10

The Effect of General Anesthesia and General Anesthesia Plus Epidural Levobupivacaine or Bupivacaine on Hemodynami Stress Response and Postoperative Pain

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1. Introduction

Levobupivacaine, a new long-acting local anesthetic, is reported to achieve an effective and safe epidural anesthesia, similar to the anesthesia achieved by bupivacaine. Levobupivacaine with a pharmacological structure similar to that of bupivacaine was shown to have a wider confidence interval, and less neurotoxic and cardiotoxic effects.

A large number of trials have been conducted on determining the anesthetic methods that decrease the stress response of major surgery. These trials usually compared the effects of general, epidural and general + epidural anesthetic methods on the stress response occurring in major surgery with respect to mortality and morbidity. While some authors recommended general + epidural anesthesia, some only recommended the general anesthesia.

A combination of epidural and general anesthesia is reported to reduce the requirement for analgesic and anesthetic agents. Intraoperative hemodynamic stability can be better achieved and the metabolic, endocrine and immunologic responses better suppressed. Management of these responses is important in reducing postoperative morbidity and mortality. With the combination of epidural and general anesthesia, recovery is faster, a higher anesthetic quality can be achieved and patients can be mobilized earlier (1-4). There are no adequate trials on the novel agent, levobupivacaine.

This trial was designed to compare the epidural bupivacaine or levobupivacaine combined with general anesthesia and general anesthesia alone in patients who will undergo TAH-BSO, with respect to stress response to surgery, intraoperative hemodynamics, requirement for peroperative anesthetics and analgesic agents, the quality of the postoperative analgesia, recovery from anesthesia and postoperative side effects.

2. Methods

This trial included 54 ASA I-II group patients in the age range of 18-65 who were scheduled to undergo TAH-BSO and who gave written consent to participate in the trial. Those with

severe cardiac, pulmonary, hepatic diseases, renal failure, hemorrhagic diathesis, fever, infection and those with known hypersensitivity to investigational drugs were excluded from the trial. Non-premedicated cases were randomly assigned to three groups: general anesthesia + epidural bupivacaine (Group I, n=18), general anesthesia + epidural levobupivacaine (Group II, n=18) and general anesthesia (Group III, n=18). All the patients were monitored for EKG, non-invasive blood pressure, peripheral oxygen saturation (SpO_2), end-tidal carbon dioxide pressure ($EtCO_2$) and body temperature.

In Groups I and II, the epidural space was entered by a 16-gauge Tuohy epidural needle before the surgery using the loss of resistance method through the L3-L4 space while the patient was in the sitting position and an 18-gauge epidural catheter was inserted (Perifix, Braun, Germany). As a test dose, 2 ml of 2% lidocaine (Aritmal Ampul® Osel) was administered; five minutes later, Group I and Group II were administered 5 ml of 0.25% bupivacaine (Marcaine flacon® Eczacıbaşı, Turkey) and 0.25% levobupivacaine (Chirocaine flacon® Abbott, USA) respectively via epidural catheter, followed by administration of 10 ml of 0.25% bupivacaine to Group I and 10 ml of 0.25% levobupivacaine to Group II via epidural catheter five minutes later. The sensory block upper level, time to achieve sensory block at T6 dermatome and the Bromage Scale values were assessed.

Anesthetic induction was achieved in all patients (when reached the sensorial block level dermatome of T6 in Group I and Group II) by 2 mg kg^{-1} propofol (Propofol ampul® Fresenius Kabi) and 1 µg kg^{-1} remifentanil (Ultiva® Glaxo Wellcome) administered in 60 seconds. 0.6 mg kg^{-1} rocuronium (Esmeron® Organon) was used for achieving neuromuscular block. For all three groups, the maintenance of anesthesia was achieved using 1% sevoflurane (Sevorane® Abbott, USA) in 50% O_2-air mixture and 0.1 µg kg^{-1} min^{-1} remifentanil infusion (Perfusor Compact-Braun). Regarding the patients who would require an anesthesia duration of more than two hours, Group I was scheduled to receive an additional 5 ml of 0.25% bupivacaine and Group II was scheduled to receive an additional 5 ml of 0.25% levobupivacaine from the epidural catheter.

