidocaine.

The patients were randomly assigned to one of four treatment groups [Table 1]. Patients in Group S ( $n = 15$ ) received 6–8 ml of 0.9% saline via the epidural catheter, patients in Group F ( $n = 15$ ) received 6–8 ml of 0.9% saline and 0.05 mg fentanyl via the epidural catheter, patients in Group B ( $n = 15$ ) received 6–8 ml of 0.25% bupivacaine and 0.05 mg fentanyl via the epidural catheter, and patients in Group L ( $n = 15$ ) received 6–8 ml of 0.25% levobupivacaine and 0.05 mg fentanyl via the epidural catheter for bolus doses, respectively. To achieve standardization with the control group, Group S; epidural bolus was administered and 15 min after confirming the establishment of sensory block at the level of T6 general anesthesia was induced in the study groups. Cases with inadequate block were excluded from the study. The success rate of epidural anesthesia was 80%. After confirming upper sensory block up to the T6 level, all study patients received 3–6 mg/kg of thiopental sodium followed by 0.1 mg/kg of intravenous (IV) vecuronium and 0.01 mg/kg fentanyl. They were intubated, and anesthesia was maintained with 5–6% desflurane in 50% oxygen and 50% air. Intraabdominal CO<sub>2</sub> pressure was kept between 12 and 15 mmHg and was not exceeded 15 mmHg during the surgery. Intraoperative muscle relaxation was facilitated by vecuronium.

Combined epidural analgesia was also performed with continuous infusions of 0.9% saline at a rate of 0.1 ml/kg/h in Group S, 0.9% saline and 0.05 mg fentanyl at a rate of 0.1 ml/kg/h in Group F, 0.125% bupivacaine and 0.05 mg fentanyl at a rate of 0.1 ml/kg/h in Group B, and 0.125% levobupivacaine and 0.05 mg fentanyl at a rate of 0.1 ml/kg/h in Group L. The infusions were maintained throughout the surgical procedure. Mean arterial pressures (MAP), heart rate (HR), and peripheral oxygen saturation (SpO<sub>2</sub>) values were recorded before and after epidural catheterization, before and after induction,

after intubation, after skin incision, 15 and 30 min and 1 and 2 h to the operation, and after extubation. At the end of the surgery, epidural catheter infusion was stopped. The inhaled anesthetic agents were discontinued, and neostigmine 0.05 mg/kg and atropine 0.015 mg/kg IV were administered to reverse residual neuromuscular blockade. HR, MAP, and VAS were recorded 15 and 30 min in the postanesthesia recovery unit and then 1, 2, 4, 6, 12, 24, and 48 h after the completion of surgery. To ensure standardization, IV 50 mg tramadol was administered to all cases 12 h postoperatively. No additional analgesic was needed in any of the cases during this period. Blood samples were obtained before the surgery and after the operation at 2<sup>nd</sup>, 4<sup>th</sup>, and 24<sup>th</sup> h. Blood was collected into EDTA tubes and centrifuged at 3000 rpm for 5 min at 4°C immediately after sampling. Thereafter, plasma was stored at - 80°C until assayed. Plasma concentrations of IL-6, IL-8, and IL-10 were measured with commercially quantitative sandwich ELISA kits.

