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Original Article / Özgün Makale

Evaluation of pain scoring and free cortisol levels of postoperative analgesic methods in cardiac surgery: A new perspective

Kalp cerrahisinde cerrahi sonrası analjezik yöntemlerin ağrı skorlamaları ve serbest kortizol düzeylerinin değerlendirilmesi: Yeni bir yaklaşım

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ABSTRACT

Background: This study aims to evaluate the most appropriate analgesic method of minimizing postoperative pain to prevent complications in patients scheduled for cardiac surgery.

Methods: Between January 2016 and June 2016, a total of 60 patients with the American Society of Anesthesiologists Physical Status Class III (27 males, 33 females; mean age 63 years; range, 49 to 77 years) with an ejection fraction of above 50% who underwent elective coronary artery bypass grafting were included. The patients were divided into two groups following admission to the intensive care unit. Group 1 (n=30) was administered intravenous fentanyl citrate with patient-controlled analgesia protocol, while Group 2 (n=30) was administered 0.1% bupivacaine hydrochloride analgesia protocol with catheter placed between the sternum and subcutaneous tissue.

Results: In Group 1, pain intensity scores at two h and visual analog scale scores except at 24, 36, and 48 h were higher than Group 2 ($p<0.05$). The length of intensive care unit stay and urine cortisol levels were higher in Group 1 than Group 2 (78±12 h and 631±505 μg at 24 h vs. 66±13 h and 401±297 μg at 24 h, respectively $p<0.05$). Partial pressure of oxygen levels at 10 and 16 h during the postoperative intensive care unit stay were lower, while partial pressure of carbon dioxide levels at 24 h was higher in Group 1 than Group 2 ($p<0.05$).

Conclusion: The bupivacaine protocol is a relatively more useful analgesic method which produces improved results in blood gas analysis by reducing the effects of pain and shortens the length of intensive care unit stay. Low levels of free cortisol also confirm this finding.

Keywords: Bupivacaine, intensive care unit, length of stay, patient-controlled analgesia protocol, urine cortisol.

ÖZ

Amaç: Bu çalışmada kalp cerrahisi yapılması planlanan hastalarda komplikasyonları önlemek amacıyla cerrahi sonrası ağrıyı en aza indirgeyen en uygun analjezik yöntem değerlendirildi.

Çalışma planı: Ocak 2016-Haziran 2016 tarihleri arasında Amerikan Anesteziyoloji Derneği Fiziksel Durum Sınıf III ve ejeksiyon fraksiyonu %50 üzerinde olup elektif koroner arter baypas greftleme yapılan toplam 60 hasta (27 erkek, 33 kadın; ort. yaş 63 yıl; dağılım, 49-77 yıl) çalışmaya alındı. Hastalar yoğun bakım ünitesine kabullerinin ardından iki gruba ayrıldı. Grup 1'e (n=30) intravenöz hasta kontrollü analjezi protokolü ile intravenöz fentanil sitrat uygulanırken, Grup 2'ye (n=30) sternum ile cilt altı dokusu arasına yerleştirilen kateter ile %0.1'lik bupivakain hidroklorür analjezi protokolü uygulandı.

Bulgular: Grup 1'de ikinci saatteki ağrı şiddet skorları ve görsel analog ölçeği skorları 24, 36. ve 48. saatler haricinde Grup 2'den daha yüksekti ($p<0.05$). Grup 1'de yoğun bakım ünitesinde yatış süresi ve idrar kortizol düzeyleri Grup 2'ye kıyasla daha yüksekti (sırasıyla 78±12 saat ve 631±505 μg/24. saate kıyasla 66±13 saat ve 401±297 μg/24. saat, $p<0.05$). Grup 2'ye kıyasla Grup 1'de cerrahi sonrası yoğun bakım ünitesinde yatış sırasında 10. ve 16. saatlerdeki parsiyel oksijen basıncı düzeyleri daha düşük iken, 24. saatte parsiyel karbondioksit basınç düzeyleri daha yüksekti ($p<0.05$).

Sonuç: Bupivakain protokolü, ağrının etkilerini azaltarak ve yoğun bakım ünitesinde yatış süresini kısaltarak, kan gazı analizinde daha iyi sonuçlar sağlayan, nispeten daha kullanışlı bir analjezi yöntemidir. İdrarda serbest kortizol düzeylerinin düşüklüğü de, bu bulguyu doğrulamaktadır.

Anahtar sözcükler: Bupivakain, yoğun bakım ünitesi, yatış süresi, hasta kontrollü analjezi protokolü, idrar kortizol.