When the heart beat rate (HBR) and the mean blood pressure (MBP) was reduced by 20% of the control value, the concentration of the inhalation agent was reduced by 50%. 250 ml of ringer lactate solution was rapidly administered. In case of absence of improvement, the dose of remifentanil was decreased by 50%. If the low level persisted, atropine or ephedrine was administered as required. When the HBR and MBP increased by more than 20% of the control value, the concentration of the inhalation agent was increased by 50%. In the case of persistence of the high level, the dose of remifentanil was increased by 50%. For maintenance of the neuromuscular blockage, 0.15 mg kg^{-1} rocuronium iv was administered, where necessary.

The hemodynamic parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP), MBP, HBR, and SpO_2 were recorded 2 and 5 minutes after the intubation, 2, 5, 10, 15, 30, 45, 60, 90 and 120 minutes after the skin incision and after the extubation. For measuring the glucose, cortisol, insulin and CRP levels, preoperative venous access was achieved followed by blood sampling in the first and 24^{th} hours of operation. The glucose, glucose oxidase, cortisol and insulin values were measured by chemiluminescent immunoassay, CRP, and the immunoturbidimetric methods.

The postoperative recovery was evaluated by the spontaneous breathing time, extubation time, eye opening time and the time to reach an Aldrete recovery score of ≥9. Data were recorded on the amount of sevoflurane used (ml) (Datex Ohmeda, S5. Sweden), the total dose of remifentanil (mg), whether muscle relaxant was added and whether atropine or

ephedrine were required. Pain intensity was evaluated by the visual analogue scale (VAS) and the motor block was assessed by the Bromage scale; the hemodynamic data and the side effects (hypotension, respiratory depression, motor block, nausea-vomiting, itching, tremor) were recorded at 0 and 30 minutes, and 2, 6, 12 and 24 hours after the operation.

To relieve the postoperative pain, Group III was administered iv morphine and PCA at a concentration of 1 mg ml^{-1} concentration with a loading dose of 1 mg and a lock-out period of 6 minutes. In Group I, 0.125% bupivacaine + 0.025 mg ml^{-1} morphine, in Group II, 0.125% levobupivacaine + 0.025 mg ml^{-1} morphine and 5 ml of h^{-1} basal infusion were prepared for PCA with a 1 ml loading and a lock-out period of 20 minutes and PCA administration was initiated in the recovery room. The total amount of anesthetics used and the administered and requested amounts were recorded.

Statistical analysis were performed using the SPSS 12.0 software. The data were summarized as mean ± standard deviation and percentage. Comparisons between the three groups were assessed by one way variance analysis (Anova) in cases where the parametric conditions could be met and by Kruskal Wallis variance analysis in non-parametric conditions. In the three-group comparisons, post-hoc Tukey-HSD test and Bonferroni correction Mann-Whitney U test were used for significantly differing parameters. The comparison between the two groups was made with a t test. The chi-square test was used for comparing categorical data. Variance analysis was used to analysis the parametric data and Wilcoxon Signed Ranks test Bonferroni correction was used to analyze the non-parametric data for the analysis of the repeated measurements. The level of significance was set at $p<0.05$.

3. Results

The groups showed similarity in the mean values for age, weight, height, the ASA score and the duration of surgery ($p>0.05$) (Table 1).

	GROUP I	GROUP II	GROUP III	P
Age (year)	46.55 ± 4.97	47.53 ± 6.87	48.44 ± 8.75	0.246
Weight (kg)	70.88 ± 8.58	75.50 ± 15.27	79.55 ± 8.05	0.075
Hight (cm)	160.55 ± 5.29	162.16 ± 5.95	160.27 ± 4.61	0.520
Surgery time (min)	74.88 ± 18.31	72.83 ± 20.47	80.94 ± 13.35	0.365
ASA I / II	11 / 7	13 / 5	10 / 8	0.574

Table 1. Patient characteristics (Mean ± SD)

Time to achieve sensory block at T6 dermatome was 18.72±4.41 and 21.27±4.48 in Group I and Group II, respectively; the sensory block upper levels were 5.66±0.68 and 5.88±0.32 dermatome, respectively ($p>0.05$). The pre-operative Bromage scores were 0 in Group I and II ($p>0.05$).