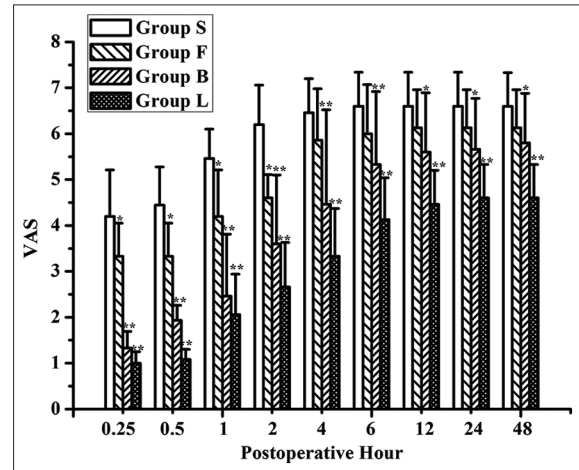
**Statistical analysis**

All values were illustrated as a mean ± standard deviation. A Shapiro–Wilk test was used to verify the normality of distribution of variables. Differences between the saline and drug groups (fentanyl, bupivacaine, and levobupivacaine) in terms of some demographic characteristics (age, weight, duration of anesthesia, and duration of operation), cytokine levels (IL-6, IL-8, and IL-10), and VAS pain scores were determined and analyzed by Kruskal–Wallis one-way analysis of variance (ANOVA) followed by a pairwise comparison between saline and each drug-treated group using a Turkey’s honest significant difference test. Time-dependent effects of cytokine levels (IL-6, IL-8, and IL-10) were evaluated using two-way repeated measures ANOVA followed by the Student–Newman–Keuls multiple range test as a *post-hoc* test. For all analyses, *P* < 0.05 was accepted as evidence of significance.

**Results**

The groups were similar with respect to preoperative HR, MAP, and SpO<sub>2</sub> and postoperative HR and MAP. VAS pain scores at 15 min after surgery were significantly

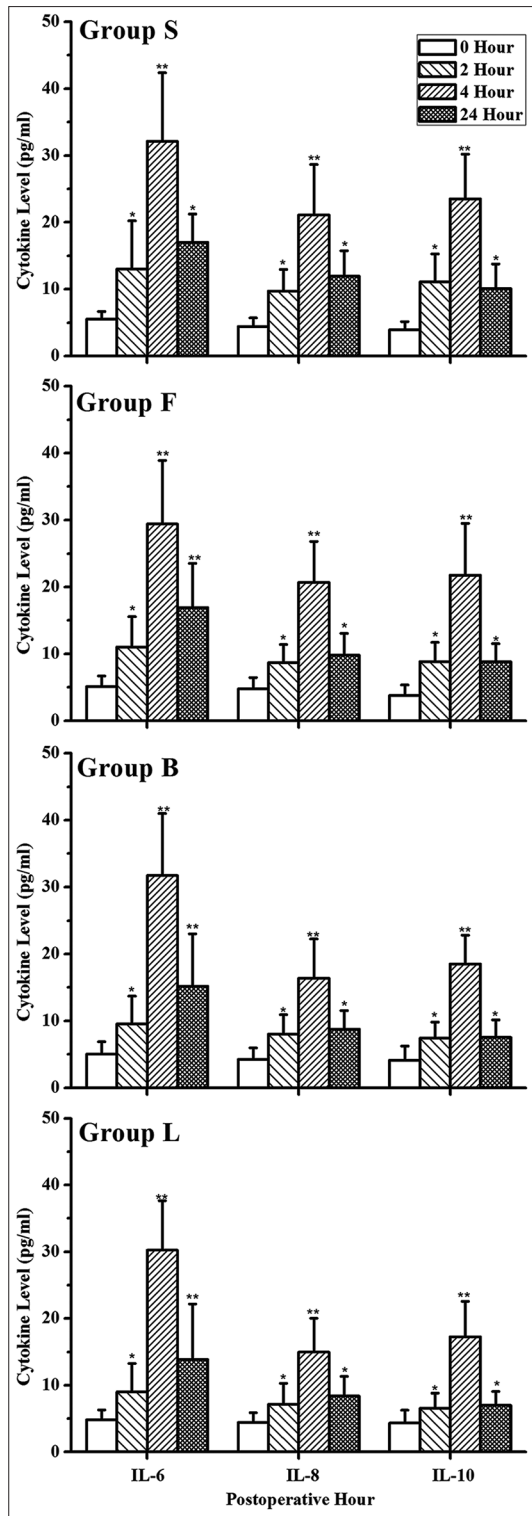
lower in Groups B and L compared to Group S (*P* < 0.01, Figure 1). Although not statistically significant, the VAS score of the Groups B and L was lower than the Group F. Similarly, VAS pain scores at 30 min, 1 h, and 2 h after surgery were significantly lower in Groups F, B, and L compared to Group S (*P* < 0.01, Figure 1). VAS pain scores at 4 h, 6 h, 12 h, 24 h, and 48 h after surgery were significantly lower in Groups B and L compared to Group S (*P* < 0.05, *P* < 0.01, Figure 1). When compared to Group F, although not significant, VAS scores of Groups B and L were lower. [Figure 2] presents increased levels of IL-6, IL-8, and IL-10 when compared to their respective preoperative levels (postoperative 2<sup>nd</sup> h, 4<sup>th</sup> h, and 24<sup>th</sup> h). The saline group showed the largest increase in the levels of IL-6, IL-8, and IL-10. IL-6, IL-8, and IL-10 levels were measured before the operation, 2 h after the start of the operation, and 4 h and 24 h after surgery. Preoperative levels being similar, the cytokine levels increased at 2 h and peaked at 4 h, returning to preoperative levels 24 h after the surgery in all groups. The results revealed no statistically significant difference between saline group and other groups in IL-6 levels. However, at 4 h and 24 h, IL-8 levels were significantly lower in levobupivacaine group compared to saline group (*P* < 0.05, *P* < 0.01, Figure 3). IL-10 levels at 2 h, 4 h, and 24 h were significantly lower