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Pain due to sternal splitting in cardiac surgery is one of the most unbearable pain.[1] In addition to splitting of the sternum, chest tubes and endotracheal tubes also contribute to post-sternotomy pain. This pain is a powerful stressor associated with tissue damage and capable of affecting hemodynamic and physiological processes.[2] Pain is harmful, since it gives rise to several ischemic, endocrine-metabolic, inflammatory, homeostatic, hematological and respiratory pathologies, and organ dysfunctions. In addition, uncontrollable pain may become chronic which may prolong the length of hospital stay for various reasons, thereby, increasing postoperative morbidity and mortality.[3]

General anesthetics used in major operations such as cardiovascular surgery may cause diffuse neurodepression which suppresses responses in the central nervous system associated with tissue injury by increasing inhibitory neurotransmission, gamma-aminobutyric acid (GABA), and reducing excitatory neurotransmission, glutamate and acetylcholine. Neuromuscular blocking agents, however, prevent the transmission of nerve signals which cause skeletal muscle relaxation by competing with acetylcholine. As a result, they facilitate endotracheal intubation and produce skeletal muscle relaxation during surgery.[4] However, neither general anesthetics nor neuromuscular blockers are always able to prevent sympathetic, neuroendocrine, and biochemical responses associated with postoperative pain. Novel and various analgesics and different doses and techniques are, therefore, still being tested for the purpose of overcoming or controlling postoperative pain.

Fentanyl, an opioid derivative, and bupivacaine, a local anesthetic, are two analgesics used to overcome postoperative pain.[3,5] Bupivacaine is one of the longest-acting local anesthetics which produces sensory block more than motor block. It has, therefore, become a popular agent in postoperative analgesia.[6] Fentanyl, with its rapid onset, has for long been widely used in cardiac anesthesia and analgesia, since it does not cause cardiovascular depression.[7] However, there is a limited number of studies comparing these two analgesic substances in terms of preventing the effects of postoperative pain.

Postoperative pain has been reported to prolong the length of hospital and intensive care unit (ICU) stay, to cause skeletal muscle spasm and hemostatic, gastrointestinal, respiratory and circulatory disorders associated with immobility, and to compromise the patient comfort.[8] It has been also reported to suppress the immune response to infections.[9] Analgesics to be used in the control of postoperative pain must, therefore, produce positive changes in at least some of the aforementioned complications. The efficacy of analgesics for the control of postoperative pain has been shown to be evaluated using tools such as the visual analog scale (VAS) and Pain Intensity Scale (PIS).[10]

In the light of these data, we aimed to evaluate the most appropriate analgesic method of minimizing postoperative pain to prevent complications with blood gas analysis and urine cortisol levels in patients scheduled for cardiac surgery.

PATIENTS AND METHODS

Between January 2016 and June 2016, a total of 60 patients with the American Society of Anesthesiologists (ASA) Physical Status Class III (27 males, 33 females; mean age 63 years; range, 49 to 77 years) with a left ventricular ejection fraction (LVEF) of above 50% who underwent elective coronary artery bypass grafting (CABG) at Department of Cardiovascular Surgery of Erzurum Regional Training and Research Hospital were included in this prospective, randomized study. Randomly selected patients with no allergy to opioids, local anesthetic or other drugs, with no previous history of chronic pain treatment, and scheduled for cardiac surgery with cardiopulmonary bypass (CPB) for the first time were included. Patients with an LVEF ≤50%, with a history of opioid use and/or allergy, with allergy to any drug, with a history of cerebrovascular disease, renal failure, chronic obstructive pulmonary disease or diabetes mellitus, with a body mass index (BMI) of ≥30 kg/m^2, undergoing valve surgery in the same session, receiving emergency surgery, with intraoperative sternum or rib fracture, admission to the ICU with an intra-aortic balloon pump, with a history of nonsteroidal anti-inflammatory drug or steroid use within 24 h before surgery, with a history of chronic alcohol use, or with postoperative mechanical ventilation exceeding 24 h were excluded from the study. Since cortisol levels vary significantly over the day, patients taken for CABG in the afternoon were also excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (2015/9-63). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were divided into two groups following admission to the ICU. Group 1 (n=30) was administered intravenous fentanyl citrate with patient-controlled analgesia protocol (PCA) in the form of basal infusion 0.2 μg/kg/h, bolus dose 0.1 μg/kg and a lockout period

of 15 min. Since the splitting of the sternum is the major component of postoperative pain in cardiac surgery, Group 2 (n=30) was administered 0.1% bupivacaine hydrochloride PCA protocol prepared with 0.9% NaCl through a catheter inserted between the sternum and subcutaneous tissue in the form of basal infusion 10 mL/h, bolus dose 10 mL, and a lockout period of 60 min. The patients in both groups routinely received 75 mg intramuscular diclofenac sodium at the time of admission to the ICU and 12 h subsequently for saphenous and chest tube pain. Rescue analgesia was administered with 1 mg/kg intravenous tramadol for patients with VAS scores ≥4 at any time.