The total doses of the intra-operatively administered remifentanil and sevoflurane were similar between Group I and Group II, however, statistically higher in Group III ($p<0.000$) (Table 2). While there was no statistically significant difference between Group I and Group II in the postoperative recovery evaluated by spontaneous respiratory time, extubation time, eye opening time and the time to reach an Aldrete recovery score of ≥9, Group III had a significantly longer recovery time compared to Groups I and II ($p<0.000$) (Table 2).

	GROUP I	GROUP II	GROUP III	P
Remifentanil (mg)	0.78 ± 0.38	0.77 ± 0.27	1.24 ± 0.38 *	0.000
Sevoflurane (ml)	21.38 ± 7.63	21.94 ± 8.93	44.44 ± 14.84 *	0.000
Spontaneous breathing time (min)	4.58 ± 2.46	4.11 ± 1.17	7.58 ± 2.68 *	0.000
Extubation time (min)	5.19 ± 2.81	4.27 ± 1.14	8.36 ± 2.66 *	0.000
Eye opening time (min)	6.36 ± 3.27	5.16 ± 1.79	9.80 ± 3.79 *	0.000
Time to Aldrete Score ≥9 (min)	7.91 ± 3,19	7.75 ± 2.49	13.11 ± 3.67 *	0.000

* p< 0.05 Compared with Group I and Group II
(Mean ± SD)

Table 2. Mean doses of drugs used in the operation and recovery times.

There was no statistically significant difference between the groups with respect to requirement for atropine and ephedrine ($p>0.05$). One, two and nine patients received additional muscle relaxant administration in Group I, II and III respectively. There was a statistically significant difference between the groups with respect to the requirement of muscle relaxant ($p=0.002$), which was higher in Group III relative to Groups I and II.

Regarding the MBP values, Group III had the highest values at 5, 10, 15, 30, 45 and 60 minutes of incision and after extubation ($p<0.05$).

The intra-group MBP values showed significant reductions relative to the control values during induction, 2, 5 minutes after intubation and 2, 5, 10, 15, 30, 45, 60 and 90 minutes after the surgical incision in Group 1; during induction, five minutes after the intubation, and 2, 5, 10, 15, 30, 45 and 60 minutes after the surgical incision in Group II; and during induction, 2, 5 minutes after the intubation and 2, 30 and 45 minutes after the surgical incision in Group 3 ($p<0.05$). While there was no statistically significant difference between the post-extubation MBP values and the control MBP values in Groups I and II ($p>0.05$), Group III exhibited a significant increase relative to the control value in Group III ($p<0.013$).

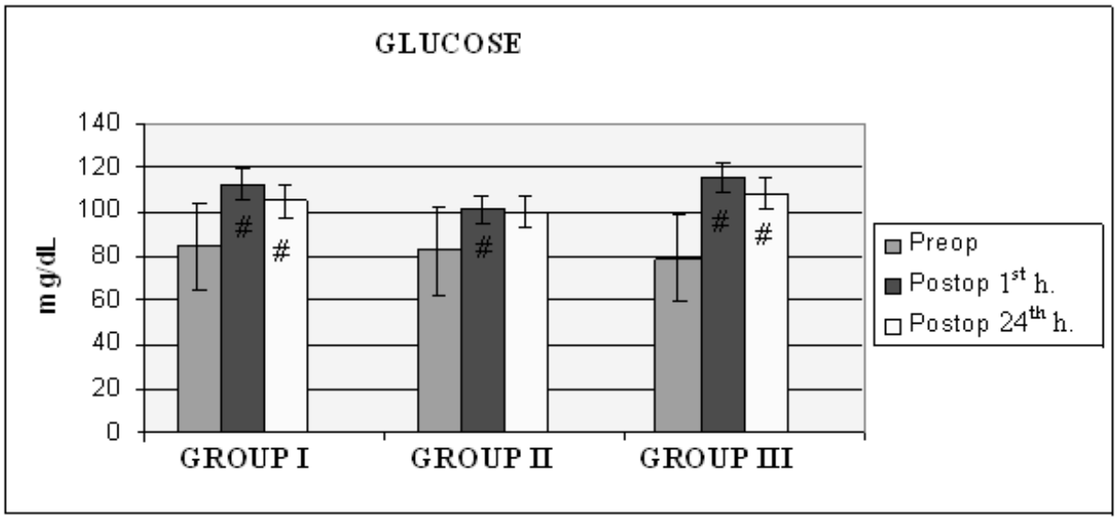
The HBR values were lower in Group III compared to Groups I and II in the 2^{nd} and 5^{th} minutes of intubation ($p<0.05$).

