ORIGINAL RESEARCH

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The Effect of General Anesthesia and Thoracic Epidural Analgesia on Stress Response and Homocysteine Levels in Major Upper Abdominal Surgery: A Prospective Randomised Study

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ABSTRACT Objective: To examine the effect of general anesthesia and epidural analgesia on hemodynamic parameters, acute phase reactant, serum albumin and homocysteine levels, in elective major abdominal surgery. **Material and Methods:** 60 ASA I-II cases scheduled for upper abdominal surgery were divided into two groups, general anesthesia (GA) and general anesthesia+epidural analgesia (GA+EA). In the GA+EA group a 10 ml bolus of 0.1% bupivacaine was administered through a T6-T7 or T7-T8 epidural catheter. Both groups received general anesthesia of i.v. 1 mg/kg lidocaine, 2 mg/kg propofol and 0.6 mg/kg rocuronium. Maintenance anesthesia was established with 1.5% sevoflurane in 50% N2O and 50% O2. N2O was not given in the group receiving GA+EA. Plasma Stress Hormone Levels were investigated preoperatively, at the end of surgery and 8 and 24 h postoperatively. **Results:** Demographic data and C-reaktif protein (CRP), Erythrocyte Sedimentation Rate (ESR), prealbumin, neutrophil and cortisol counts did not differ significantly between the groups. Glucose at the end of surgery (p=0.030) and albumin at the 24[th] h postoperatively (p=0.031) were higher in the GA+EA group. In the GA group, homocysteine levels at the end of surgery were higher than those in the GA+EA group (P=0.049). **Conclusion:** We conclude that EA establishes better hemodynamics in major abdominal surgery, but has a limited effect on hormonal, metabolic and inflammatory response. We think that epidural anesthesia and analgesia may represent alternative techniques in patients with homocystinuria or hyperhomocysteinemia and that a nitrogen protoxide-related increase occurs in homocysteine levels.

Keywords: Anesthesia, analgesia, epidural; homocysteine; stress, physiological

Although anesthesia and surgical procedures are alone sufficient to cause endocrine and metabolic changes by creating stress, this response can be reduced, and even prevented, by different anesthetic techniques.[1,2] General anesthetics reduce sympathoadrenal response in a dose-dependent manner, but cannot prevent it completely.[2] Spinal and EA have been shown to suppress increases in plasma catecholamine, adrenocorticotropic hormone (ACTH), aldosterone, cortisol, renin, growth hormone (GH), prolactin and antidiuretic hormone (ADH).[3]

Morbidity and mortality may increase following pathophysiological events caused by perioperative pain. A disposition to myocardial ischemia develops with increased myocardial oxygen consumption resulting from sympathetic activation, while gastrointestinal return is delayed. A negative nitrogen balance and protein catabolism can delay healing, while depression may occur in the reticuloendothelial system. Fibrinolysis inhibition, increased platelet reactivity and plasma viscosity and neuroendocrine stress response are also involved in the development of postoperative hypercoagulability.[3] This results in an increased incidence of events such as deep vein thrombosis, vascular graft loss and myocardial infarction.[4]

Elevated plasma homocysteine levels leading to endothelial dysfunction and thrombogenesis are a significant risk factor for increased arterial and venous thrombosis, stroke, and myocardial infarction.[5] Homocysteine is a sulfur-containing amino acid and branch point intermediate on the methionine cysteine pathway.[6] Nitrous oxide is frequently used in anesthesia and inhibits, via Vitamin B12, methionine synthase, which permits the conversion of homocysteine and methyltetrahydrofolate into methionine and tetrahydrofolate and increases homocysteine levels.[6,7] The purpose of this study was to investigate the effect of GA and EA on hemodynamic parameters, acute phase reactant, and serum albumin and homocysteine levels, in patients undergoing elective major surgical procedures.