Height, weight, BMI, and waist circumference (WC) values were measured for all patients. Age, gender, and smoking histories were recorded. Preoperative serum glucose, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), CK-MB, blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), high-sensitivity C-reactive protein (hsCRP), and troponin I (TnI) were studied from blood collected on the same day. The PIS scores were recorded during intubation in the ICU, and VAS scores were recorded after extubation during both at rest and breathing and coughing exercises. Hourly blood gas and 24-h urine cortisol levels were measured in the postoperative period. Duration of extubation (time from arrival at ICU to the removal from mechanical ventilation), surgery (from induction to arrival at ICU), pump (time spent on a heart-lung pump), and cross-clamp, length of stay in the ICU and hospital stay, total levels of analgesics used, and postoperative complications including nausea, vomiting, atelectasis, respiratory depression, and pruritus were recorded.

The patients were randomly assigned into one of two groups by an anesthetist who was not involved in the study. The ICU monitoring was performed by a third, independent anesthetist. Venous access was established from the back of the hand with a 22-G cannula, after the patient was taken to the operating room. Standard monitoring was performed with five-lead electrocardiogram (ECG), peripheral oxygen saturation (SpO_2), and non-invasive blood pressure, and the initial measurements were recorded. We used 5 μg/kg fentanyl citrate, 2 mg/kg propofol, and 0.6 mg/kg rocuronium bromide for anesthesia induction in all patients. Maintenance anesthesia was established with 50% O_2/air, 5% desflurane, and 2-3 μg/kg remifentanil infusion and rocuronium (0.1 mg/kg/30 min).

Standard surgical and CBP techniques were used in all patients. Median sternotomy was performed, and the left internal mammary artery (IMA) and saphenous grafts were used. Cardiopulmonary bypass was performed under moderate hypothermia (28 to 32°C). Anesthetic drug doses were regulated such as to maintain mean arterial blood pressure at 50 to 80 mmHg. Dopamine and noradrenaline were administered at appropriate dosages, if blood pressure was low, and vasodilators (i.e., nitroglycerine, or sodium nitroprusside), when the pressure was high. Urine output was maintained at 0.5 mL/kg/h throughout surgery, and the pump blood flow rate was set at 2 to 2.2 L/m^2/min. Target hematocrit values were 20 to 25%. After surgery, the patients were taken to the cardiovascular ICU. Monitoring was recorded for 48 h after transfer to the ICU.

The following parameters were recorded for all patients:

1. Arterial blood gas including pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), bicarbonate (HCO_3), and base excess in extracellular fluid (Be-ecf):

Values were measured before the initiation of surgery, following induction of anesthesia, at the end of surgery, and at baseline, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 42, and 48 h postoperatively.

2. Pain scoring:

The PIS: The pain score (1- no pain, 2- mild pain, 3- moderate pain, 4- severe pain, 5- very severe pain, 6- worst possible pain) given by the observer, while mechanical ventilation was still being applied was recorded at postoperative baseline, 2, 4, 6, 8, 10, and 12 h.

The VAS: The severity of pain assessed by the patient after extubation while at rest and during coughing and breathing was scored from 0 (no pain) to 10 (unbearable pain) was measured at baseline, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 42, and 48 h following extubation.

3. Free cortisol in urine:

A 24-h urine samples were collected from all patients from the time of their arrival at the ICU to measure levels of free cortisol in urine, regarded as a marker of hormonal and metabolic response to surgery-related pain and stress. Total urine volume was recorded. One part was placed into a 10 mL no additive tube and centrifuges at 3,000 rpm for 10 min and, then, stored at -80°C until analysis.

4. Other parameters:

The numbers of drains used, opioid-associated complications such as nausea, vomiting, and pruritus,

total amount of fentanyl consumed with PCA (at postoperative 24 and 48 h) and total amount of bupivacaine consumed with PCA (at postoperative 24 and 48 h) were recorded for all patients.