The intra-group HBR values showed significant reductions relative to the control values during induction, and 2, 5, 10, 15, 30, 45 and 60 minutes after the surgical incision in Group I; during induction, and 10, 15, 30, 45 and 60 minutes after the surgical incision in Group II; and during induction, five minutes after intubation, and 2, 5, 10, 45 and 60 minutes after the surgical incision in Group III ($p<0.05$).

Since the duration of surgery was below 100 minutes in all patients, there was no requirement for additional epidural local anesthetic administration and the follow-ups at 120 minutes could not be conducted (Table 1).

The mean control values for the parameters used to assess the response to surgical stress including glucose, insulin, cortisol and the CRP values were statistically similar between the three groups ($p>0.05$).

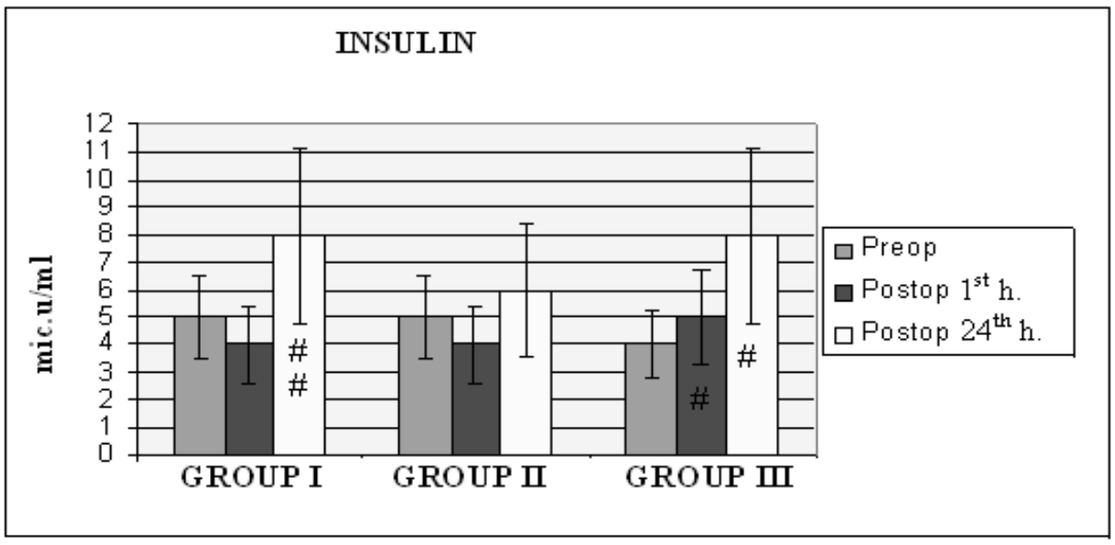
While the postoperative glucose values in the first and 24^{th} hours were not significantly different, they were higher in Group III relative to Groups I and II ($p>0.05$). Regarding the intra-group comparison, the glucose values exhibited a significant increase relative to the control values one hour after the operation in all groups, and 24 hours after the operation in Groups I and III ($p<0.05$) (Figure 1).



Compared with the control values (p<0.05)

Fig. 1. Changes in Glucose values when compared to Groups

There was no statistically significant difference between the groups in the 1st and 24th hour measurements of the insulin values (p>0.05). In Group I, the postoperative 1st and 24th hour values were different and the 24th hour values were higher (p<0.05). In Group III, the postoperative values in the first and 24th hours were higher than the control values (p<0.05) (Figure 2).