MATERIAL AND METHODS

STUDY POPULATION

Sixty ASA I-II cases scheduled for upper abdominal surgery by the general surgery department under elective conditions between May and October, 2014, were included in the study following receipt of approval from the Atatürk University Faculty of Medicine ethical committee (B.30.2.ATA. 0.01.00/ 55 25.02..2014, the protocol number: 5) and of signed, informed consent from patients. Patients aged under 18 or over 65, with a history of allergy, diabetes mellitus, hypertension, congestive heart failure or psychotic problems, with bacteremia or sepsis, with endocrine or metabolic disorders, definitively contraindicated for epidural procedures, with a body mass index ≥ 35 or a history of narcotic or alcohol addiction were excluded.

PATIENT MANAGEMENT

Cases were randomly assigned into two 30-member groups, GA group and GA+EA group. ECG, oxygen saturation and noninvasive arterial pressure were monitored in the operating room (Datex Ohmeda S/5, Helsinki, Finland). Vascular access was established with a 22 G intravenous cannula. Infusion of 0.9% NaCl was started at a rate of 8 ml/kg/h. Cases were randomly assigned into two 30-member groups, a general anesthesia group (GA) and a general anesthesia + epidural analgesia group (GA+EA).

Patients in the GA+EA group received infiltration anesthesia with administration of 3 ml 2% lidocaine (Aritmal ampoule 2%, 5 ml®, Osel, Istanbul) to the skin where the procedure was to be performed in line with the appropriate asepsis-antisepsis rules, in a seated position. A test dose of 2 ml lidocaine (Aritmal ampoule 2%, 5 ml®, Osel, Istanbul) was administered using the dropping method with an 18G Tuohy needle (Egemen epidural set, Izmir, Turkey) through the T6-T7 or T7-T8 intervertebral space. The epidural catheter was left in a 5 cm epidural space. A 10 ml bolus of 0.1% bupivacaine (Marcaine® 0.5%, 20 ml ampoule, AstraZeneca, England) was given. Bilateral warm-cold anesthesia induction was performed when the T4 level was reached on the mid-clavicular line. In the event of an increase exceeding 10% in the patient's heart rate and blood pressure, an additional 5 cc 0.1% bupivacaine was administered.

General anesthesia in both groups was administered with 1 mg/kg lidocaine i.v. (Aritmal ampoule 2%, 5 ml®, Osel, Istanbul) 2 mg/kg propofol i.v. (Propofol ampoule 2% 50 ml®, Fresenius Kabi, Germany) and 0.6 mg/kg rocuronium i.v. (Esmeron ampoule 50 mg/5 ml®, Organon, Holland). When necessary, 0.1 mg/kg rocuronium was administered for muscle relaxation throughout the operation. In the GA group, maintenance anesthesia was provided with 1.5% sevoflurane (Sevorane Liquid 250 ml®, Abbott, England) in 50% N_2O and 50% O_2 (tidal volume= 6-8 ml/kg, frequency= 12/min). N_2O was not given to the group receiving epidural analgesia. In the GA group, 50 mcg fentanyl (Fentanyl citrate® ampoule, Antigen Pharmaceuticals, Munich, Germany) was administered at induction and at hourly intervals for intraoperative analgesia. In the GA+EA group, intraoperative analgesia was achieved by an initial bolus of 10-12 ml of 1.25 mg/mL bupivacaine and 2µg/mL fentanyl depending on patient size and catheter placement. The same dose of the same solution was administered and every hour throughout operation. intraoperative analgesia was established with the injection of 10 ml 0.1% bupivacaine once per hour through the epidural catheter. Crystalloid-colloid infusion at a ratio of 2:1 was performed in both groups. Hypotension (a 20% decrease in Systolic blood pressure (SBP) below preanesthesia levels or SBP\100 mmHg), was treated immediately with 5 mg of intravenous ephedrine, and bradycardia (Heart Rate\60 beats/min) was treated with 0.5 mg of i.v. atropine. Bleeding levels were recorded. Muscle relaxant antagonism was established with 1.5 mg neostigmine (Neostigmin® ampoule 0.5 mg/ml, Adeka, Samsun, Turkey) and 0.5 mg atropine (Atropin Sulfate® ampoule 0.25 mg/ml, Galen, Istanbul, Turkey). Following extubation, patients were monitored for 30 min in the recovery room and then transferred to the general surgery ward or general surgery intensive care unit.