Glucose, urea, creatinine, AST, ALT, CK, CK-MB, albumin, Na, K, and hsCRP levels were measured using an ARCHITECT c16000 Clinical Chemistry Analyzer (Abbott Diagnostics, Abbott Park, USA). The TnI levels were measured using an ARCHITECT i2000SR immunoassay analyzer (Abbott Diagnostics, Abbott Park, IL, USA). Urine cortisol was measured using a standard (hydrocortisone, Sigma), internal standard (triamcinolone acetonide), ACE 5 C18 (250×4.6 mm, 5 μm) analytic column and 28% acetonitrile mobile phase on a high performance liquid chromatography device (Agilent 1200 HPLC, Agilent Technologies, USA). Blood gasses were measured using an ABL 800 FLEX blood gas device (Radiometer, USA).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and InStat3 GraphPad software (GraphPad Software Inc., CA, USA). Before the study began, a pilot study with five-member groups and using the same protocols applied in Group 1 and Group 2 in the main study was performed to determine the number of experimental subjects needed for the difference in lengths of stay in the ICU to be statistically significant. Based on the pilot study with five members in each group, the mean length of stay in the ICU was 74±13 h and 64±11 h in Group 1 and Group 2, respectively (Type 1 error α=0.05, Type 2 error β=0.20). In a priori power analysis based on a study of free cortisol by Pruessner et al.,[11] we calculated that at least 22 controls and 22 patients were required for the study. Accordingly, the study was conducted with 30 patients in each group.

The PS power and sample size calculation software was used a priori power analysis applied for independent groups using the data obtained. The unpaired t-test was used to compare parametric data between two independent groups and the Mann-Whitney U test to compare non-parametric data. The Pearson correlation

Table 1. Baseline demographic and clinical characteristics of patients

	All patients (n=60)			Group 1 (n=30)			Group 2 (n=30)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p
Gender										0.7994†
Female	33	55		17	57		16	53		
Age (year)			63±6.3			63±7.1			63±5.6	0.9678‡
Body mass index (kg/m^2)			25.3±1.8			25.2±2.0			25.4±1.6	0.6064‡
Waist circumference (cm)			85±6.5			84±6.4			85±6.7	0.7694‡
Cigarette use	22	37		10	34		12	40		0.7282†
Ejection fraction			58.1±3.5			58.1±3.7			58.0±3.4	0.9762†
Glucose (mg/dL)			83±7.8			83±7.7			83±8.1	0.9870‡
AST (IU/L)			19±7.0			21±6.8			19±7.1	0.3141‡
ALT (IU/L)			19±7.4			21±7.7			18±6.6	0.1021†
CK (IU/L)			131±84			126±84			136±86	0.6275‡
BUN (mg/dL)			14.9±3.9			14.8±4.0			14.9±3.8	0.9754‡
Creatinine (mg/dL)			0.8±0.1			0.8±0.1			0.9±0.1	0.8260‡
Albumin (g/dL)			4.3±0.4			4.2±0.4			4.4±0.4	0.3246‡
Sodium (mEq/L)			139±1.9			139±1.9			13±1.8	0.8369‡
Potassium (mEq/L)			4.0±03			4.0±0.4			4.0±0.3	0.9295‡
hsCRP (mg/L)			4.2±2.7			4.3±2.7			4.1±2.8	0.8245‡
CK-MB (IU/L)			15.5±5.7			16.3±5.8			14.8±5.7	0.3244‡
TnI (ng/mL)			0.7±0.5			0.7±0.5			0.6±0.6	0.6707‡

SD: Standard deviation; * Comparison between Group 1 and Group 2; † Mann-Whitney U test; ‡ Unpaired t test; AST: Aspartate aminotransferase; ALT: Alanine amino transferase; BUN: Blood urea nitrogen, CK: Creatine kinase, hsCRP: high-sensitivity C-reactive protein, TnI: Troponin I.