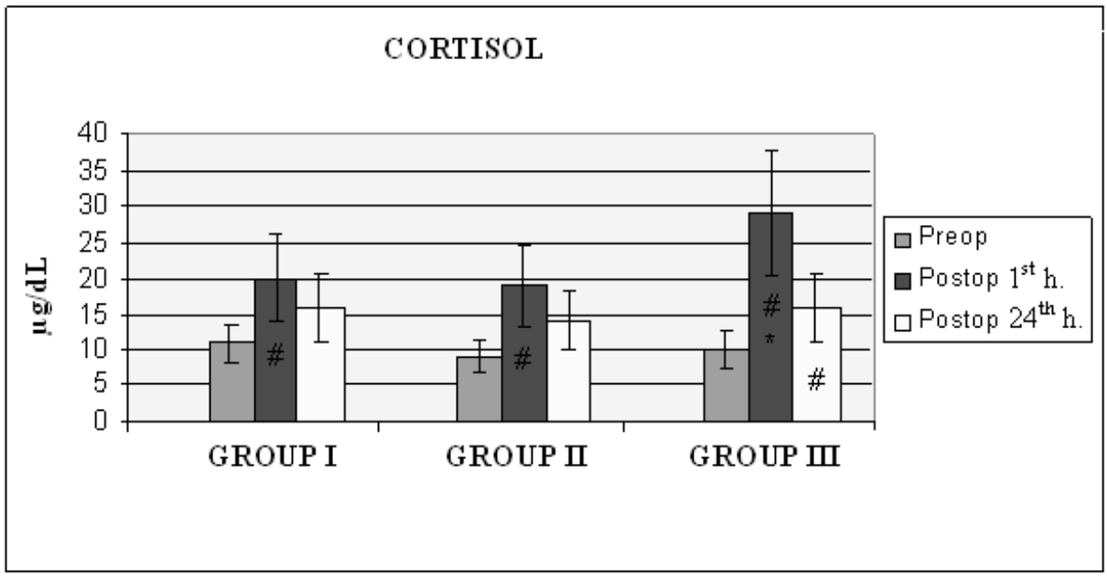


Compared with the control values (p<0.05)
Compared in Group I post op. 1th and 24th hours values (p<0.05).

Fig. 2. Changes in Insulin values when compared to Groups

The postoperative cortisol values at 1 hour differed between the groups and were highest in Group III (p<0.05). The intra-group comparison of the cortisol values revealed higher measurements one hour after the operation relative to the control values (p<0.05). The 24th

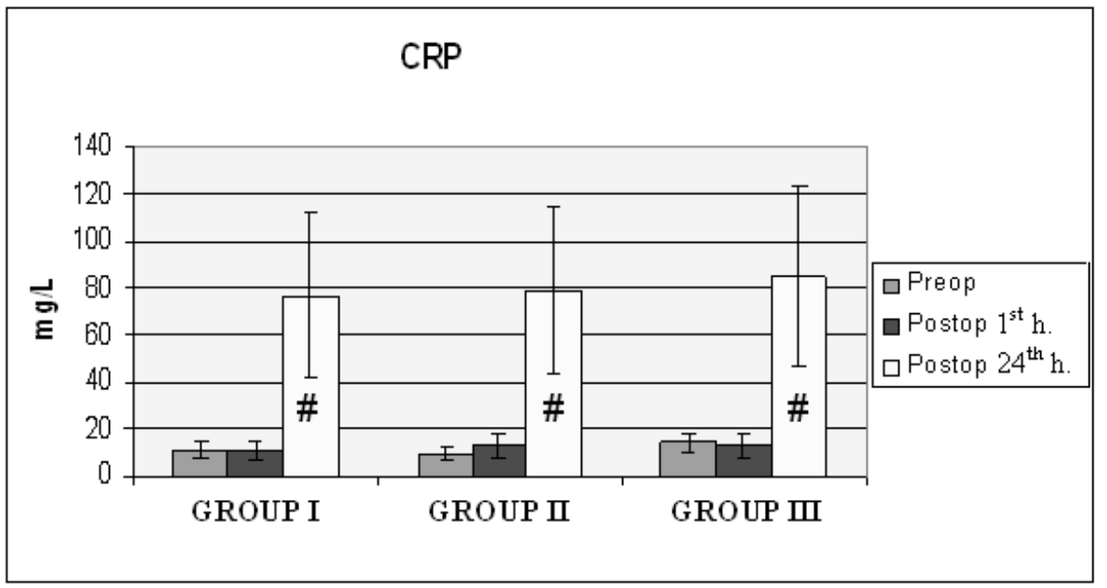
hour postoperative cortisol values were higher than the control value only in Group III ($p<0.05$) (Figure 3).