Postoperative analgesia in the GA group was established using intravenous patient-controlled analgesia (PCA) with 1000 mcg (10 mcg/ml) fentanyl in 100 ml 0.9% isotonic solution. The PCA device (Abbott Pain Management Provider, Chicago, USA) was adjusted to a 50 mcg bolus, 20 mcg/st basal infusion, 15 mcg patient-controlled bolus and a 15-min key period.

Postoperative analgesia in all patients in the GA+EA group was administered at the end of surgery with 3 mg morphine sulfate (Morphine HCl® ampoule 10 mg, Galen, Istanbul, Turkey) + 50 mcg fentanyl (Fentanyl citrate® ampoule, Antigen Pharmaceuticals, Munich, Germany) in 15 ml 0.9% NaCl through the epidural catheter. At evaluation after 60 min, patients with inadequate analgesia following one dose of epidural fluid were given another dose of the same fluid (inadequate epidural analgesia was defined as a visual analogue score >3 sixty min after administration of first epidural fluid). Hemodynamic parameters were measured non-invasively in all patients before induction and 1, 5, 10, 15, 30, 60 and 120 min after surgical incision.

LABORATORY ASSAY

Blood specimens were studied before anesthesia, at the end of surgery and at 8 and 12 h postoperatively. Complete blood count, sedimentation, glucose, cortisol, prealbumin and CRP were studied immediately following blood collection, while homocysteine specimens were centrifuged for serum separation and stored at +4°C. Complete blood count was studied using the volume, conductivity and light scatter (VSC) method on a Beckman Coulter LH780 device. Erythrocyte sedimentation rate was studied spectrophotometrically from complete blood specimens on an Alifax device. Glucose was studied spectrophotometrically from blood specimens on a Beckman Coulter AU5800 device, and cortisol using electroluminescence on a Beckman Coulter DXI 800 device. Albumin and prealbumin were studied using spectrophotometric, immunoturbidometric and electrochemiluminescence methods on a Beckman Coulter AU5800 device. Homocysteine was studied using LC-MS/MS on a Zivak Technologies Tandem Gold device. CRP measurements were performed from blood specimens using the immunonephelometric method using the NFL BN-II (Siemens Dade Behring, Germany) system in the microbiology laboratory.

STATISTICAL ANALYSIS

Data analysis was performed on SPSS software. Data were expressed as number, percentage, median, mean and standard deviation. Groups' compatibility with normal distribution was analyzed using the Kolmogorov-Smirnov test. Student's t test was used for the analysis of variables such as age and pre-induction Mean blood pressure (MAP), in the group administered GA and GA+EA (at analysis of numerical variables establishing the appropriate conditions (such as compatibility with normal distribution, etc.). The Mann Whitney U test was used to analyze variables such as weight and height. Friedman's test was used to compare values for cortisol, glucose etc. measured at four different time intervals in the group administered GA and GA+EA. Repeated measures analysis of variance was used in the comparison of values such as albumin and prealbumin. Bonferroni correction was applied to determine the source of variance at analyses performed with the Friedman test, while the Wilcoxon test was performed in two-way comparisons. Significance (p/two-way comparison number=p/6) was set at p<0.008. Significance at all other analyses was set at p<0.05.

RESULTS

DEMOGRAPHIC AND HEMODYNAMIC ASSESMENT

There was no significant difference between the demographic characteristics in terms of anesthesia and duration of surgery (Table 1). Mean arterial pressure was significantly higher in cases receiving general anesthesia at 5, 10, 15 and 30 min after surgical incision compared to the GA+EA group (*P=0.006, 0.043, 0.006, and 0.009*, respectively). Heart rate was significantly higher at 10, 15, 30 and 60 min after surgical incision in the GA group compared to the GA+EA group (*P=0.014, 0.005, 0.046 and 0.005*, respectively) (Figure 1). No significant differences were determined between the two groups in terms of amount of bleeding, crystalloid and colloid fluid or erythrocyte suspension (p>0.05) (Table 2). VAS score was significantly higher in cases receiving general anesthesia at postoperative 1., 2., 4., 8. hours compared to the GA+EA group (Figure 2).