**Figure 1:** Visual Analogue Scale pain scores (\**P* < 0.05 compared with Group S, \*\**P* < 0.01 compared with Group S). S = Saline; F = Fentanyl; B = Bupivacaine; L = levobupivacaine

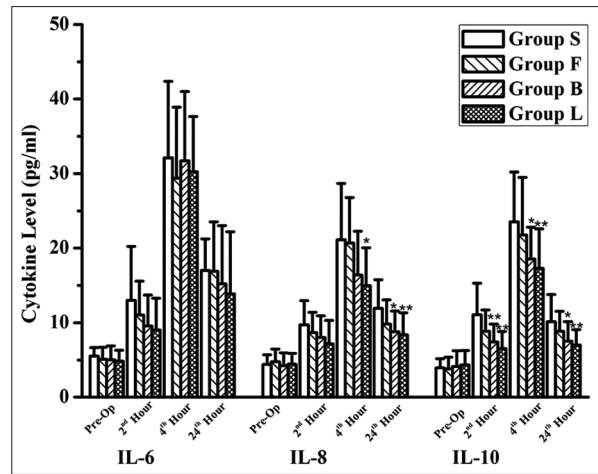
	Group S (n=15)	Group F (n=15)	Group B (n=15)	Group L (n=15)
Gender (female/male)	8/7	8/7	9/6	8/7
Age (years)	53.77±12.25	52.75±11.82	55.22±12.61	54.55±11.16
Weight (kg)	72.11±13.36	70.23±15.81	74.24±10.36	72.11±13.36
ASA (I/II/III)	12/3/0	9/5/1	10/4/1	10/5/0
Duration of operation (min)	75.68±12.31	77.27±14.12	76.84±15.11	70.55±14.76
Duration of anesthesia (min)	97.67±12.65	101.33±13.38	103.41±17.36	96.49±11.37

S=Saline; F=Fentanyl; B=Bupivacaine; L=levobupivacaine; ASA=American Society of Anesthesiologists



**Figure 2:** Time-dependent change of interleukin-6, -8 and -10 levels (\* $P < 0.01$  compared with preoperative values, \*\* $P < 0.001$  compared with preoperative values). S = Saline; F = Fentanyl; B = Bupivacaine; L = levobupivacaine

in bupivacaine and levobupivacaine groups compared to saline group ( $P < 0.05$ ,  $P < 0.01$ , respectively) [Figure 3].