* Compared with the Groups ($p<0.05$)
# Compared with the control values ($p<0.05$).

Fig. 3. Changes in Cortisol values when compared to Groups

There was no difference between the groups in the CRP values. The intra-group comparison of the CRP values showed higher postoperative 24th hour values relative to the control values and the postoperative 1st hour values in all groups ($p<0.05$) (Figure 4).



Compared with the control values ($p<0.05$)

Fig. 4. Changes in CRP values when compared to Groups

The comparison of the postoperative pain scores between the groups demonstrated the highest VAS value at minute 0 in Group III ($p<0.000$). Regarding the other measurement times, no significant difference was detected between the groups ($p>0.05$) (Table 3).

	GROUP I	GROUP II	GROUP III	P
Postop 0th min.	0.38 ± 1.14	1.33 ± 2.02	5.88 ± 1.99 *	0.000
Postop 30th min.	4.77 ± 1.95 #	4.50 ± 2.22 #	5.83 ± 1.75	0.172
Postop 2nd h	3.77 ± 2.21 #	3.22 ± 2.43	2.55 ± 1.72 #	0.388
Postop 6th h	2.11 ± 2.13	1.33 ± 1.74	1.33 ± 1.13 #	0.465
Postop 12th h	0.38 ± 0.69	0.50 ± 1.42	0.77 ± 1.16 #	0.325
Postop 24th h	0.25 ± 0.23	0.27 ± 0.75	0.33 ± 0.76 #	0.355
P	<0.05	<0.05	<0.05	

*Comparisons between-groups ($p<0.05$)
Comparison intra-groups ($p<0.05$).

Table 3. VAS values (Mean ± SD)

The comparison of the postoperative hemodynamic data revealed the highest MBP at minute 0 in Group III ($p<0.002$). None of the three groups exhibited postoperative hypotension or respiratory depression. Regarding the motor block, there was no significant difference between Groups I and II with respect to nausea-vomiting, itching, or tremor ($p>0.05$).

4. Discussion

In this trial investigating the extent of suppression of the stress response to surgery in patients undergoing general anesthesia + epidural anesthesia achieved with two different local anesthetics relative to the patients only receiving general anesthesia, the intraoperative hemodynamics, intraoperative anesthetic and analgesic agent requirement, the postoperative analgesia quality, the side effects and the recovery were also compared between the groups.

Bupivacaine is commonly used in epidural analgesia owing to its long-lasting effect and the sensory block it achieves that is more marked than the motor block. However, levobupivacaine was reported to be safer with respect to the central nervous system toxicity and cardiotoxicity in addition to exhibiting a local anesthetic effect similar to bupivacaine in the clinical trials. The tendency for sensory block is longer with levobupivacaine relative to bupivacaine. Following epidural administration of levobupivacaine, the duration of the motor block was observed to be shorter than that of the sensory block. Levobupivacaine was reported to be as effective as bupivacaine when combined with morphine or fentanyl in the treatment of postoperative pain. Some trials demonstrated that levobupivacaine exhibited small increases in the sensory block time relative to bupivacaine, in line with the results from this trial. This finding may be attributed to the relatively increased vasoconstrictor effect of levobupivacaine compared to bupivacaine (5-8).

In this trial, there was no difference between Group I and Group II in the time to achieve sensory block at T6. There was no difference between the two groups in the motor block levels measured until the time to achieve sensory block at T6 dermatome. The follow-ups

conducted during the 24th postoperative hour revealed a smaller number of patients developing motor block in the group using levobupivacaine.