PLASMA STRESS HORMONE LEVELS

Cortisol values did not differ significantly between the groups at any time interval (p>0.05). Significant elevation was observed in preoperative values in both groups compared to all other measurement intervals (p<0.001). Glucose values at end of surgery were significantly higher in Group GA+EA compared to Group GA (p=0.03), but there was no difference at other intervals (p>0.05). Glucose values in both groups were higher at all measurement intervals compared to preoperative values (p<0.001) (Table 3). There was no significant difference between the groups in terms of prealbumin or neutrophil values (p>0.05). Prealbumin levels were lower at all intervals compared to preoperatively in both groups (p<0.05). (Table 3). Neutrophil values in both groups were higher at all intervals compared to preoperative levels (p<0.05) (Table 4).

There was no difference in CRP values between the groups, but values at postoperative hours 8 and 24 were higher than preoperative values in both groups (p=0.001). There was no difference in erythrocyte sedimentation rates between the groups (p>0.05), but the rates were higher in both groups at the 24th h postoperatively compared to preoperative values (p<0.05).

TABLE 1: Demographic and surgery characteristics.

	Group GA (n=30)	Gorup GA+ EA (n=30)	P değeri
Sex(E/K)	15/15	19/11	
Age	49.33±13.8	53.43±12.58	0.235
Weight (kg)	69.0±10.20	68.00±7.65	0.237
Height(cm)	67.0±6.87	167.00±5.33	0.893
Anesth Duration(min)	155.0±53.06	157.50±74.10	0.374
Surgery Duration(min)	130.0±43.93	127.50±68.59	0.882
Type of surgery (n)			
Gastric CA	10	17	
Choledoc stone	3	2	
Hydatic cyst	9	4	
other	8	7	

Group GA; Group administered general anesthesia, Group GA+EA; Group administered general anesthesia + epidural analgesia All values are expressed as mean ± standard deviation (p>0.05). No statistically significant difference was determined (p>0.05).

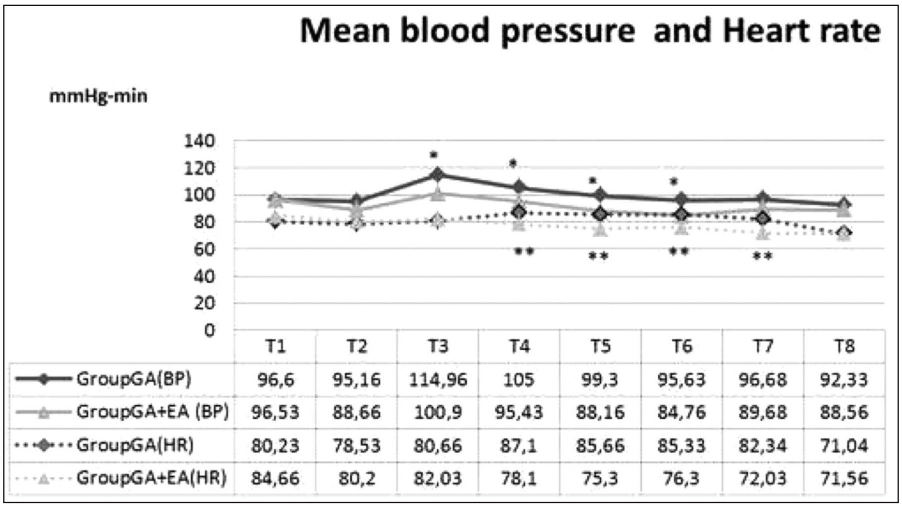

FIGURE 1: Group GA; Group administered general anesthesia, Group GA+EA; Group administered general anesthesia + epidural analgesia. All values are expressed as mean ± standard deviation (p>0.05).
Pre-anesthesia (T1), Surgical incision; 1st min (T2), 5th min (T3), 10th min (T4), 15th min (T5), 30th min (T6), 60th min (T7), 120th min (T8).
* The Blood pressure was higer in Group GA at T3, T4, T5 and T6 (P= 0.006, 0.043, 0.006 and 0.009).
** The Heart rate was higer in Group GA at T4, T5, T6 and T7 (P=0.014, 0.005, 0.046 and 0.005).