**Figure 3:** Mean plasma concentrations of interleukin-6, -8, and -10 concentrations in all groups (\* $P < 0.05$  compared with Group S, \*\* $P < 0.01$  compared with Group S). S = Saline; F = Fentanyl; B = Bupivacaine; L = levobupivacaine

### Discussion

By aiming to investigate the effects of combination of general anesthesia and TEA on cytokine reaction in patients undergoing laparoscopic cholecystectomy we found that patients who received 6–8 ml of 0.25% levobupivacaine and 0.05 mg fentanyl via the epidural catheter (Group L) had lower postoperative VAS score compared to the other groups ( $P < 0.01$ ). IL-6, IL-8, and IL-10 levels started to increase at 2 h and returned to the basal level at 24 h in all groups. IL levels increased in the epidural saline-administered group compared to other groups ( $P < 0.05$ ).

Laparoscopic cholecystectomy has now become the standard procedure for the surgical treatment of symptomatic gallstone patients. This procedure has some advantages such as minimum incision, less blood loss, and shorter hospital stay. However, pneumoperitoneum causes hemodynamic changes such as an increase in MAP and systemic vascular resistance and a decrease in cardiac output.<sup>[8,9]</sup> Factors such as anesthesia, surgery, fluid-electrolyte changes, hemorrhage, hypoxia, and pain cause different responses in the neuro-immuno-endocrine systems. However, anesthetic agents, anesthesia type, and anesthesia duration influence this response.<sup>[5]</sup> Local and systemic inflammatory response during and after surgery is associated with the development of postoperative complications and recovery after surgery. Epidural analgesia that blocks sympathetic and somatic afferent and efferent pathways is known to suppress the activation of the neuroendocrine system.<sup>[10,11]</sup> Hemodynamic effects of the neuraxial blockade are dependent on some factors such as sympathetic blockade level, age of the patient, hydration status, and cardiac diseases, among others. One of the important effects of the sympathetic block



is on the cardiovascular system. Total peripheral resistance and arterial pressure also decrease due to the dilated arteries and arterioles in the sympathetic denervation region.<sup>[12-14]</sup> Casati *et al.*<sup>[15]</sup> scheduled 60 patients for colon resection. They were randomly distributed into six groups that received an epidural (T9–10) bolus (8 mL) followed by an infusion (8 mL/h) of saline, or bupivacaine 0.0625% plus fentanyl 2 µg/mL, or bupivacaine 0.125% plus fentanyl 2 µg/mL before the induction of anesthesia. They monitored the mean arterial blood pressure, the amount of thiopental used for induction, and the total amount of intraoperative isoflurane used. They showed that the use of epidural bupivacaine reduced intraoperative isoflurane use by 35% without changing the dose of thiopental used for induction. Patients receiving 0.125% bupivacaine showed lower MAP values compared with epidural saline-treated groups and 0.0625% bupivacaine-treated groups. Changes in MAP reflect a neuroendocrine response to pain. In parallel to this study, to achieve standardization between the study groups and the saline group, general anesthesia was induced 15 min after epidural (T9–10) administration of bolus dose, MAP values did not differ between the groups in our study, and we did not record the total dose of intraoperative desflurane used but used 5–6% of this agent in all cases. Kopacz *et al.*<sup>[16]</sup> studied the effectiveness of patient-controlled epidural analgesia with either levobupivacaine 0.125% or fentanyl 4 µg/mL alone or a combination of levobupivacaine and fentanyl in 65 patients after total joint arthroplasty. They found no significant difference between levobupivacaine and fentanyl groups in the incidence of postoperative hypotension, HR, and MAP values.