In the trial by Bader et al (9) where women undergoing cesarean section were administered 0.5% (150 mg) levobupivacaine or bupivacaine at the same dose via epidural anesthesia, the incidence of hypotension was detected to be lower in those receiving levobupivacaine (84.4% levobupivacaine, 100% bupivacaine).

Bardsley et al (10), upon administering 56.1 mg of levobupivacaine and 47.9 mg of bupivacaine via the iv route, and Kopacz and Allen (11), upon accidentally administering 17 ml of 0.75% of levobupivacaine intravenously to a patient, reported that levobupivacaine was safer for achieving direct depression of the myocardial contractility relative to bupivacaine.

In this trial, there was one patient in Group I and four patients in Group II who required intraoperative ephedrine for hypotension, although this was not statistically significant. In Group III, the arterial blood pressure values were higher at various measurement times and required higher anesthetic doses to achieve hemodynamic stability. None of the three groups exhibited EKG changes. The absence of EKG changes in Groups I and II may be attributed to the low concentration of the epidural local anesthetic used.

Luchetti M et al (12) compared epidural + general anesthesia and total intravenous anesthesia in patients undergoing laparoscopic cholecystectomy and reported that the epidural + general anesthesia group did not require intraoperative opioid use, did not exhibit an increase in side effects and had a faster recovery. In our trial, the amount of sevoflurane and remifentanil used was lower in the epidural + general anesthesia groups relative to the general anesthesia group and thus, recovery was faster in Groups I and II relative to Group III; this finding is in line with the literature.

In their trial where they compared general anesthesia combined with epidural anesthesia achieved by 2% lidocaine to general anesthesia alone, Lu CH et al (13) reported that the requirement for volatile anesthetics was lower in the epidural + general anesthesia group, in line with our results.

The stress response can be avoided and the mediator levels can be maintained at the preoperative values by epidural anesthesia administered before surgical stimulation (14). In addition, epidural analgesia achieved by local anesthetics or opioids should also be maintained in the postoperative period to be able to reduce the stress response at the maximum level (15). In this trial, Group I and Group II were administered local anesthetic solution from the epidural space approximately 20 minutes before the surgery. As the sensory block level reached the T6 dermatome, general anesthesia induction was performed and the surgery was initiated. Maintenance of analgesia was achieved by using postoperative epidural PCA. Postoperative iv morphine PCA was used in Group III. As such, suppression of the stress response was observed similarly to these trials (14, 15).

Latterman et al (16) demonstrated that the glucose response was more limited in the patients receiving epidural anesthesia relative to the group undergoing general anesthesia. In this trial, the plasma glucose value showed a limited increase relative to the control value at the 1st and 24th postoperative hours; this increase was slightly more in Group III. None of the groups exhibited an increase in the glucose level above 150 mg dL^{-1}.

The blood glucose level was detected to be lower with postoperative epidural fentanyl administration relative to iv fentanyl administration (17). Again after general anesthesia, the blood glucose level was observed to be better suppressed in association with general anesthesia + paravertebral anesthesia and analgesia versus postoperative iv morphine

administration (18). In this trial, epidural morphine was combined with local anesthetic agents to achieve postoperative analgesia in Groups I and II. Iv morphine was used in Group III. Glucose level was better suppressed in Groups I and II relative to Group III.

The trials detected that the cortisol levels increased starting from the skin incision in cases undergoing general anesthesia + epidural analgesia; however, the blood cortisol levels were suppressed relative to the group receiving general anesthesia (19, 20). In another trial (21), epidural + general anesthesia and postoperative morphine administration were claimed to provide a better suppression of the blood cortisol level relative to the general anesthesia + postoperative iv morphine administration. In this trial, the postoperative 1st hour cortisol value was higher in Group III relative to Groups I and II. In all groups, the postoperative 1st hour cortisol value was higher than the control value; the postoperative cortisol value at 24 hours was significantly increased only in Group III. This shows that the cortisol response was better suppressed in the groups receiving epidural anesthesia and postoperative epidural analgesia relative to the group receiving general anesthesia and postoperative iv analgesia, even if partially.