TABLE 2: Blood loss and transfusion between the groups.

	Group GA (n=30)	Group GA+EA (n=30)	Mann-Whitney U	P value
Total crystalloid (ml)	2050.00	2000.00	387.00	0.348
Total colloid:				
HES (ml)	500.00	500.00	376.50	0.257
TDP (units)	0.50	1.00	438.00	0.849
Total ES (units)	0.00	0.00	435.50	0.750
Total bleeding (ml)	225	200	449.00	0.988

Group GA; Group administered general anesthesia, Group GA+EA; Group administered general anesthesia + epidural analgesia *(p>0.05). No statistically significant difference was determined (p>0.05).

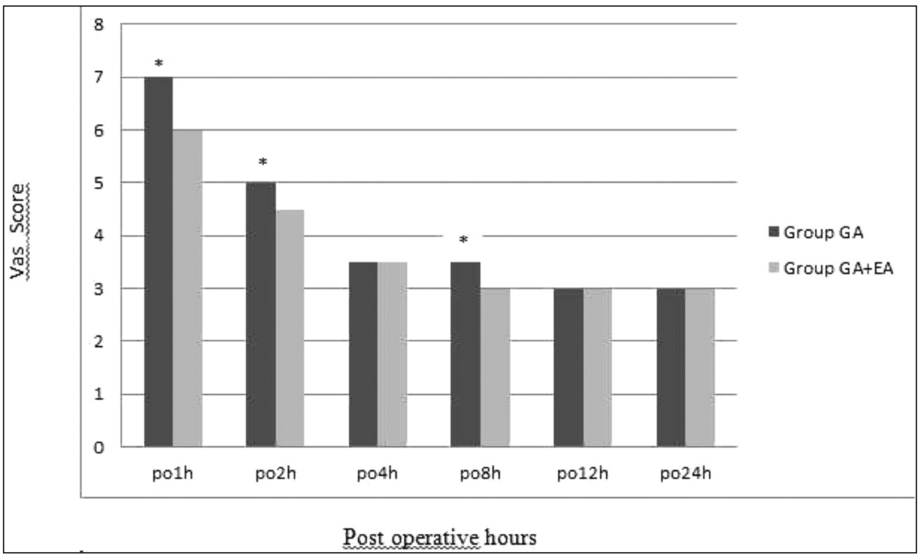

FIGURE 2: VAS score
VAS score was higer in Group GA at postoperative (po) 1, 2, and 8 hours. (P=0.03, 0.04, 0.025).

TABLE 3: Changes in plasma stress hormone levels 1.

	Gr GA (n=30)	Gr GA+ EA(n=30)	P (between groups)
Glucose (mg/dl)			
T1	89.36±18.98	99.23±21.43	0.055
T2	140.80±35.95†	162.46±39.25†	0.030*
T3	150.30±46.71†	166.30±52.93†	0.220
T4	131.16±38.86†	144.13±44.57†	0.035
Cortisol (µg/dl)			
T1	12.86±4.28	13.90±4.81	0.379
T2	25.80±9.33†	25.97±8.71†	0.942
T3	23.59±12.96†	21.78±10.31†	0.813
T4	19.17±8.32†	19.60±7.65†	0.836
Albumine (g/dl)			
T1	3.44±0.50	3.51±0.52	0.603
T2	2.80±0.46†	3.05±0.57†	0.065
T3	3.01±0.38†	3.21±0.45	0.067
T4	2.86±0.36†	3.10±0.4†	0.031*
Prealbumine(mg/dl)			
T1	0.17±0.05	0.17±0.05	0.776
T2	0.15±0.04†	0.14±0.04†	0.001
T3	0.16±0.03†	0.14±0.03†	0.002
T4	0.13±0.03†	0.12±0.03†	0.477

All values were given as Mean ± Standard Deviation. T1 Immediately before induction of anesthesia, T2 End of surgery, T3 Postoperative 8th hour, T4 Postoperative 24th hour.
*p<0.05 when comparison was made between groups
†p<0.05 when intragroup comparison was made with the baseline value (T1) of the group.