Pain, as well as intraoperative surgical stress, leads to an autonomic response that markedly increases adrenergic nerve activity and plasma catecholamine concentrations. Some consequences are peripheral vasoconstriction, reduced perfusion, and decreased tissue oxygen partial pressure with subsequent hypoxia of the tissue.<sup>[17]</sup> Thoracic epidural anesthesia blunted the decrease of SpO<sub>2</sub> tension caused by surgical stress and adrenergic vasoconstriction during major abdominal surgery in the unblocked area. This suggested that supplemental thoracic epidural anesthesia might be beneficial in improving peripheral oxygenation during prolonged abdominal surgery.<sup>[18]</sup> In this study, we found no statistically significant difference in SpO<sub>2</sub> between the groups. TEA combined with general anesthesia is useful in stabilizing hemodynamic parameters intraoperative and reducing the consumption of opioids and anesthesia agents, especially among candidates for major abdominal surgery. It has also positive effects on early recovery criteria, lowers side effects, and enhances early mobilization.<sup>[19]</sup> TEA reduce endocrine and metabolic stress response, as well as opioid dose, accelerating the return of bowel function and dietary intake, providing better pain relief, and early mobilization.<sup>[20]</sup> In our study, hemodynamic data were evaluated for the first 48 h after induction of

anesthesia. We found no statistically significant difference between groups on HR, MAP, and SpO<sub>2</sub> values. Preemptive analgesia and provision of postoperative hemodynamic stabilization suppressed the endocrine and metabolic stress response. Epidural analgesia with a bupivacaine/fentanyl combination provided a statistically and clinically significant improvement in postoperative pain control compared with IV analgesia during the first 24 h following laparoscopic cholecystectomy.<sup>[21]</sup> Badner *et al.*<sup>[22]</sup> demonstrated that the addition of 0.125% and 0.25% bupivacaine to continuous postoperative epidural infusions of fentanyl in a 10 µg/ml concentration in 39 patients following abdominal or thoracic surgery. There was a difference among the three groups in analgesia (means VAS scores) over time, with the fentanyl-alone group producing less analgesia compared to the 0.125% bupivacaine group. No difference between bupivacaine groups was found. In parallel to this, in our study postoperative VAS scores of patients who received fentanyl infusion alone as intraoperative epidural analgesia scored lower than the control group but higher than those who received bupivacaine and levobupivacaine though this was not statistically significant.

Thoracic epidural anesthesia–analgesia compared with morphine patient-controlled analgesia for pain relief after laparoscopic colectomy, and TEA significantly improved better and early analgesia following laparoscopic colectomy but did not affect the length of hospital stay.<sup>[23]</sup> In the latest study, epidural infusion of bupivacaine was initiated before surgical incision and continuously infused through the postoperative period. In our study, epidural infusion of bupivacaine was started before surgical incision but stopped as the operation ended. It was shown that, intraoperatively infused epidural bupivacaine and levobupivacaine provided postoperative analgesia. In our study, VAS pain scores were significantly lower in levobupivacaine group compared with other groups after surgery ( $P < 0.01$ ). Similarly, VAS pain scores were significantly lower in the bupivacaine group although these values were significantly higher compared to those of levobupivacaine. However, VAS pain scores at 30 min, 1 h, and 2 h after surgery were significantly lower in fentanyl group compared to saline group ( $P < 0.01$ ). We suggested that local anesthetics and fentanyl provide better pain control in epidural analgesia. Postoperative or posttraumatic cytokine response depends on the degree of tissue damage. Epidural anesthesia is associated with less postoperative complication and causes lower cytokine response.<sup>[24]</sup> Regional anesthesia causes a reduction in the level of monocyte stimulator factor and leads to reduced plasma cytokine response.<sup>[25]</sup> Regardless of the methods of anesthesia, level of IL-6 depends on the duration of the surgical procedure.<sup>[26]</sup> Serum IL-6 level is an early marker of tissue damage after operations, and its levels tend to be high with major surgery.<sup>[24]</sup> However, IL-6 levels return to preoperative value 24–36 h postoperatively due to their decreased production. The effects of TEA and lidocaine