Insulin, an anabolic and hypoglycemic hormone decreases following trauma as opposed to glucose and cortisol. This helps to maintain hyperglycemia and protect the metabolic status of the vital organs (22). In this trial, there was no difference between the groups in the insulin values measured preoperatively and in the first and 24th hours postoperatively. The increase in the insulin values in the 24th postoperative hour in Groups I and III may be related to the increase in glucose values.

Compared to general anesthesia, the increase in TNF-a and CRP levels was observed to be less with general + epidural anesthesia (1). In this trial, the 24th postoperative hour CRP values exhibited an increase compared to the control values in all groups. While there was no statistically significant difference between the groups, the values in Group III were higher relative to Groups I and II.

Chu CPW et al (2) compared general anesthesia followed by iv morphine, and combined spinal epidural anesthesia followed by epidural 1% bupivacaine and 2 μg ml^{-1} fentanyl, and detected lower VAS scores in the first, 12th and 48th postoperative hours in the group receiving epidural anesthesia and postoperative epidural analgesia ($p<0.05$).

In this trial, morphine was combined with low-dose local anesthetic in patients using epidural PCA. Iv morphine PCA was used in the general anesthesia group. In the treatment of postoperative pain, the VAS scores were higher during the first hours in Group III relative to Groups I and II ($p<0.05$). This may result from the postoperative maintenance of analgesia in groups receiving preoperative epidural anesthesia. In the group receiving intravenous morphine PCA, the VAS scores gradually decreased and exhibited no significant difference compared to the other groups.

Enquist et al (3) demonstrated that epidural anesthesia blocking the neural afferent conduction whether combined with general anesthesia or alone resulted in suppression of the stress response to surgery in their trial on the effects of epidural anesthesia at various doses on surgical stress. The blood pressure values were higher during the first postoperative hours in the group of patients receiving epidural + general anesthesia relative to the general anesthesia group with no difference detected between the groups after three hours. In this trial, the MBP values were similarly higher in Group III during the first two hours relative to Groups I and II.

Nabil W. Doss et al (4) compared the thoracic epidural anesthesia and general anesthesia techniques in their trial performed using 0.2% ropivacaine in patients undergoing

mastectomy and detected higher rates of nausea and vomiting in the general anesthesia group. Regarding hemodynamics, hypertension was more common in the general anesthesia group. The Aldrete recovery scores measured 1, 2 and 3 hours after the operation exhibited significant differences between the groups only in the first hour and were better in the thoracic epidural anesthesia group. In our trial, nausea-vomiting was less and the time of recovery from anesthesia was shorter in Groups I and II relative to Group III.

Morphine-related postoperative complications were most commonly in the form of nausea-vomiting, similar to the other trials. There was no significant difference between Groups I and II, and Group III with respect to nausea and vomiting. However, the number of patients with nausea and vomiting was higher in Group III. None of the patients had hypotension that required postoperative rapid fluid replacement or vasopressor agent use. Similarly, none of the patients developed respiratory depression. While there was no difference between the groups in itching, there were more patients with this compliant in Group III. There was no significant difference between the groups in tremor and only one patient in Group II had tremor.

In avoiding stress response, individual differences, the type and duration of surgery, tissue injury in major surgeries, the type of analgesia and the drugs used are also important as well as the method of anesthesia used.

As a result, we concluded that bupivacaine and levobupivacaine used in epidural anesthesia had similar effects, epidural + general anesthesia provided a better intraoperative hemodynamic stability relative to general anesthesia and reduced the requirement for anesthetic agents, provided a faster recovery, resulted in less side effects and achieved a better analgesia, particularly during the first postoperative hours. We believe that the stress response can be better suppressed by epidural + general anesthesia.

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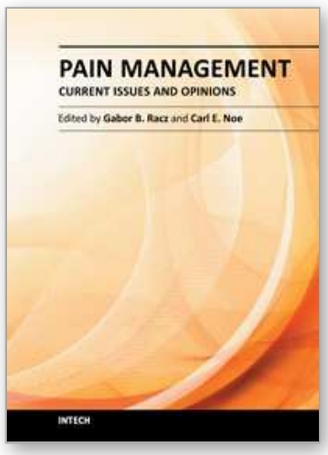

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