TABLE 4: Changes in plasma stress hormone levels 2.

	GrGA(n=30)	GrGA+EA(n=30)	P(betweengroups)
Neutrophil (u/L)			
T1	4.25±2.74	4.09±1.42	0.994
T2	9.76±4.55†	8.18±3.26†	0.128
T3	11.87±4.05†	11.03±4.44†	0.444
T4	11.78±5.09†	10.01±3.96†	0.139
CRP (mg/L)			
T1	8.86±15.12	14.01±20.01	0.090
T2	11.35±13.28†	11.59±12.17†	0.812
T3	44.56±46.37†	40.76±35.56†	0.652
T4	110.24±54.31†	138.18±59.17†	0.062
ESR (mm/hour)			
T1	16.73±17.47	19.93±17.99	0.350
T2	14.23±13.55†	9.73±12.17†	0.076
T3	16.80±14.19†	16.26±13.65†	0.883
T4	24.10±14.5†	30.30±16.16†	0.123
Homocysteine (mmol/L)			
T1	15.14±9.56	15.19±9.65	0.906
T2	19.10±10.73†	15.53±12.04	0.049*
T3	11.42±7.87†	9.27±6.58†	0.212
T4	11.14±8.70†	10.11±7.23†	0.620

Erythrocyte Sedimentation Rate (EST). All values were given as Mean ± Standard Deviation. T1 Immediately before induction of anesthesia, T2 End of surgery, T3 Postoperative 8th hour, T4 Postoperative 24th hour.
*p<0.05 when comparison was made between groups
†p<0.05 when intragroup comparison was made with the baseline value (T1) of the group.

Albumin levels at 24 h were significantly higher in the GA+EA group than in the GA group (p=0.031), but there was no significant difference at other times. Albumin levels were lower at all intervals compared to preoperatively in both groups (p<0.05). Homocysteine values at the end of surgery were significantly higher in the GA group than in the GA+EA group (p=0.049), but there was no significant difference between the groups at other times (p>0.05). Values at all other times differed significantly from preoperative values in the GA group (p<0.05), while in the GA+EA group there were significant differences at postoperative hours 8 and 24 compared to preoperative values (p<0.05) (Table 4).

DISCUSSION

The results of the study can be summarized as follows: intraoperative thoracic EA provides better hemodynamic parameters in patients undergoing major abdominal surgery but that it has a limited effect on hormonal, metabolic and inflammatory response. Some studies have reported increased homocysteine levels with nitrous oxide use.[38] Homocysteine levels compared at the end of surgery in our study were significantly elevated in the GA group, but there was no significant difference at other time intervals.

Stress response to surgery begins with GA and ends on days 3-4 postoperatively.[2] Various methods are employed to reduce surgical stress. EA interrupts afferent pain transmission with local anesthetic and/or opioids, and this can be controlled with effective agent selection, concentration, dosage and injection levels.[8] EA combined with GA established better hemodynamic parameters. We think that EA did not greatly suppress cortisol as a marker of hormonal response to stress, glucose for metabolic response, CRP as an acute phase reactant or neutrophil and homocysteine levels as cellular immune response. Homocysteine is an amino acid, elevation of which increases the risk of heart diseases. We identified a nitrogen protoxide-related increase in homocysteine levels and investigated the effect of EA on homocysteine levels, a subject which has been little investigated previously.

Previous studies have investigated the effects of anesthesia techniques on HR and MAP. Siniscalchi et al. reported significantly low MAP and heart rate in an epidural group in major liver surgeries 15 min after induction of anesthesia, but no difference at any other times Ersoy et al. determined significantly lower MAP and heart rate with general anesthesia combined with lumbar epidural anesthesia in major abdominal surgery, while SpO_2 values were unaffected.[8,9] In our study, MAP at mins 5, 10, 15 and 30 and HR at mins 10, 15, 30 and 60 after incision were all lower in the epidural analgesia group. We observed that epidural analgesia had a positive effect on MAP and HR compared to similar studies.