(IV) on cytokines, pain, and bowel function after colonic surgery were compared, and IL-6 levels are detectable in the circulation at 60 min after injury, peak at between 4 and 6 h, and return to baseline 24 h after operation.<sup>[27]</sup> In agreement with this study, IL-6 levels started to rise at 2 h peaking at 4 h and started to decrease at 24 h. Kato *et al.*<sup>[28]</sup> evaluated the influence of major abdominal surgery on the plasma levels of inflammatory cytokines, giving all patients combined general-epidural anesthesia. They reported that the plasma levels of IL-6 and IL-8 increased gradually after skin incision and reached the maximal value at the end of surgery. However, this high level of IL-6 remained 3 days after surgery. In our study, we evaluated the cytokine levels for 24 h after surgery, and we have detected that IL-6 and IL-8 levels almost returned to baseline 24 h after the surgery in all groups but these levels were higher than preoperative levels. IL-10 might control the production of inflammatory cytokines, thereby modulating the inflammatory responses in the perioperative period.<sup>[29]</sup> Innate immune system was suppressed from the early period of upper abdominal surgery. The plasma IL-10 concentration increased significantly 2 h after the start of surgery and peaked at the end of the operation.<sup>[30]</sup> Kato *et al.*<sup>[29]</sup> determined the IL-10 levels in preanesthesia, 0, 2, and 4 h during surgery, and the end of surgery, and 1 and 3 days postoperatively among patients who received combined general-epidural anesthesia for upper abdominal surgery. The plasma levels of IL-10 showed significant elevations and achieved maximal value 4 h after the skin incision. IL-10 levels returned to preanesthesia levels 3 days postoperatively. In our study, IL-10 levels increased at 2 h and peaked at 4 h, returning to baseline 24 h after the surgery in all groups. IL-10 is an anti-inflammatory cytokine that might control the production of inflammatory cytokines. The plasma levels of anti-inflammatory cytokine IL-10, as well as IL-6 and IL-8 decreased at the end of the surgical stress. We noted that by stopping epidural infusion at the end of the surgery, postoperative pain control became inadequate. IL-6, IL-8, and IL-10 levels were measured before the operation, 2 h into the operation, and 4 h and 24 h after the surgery in all groups. Cytokine levels increased at 2 h and almost returned to baseline 24 h after the surgery in all groups but these levels were still higher than preoperative levels. Cytokine levels were higher in saline groups compared to the other groups. We have demonstrated that general anesthesia combined with epidural analgesia suppresses the stress response, but this effect is more pronounced with a combination of local anesthetics and opioids.

## Conclusion

General anesthesia together with the thoracic epidural anesthesia provided pain control and hemodynamic stabilization more efficiently during the first 24 h in