Hormonal response in stress is characterized by activation of the hypothalamic-pituitary-adrenal axis.[10] Surgical cortisol secretion are the most potent activators, and increased plasma levels can be measured within minutes of start of surgery.[11] Insulin levels are generally normal or decreased, while peripheral insulin resistance increases.[12] These hormones increase blood glucose concentrations, mobilize alternative fuels and increase peripheral resistance to insulin.[13] Insulin resistance has been shown to increase significantly on the first postoperative day in particular, and only to return to normal levels on the 9th and 21st days after surgery. Akhtar et al. determined significantly lower cortisol values in a group receiving thoracic EA.[13] Fant et al. reported significantly low cortisol and glucose values at the end of surgery in a group receiving EA, but determined no significant difference at 24 h postoperatively.[14] Brodner et al. concluded that thoracic EA was effective in reducing hormonal and metabolic stress. Cortisol levels increased with surgery, but they determined no difference between groups.[15] Tutaş et al. reported significantly high 6-h glucose values in patients undergoing laparoscopic hiatal hernia surgery and receiving EA , while there was no significant difference between the groups in terms of cortisol levels.[16] Ersoy et al. reported that lumbar EA combined with GA in major abdominal surgery established hemodynamic stability and reduced stress response and sevoflurane requirements. No difference was observed in terms of glucose values, while cortisol values were significantly higher in the GA group.[9] In our study, cortisol values were higher than preoperative basal values in both groups, but no significant difference was determined between the groups. Glucose values increased in association with surgical stress in both groups, and were higher at the end of surgery in the EA group compared to the GA group, although no significant differences were observed at other times. We think that blood glucose values increasing with surgical stress remaining high until the 24th h postoperatively is associated with insulin resistance.

Post-injury cellular immune response is established by polymorphonuclear (PMN) granulocytes, lymphocytes, monocyte / macrophages and natural killer cells. PMN granulocytes are members of the cellular immune system that exhibits the first response to trauma. Moore et al. investigated the effects of epidural anesthesia on IL-6 and acute phase response to surgery. They determined an increase in neutrophil numbers in both groups, but that values at the 2nd h of surgery were significantly lower in the epidural group.[17] Kim et al. reported significantly higher neutrophil numbers in a general anesthesia group compared to an epidural group.[18] Fant et al. compared patients receiving thoracic epidural or systemic opioid analgesia in radical retropubic prostatectomies and reported higher leukocyte numbers at 24 h in the opioid group.[14] Kawasaki et al. investigated the effects on surgically-induced immunosuppression of epidural anesthesia during upper abdominal surgery. They reported significant leukocytosis and lymphopenia during surgery, but detected no significant differences between the groups.[19] In our study, there was a significant increase in neutrophil numbers in both groups compared to basal values. Neutrophil numbers continued to rise at postoperative hours 8 and 24 compared to the values at the end of surgery. No significant difference in neutrophil numbers was determined between the groups.

CRP is synthesized in the liver. Secretion begins 4-6 h after the first stimulus and doubles by 8 h, peaking in 36-50 h. Its plasma half-life is 19 h, but levels take days to return to normal following a single stimulus such as surgery and trauma.[20] Significant elevation in CRP values has been determined at the end of surgery and at 1 and 3 days postoperatively in both groups in patients undergoing radical esophagectomy under both continuous epidural anesthesia and systemic analgesia. Peak values were recorded on the third day postoperatively.[21] Akintola et al. reported that the addition of epidural analgesia to general anesthesia did not reduce CRP values.[22] Fant et al. reported higher CRP levels on the first and third days postoperatively in a group administered systemic analgesia compared to an epidural group, but the difference was not statistically significant.[1] No significant difference was determined between the groups in our study. The highest values were observed at 24 h postoperatively in both groups.

Roth et al. determined a significant decrease in prealbumin days on the first day in patients undergoing cystectomy with combined general and thoracic EA.[23] Yuan et al. determined a fall in prealbumin levels at the 24th h postoperatively in cases receiving albumin in the early period following gastrointestinal surgery.[24] In our study, postoperative prealbumin values were significantly lower than preoperative levels. No significant difference was observed between the groups. Albumin is the most important source of reduced sulfhydryl groups. These groups are also known as thiols and are involved in the removal of reactive oxygen and nitrogen species such as superoxide, hydroxyl and peroxynitrite.[25] Engin et al. determined a decrease in albumin and homocysteine levels proportional to severity of surgical trauma in the postoperative period. They suggested that the fall in serum albumin together with a decrease in homocysteine in the postoperative period was secondary to oxidative stress.[7] An acute increase in homocysteine concentrations raises the risk of perioperative myocardial infarct and leads to endothelial dysfunction and thrombogenesis.[26-28] Considerable epidemiological evidence has shown that mild hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cerebral and peripheral vessels.[29,30] N_2O, which is frequently used in anesthetic practice, inhibits the synthesis of methionine, which permits the conversion of homocysteine and methylenetetrahydrofolate into methionine and tetrahydrofolate.[31] Myles et al. reported significantly higher postoperative homocysteine levels in a nitrous oxide group among patients undergoing major surgery.[32] Foschi et al. compared nitrous oxide and fentanyl among general surgery patients and determined higher homocysteine levels at 24 h in the group using nitrous oxide.[33] Significantly higher homocysteine levels have been reported in both maternal and baby cord blood after Cesarean delivery under general anesthesia with nitrous oxide.[34] Badner et al. determined an increase in mean homocysteine levels in a nitrous oxide group on arrival at the PACU and after 48 h among patients undergoing endarterectomy and reported that increased homocysteine levels were associated with postoperative myocardial infarction.[35] Assadian et al. concluded that there was no increase in postoperative homocysteine levels in carotid endarterectomies performed under local anesthesia.[36] Limited data are available concerning the effects of neuroaxial anesthesia on postoperative homocysteine levels. Gavrila et al. investigated which anesthesia technique might be more appropriate in patients diagnosed with hyperhomocysteinemia and compared preoperative and postoperative homocysteine levels in 98 women in the final trimester. They reported an increase in homocysteine levels in the GA group.[37] Some studies have reported increased homocysteine levels with nitrous oxide use.[38] Homocysteine levels compared at the end of surgery in our study were significantly elevated in the GA group, but there was no significant difference at other time intervals. Homocysteine levels at 8 and 24 h postoperatively were lower than basal values in the GA group, but the difference was not statistically significant. In the EA group, values in the immediate postoperative period were similar to basal values, while levels at 8 and 24 h postoperatively were lower than basal values. As in similar studies, we attribute elevation in homocysteine values in the immediate postoperative period to N_2O. Foschi et al. suggested that the decrease in serum concentrations of essential amino acids may be associated with surgical stress-related suppression of cystathionine beta synthase and that homocysteine acts as a negative acute phase reactant as a result.[33]

The relation between a decrease in homocysteine and a decrease in albumin, itself a negative acute phase reactant and the main homocysteine transporter in plasma, is unclear. Postoperative homocysteine levels in the postoperative period in both groups were lower than the preoperative values, but there was no difference between the two groups. We think that since stress response associated with EA is not sufficiently suppressed, methionine and cysteine levels decrease and that, in association with this, plasma levels decrease since homocysteine enters more into the remethylation and transsulfuration pathway. We think that further research is now needed.

CONCLUSIONS

We conclude that thoracic EA provides better hemodynamic parameters in patients undergoing major abdominal surgery but that it has a limited effect on hormonal, metabolic and inflammatory response. We observed a nitrogen protoxide-dependent increase in homocysteine levels, but EA did not increase homocysteine levels. We think that epidural anesthesia and analgesia can represent alternative techniques in patients with homocystinuria or hyperhomocysteinemia and at high risk of myocardial ischemia, and that further study is now needed on this subject.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea and Concept of Study: *Canan Atalay, Sinan Çelik;* ***Design of Study:*** *Canan Atalay, Sinan Çelik;* ***Data Collection and Processing:*** *Sinan Çelik;* ***Analysis and Comments:*** *Canan Atalay, Sinan Çelik;* ***Article Writing:*** *Canan Atalay, Sinan Çelik;* ***Statistical Analysis:*** *Ercan Özyıldırım.*

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