intraoperative and postoperative period by suppressing stress reaction.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- Lau WY, Leow CK, Li AK. History of endoscopic and laparoscopic surgery. *World J Surg* 1997;21:444-53.
- Sherigar JM, Irwin GW, Rathore MA, Khan A, Pillow K, Brown MG. Ambulatory laparoscopic cholecystectomy outcomes. *JLS* 2006;10:473-8.
- Lujan JA, Parrilla P, Robles R, Marin P, Torralba JA, Garcia-Ayllon J. Laparoscopic cholecystectomy vs. open cholecystectomy in the treatment of acute cholecystitis: A prospective study. *Arch Surg* 1998;133:173-5.
- Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 1996;82:44-51.
- Dutton RP. Haemostatic resuscitation. *Br J Anaesth* 2012;109 Suppl 1:39-46.
- Smith WB, Gamble JR, Clark-Lewis I, Vadas MA. Chemotactic desensitization of neutrophils demonstrates interleukin-8 (IL-8)-dependent and IL-8-independent mechanisms of transmigration through cytokine-activated endothelium. *Immunology* 1993;78:491-7.
- Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery* 2000;127:117-26.
- Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. *Anesth Analg* 1993;76:1067-71.
- Struthers AD, Cuschieri A. Cardiovascular consequences of laparoscopic surgery. *Lancet* 1998;352:568-70.
- Aller MA, Arias JI, Alonso-Poza A, Arias J. A review of metabolic staging in severely injured patients. *Scand J Trauma Resusc Emerg Med* 2010;18:27.
- Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995;82:1474-506.
- Holte K, Foss NB, Svensén C, Lund C, Madsen JL, Kehlet H. Epidural anesthesia, hypotension, and changes in intravascular volume. *Anesthesiology* 2004;100:281-6.
- Goy RW, Sia AT. Sensorimotor anesthesia and hypotension after subarachnoid block: Combined spinal-epidural versus single-shot spinal technique. *Anesth Analg* 2004;98:491-6.
- Mendonca C, Griffiths J, Ateleanu B, Collis RE. Hypotension following combined spinal-epidural anaesthesia for caesarean section. Left lateral position vs. tilted supine position. *Anaesthesia* 2003;58:428-31.
- Casati L, Fernández-Galinski S, Barrera E, Pol O, Puig MM. Isoflurane requirements during combined general/epidural anesthesia for major abdominal surgery. *Anesth Analg* 2002;94:1331-7.
- Kopacz DJ, Sharrock NE, Allen HW. A comparison of levobupivacaine 0.125%, fentanyl 4 microg/mL, or their combination for patient-controlled epidural analgesia after major orthopedic surgery. *Anesth Analg* 1999;89:1497-503.
- Zhang J, Zhang W, Li B. The effect of epidural anesthesia with different concentrations of ropivacaine on sevoflurane requirements. *Anesth Analg* 2007;104:984-6.
- Kabon B, Fleischmann E, Treschan T, Taguchi A, Kapral S, Kurz A. Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. *Anesth Analg* 2003;97:1812-7.
- Von Dossow V, Welte M, Zaune U, Martin E, Walter M, Rückert J, *et al.* Thoracic epidural anesthesia combined with general anesthesia: The preferred anesthetic technique for thoracic surgery. *Anesth Analg* 2001;92:848-54.
- Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: A prospective, randomized trial. *Dis Colon Rectum* 2001;44:1083-9.
- Erol DD, Yilmaz S, Polat C, Arikan Y. Efficacy of thoracic epidural analgesia for laparoscopic cholecystectomy. *Adv Ther* 2008;25:45-52.

22. Badner NH, Bhandari R, Komar WE. Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. *Can J Anaesth* 1994;41 (5 Pt 1):387-92.
23. Senagore AJ, Delaney CP, Mekhail N, Dugan A, Fazio VW. Randomized clinical trial comparing epidural anaesthesia and patient-controlled analgesia after laparoscopic segmental colectomy. *Br J Surg* 2003;90:1195-9.
24. Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, *et al.* Responses of plasma adrenocorticotrophic hormone, cortisol, and cytokines during and after upper abdominal surgery. *Anesthesiology* 1992;77:426-31.
25. Rivera-Chavez FA, Wheeler H, Lindberg G, Munford RS, O'Keefe GE. Regional and systemic cytokine responses to acute inflammation of the vermiform appendix. *Ann Surg* 2003;237:408-16.
26. Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, *et al.* Increased plasma levels of IL-6 and IL-8 are associated with surgical site infection after pancreaticoduodenectomy. *Pancreas* 2006;32:178-85.
27. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, *et al.* Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006;97:640-6.
28. Kato M, Suzuki H, Murakami M, Akama M, Matsukawa S, Hashimoto Y. Elevated plasma levels of interleukin-6, interleukin-8, and granulocyte colony-stimulating factor during and after major abdominal surgery. *J Clin Anesth* 1997;9:293-8.
29. Kato M, Honda I, Suzuki H, Murakami M, Matsukawa S, Hashimoto Y. Interleukin-10 production during and after upper abdominal surgery. *J Clin Anesth* 1998;10:184-8.
30. Kawasaki T, Ogata M, Kawasaki C, Okamoto K, Sata T. Effects of epidural anaesthesia on surgical stress-induced immunosuppression during upper abdominal surgery. *Br J Anaesth* 2007;98:196-203.