Table 2. Arterial blood gas analysis results

	All patients	Group 1	Group 2	
	Mean±SD	Mean±SD	Mean±SD	*p**
pH				
Zero	7.389±0.048	7.395±0.053	7.383±0.042	0.3201†
At 2 h	7.397±0.062	7.392±0.065	7.403±0.059	0.4732†
At 4 h	7.415±0.051	7.418±0.051	7.413±0.051	0.7288†
At 6 h	7.423±0.055	7.423±0.049	7.423±0.061	0.9741†
At 10 h	7.434±0.055	7.438±0.045	7.429±0.064	0.5217†
At 16 h	7.431±0.049	7.431±0.049	7.431±0.051	0.9305‡
At 24 h	7.425±0.053	7.417±0.052	7.432±0.053	0.2646†
On Day 36	7.432±0.070	7.433±0.072	7.431±0.069	0.8957†
On Day 48	7.449±0.055	7.449±0.063	7.448±0.047	0.9705†
PO_2 (mmHg)				
Zero	148±59	149±65	147±54	0.4688‡
At 2 h	109±20	108±16	110±23	0.7083†
At 4 h	100±19	98±18	101±20	0.5537†
At 6 h	91±14	91±15	91±12	0.9098†
At 10 h	84±11	80±9	88±12	0.0033†*
At 16 h	76±9	74±10	79±7	0.0158†*
At 24 h	74±11	74±15	74±7	0.9379†
On Day 36	73±10	74±13	73±5	0.7348†
On Day 48	75±10	74±12	76±8	0.4494†
PCO_2 (mmHg)				
Zero	32.5±5.2	32.9±5.6	32.2±4.8	0.5947†
At 2 h	33.5±5.4	33.8±5.8	33.2±5.1	0.6458†
At 4 h	34.0±4.0	34.4±2.9	33.7±4.9	0.5136†
At 6 h	35.0±4.8	35.3±5.2	34.7±4.4	0.6484†
At 10 h	35.9±4.9	35.9±4.7	35.8±5.2	0.9667†
At 16 h	37.2±4.7	37.7±5.5	36.7±3.8	0.3837†
At 24 h	37.5±5.2	38.9±5.2	36.0±4.8	0.0278†*
On Day 36	38.1±6.2	39.3±6.1	37.0±6.3	0.1681†
On Day 48	38.8±6.8	39.9±7.9	37.8±5.4	0.2300†
HCO_{3-} (mmol/L)				
Zero	20.5±2.1	20.9±2.0	20.1±2.0	0.0960†
At 2 h	21.3±1.9	21.2±1.8	21.5±2.0	0.6012†
At 4 h	22.6±2.4	22.9±2.3	22.3±2.4	0.3599†
At 6 h	23.4±2.8	23.5±2.6	23.4±3.0	0.9089†
At 10 h	24.3±2.9	24.7±2.5	23.8±3.2	0.2468†
At 16 h	25.0±2.6	25.1±2.3	24.9±3.0	0.6939†
At 24 h	24.8±2.7	24.8±2.4	24.8±3.0	0.9874†
On Day 36	25.6±3.4	25.8±2.7	25.5±4.0	0.7171†
On Day 48	26.8±3.5	26.9±2.9	26.6±4.1	0.7403†
BE (mmol/L)				
Zero	-5.0±2.6	-4.4±2.5	-5.6±2.7	0.0843†
At 2 h	-4.0±2.3	-4.1±2.1	-3.9±2.5	0.7417†
At 4 h	-2.4±2.0	-2.0±2.7	-2.8±3.1	0.3472†
At 6 h	-1.6±3.4	-1.2±3.1	-2.0±3.6	0.3376†
At 10 h	-0.3±3.4	-1.2±3.1	-0.9±3.7	0.2290†
At 16 h	0.5±3.1	0.8±2.8	0.2±3.5	0.4596†
At 24 h	0.2±3.1	0.5±2.8	-0.2±3.4	0.3919†
On Day 36	1.2±3.8	1.7±2.9	0.7±4.5	0.3071†
On Day 48	2.5±3.2	2.9±3.2	2.0±3.2	0.2954†

SD: Standard deviation; * P value is less then 0.05, comparison between group 1 and group 2; † Unpaired t test; ‡ Mann-Whitney U test; pH: The negative log of hydrogen ion concentration, PO_2: Partial pressure of oxygen; PCO_2: Partial pressure of carbon dioxide, HCO3-: Bicarbonate, BE: Base excess.

analysis was used to evaluate correlation between the groups for parametric data and the Spearman correlation analysis for non-parametric data. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the baseline demographic and clinical characteristics of the patients (p>0.05) (Table 1). Similarly, there was no significant difference in the baseline glucose, albumin, AST, ALT, CK, CK-MB, BUN, creatinine, Na, K, hsCRP, or TrI levels between the groups (p>0.05).

Blood gas analysis revealed that PO_2 levels at 10 and 16 h of the ICU stay were lower in Group 1 than Group 2 (80±9 vs. 88±12 mmHg, p=0.0033 and 74±10 vs. 79±7 mmHg, respectively; p=0.0158). In contrast, the PCO_2 levels at 24 h in the ICU stay were higher in Group 1 than Group 2 (38.9±5.2 vs. 36.0±4.8 mmHg, respectively; p=0.0278).

There was no statistically significant difference between the groups in terms of the number of surgical drains, nausea or vomiting severity, duration of pump and cross-clamp, duration of extubation, surgery, and length of hospital stay (p>0.05). However, the length of stay in the ICU was longer in Group 1, compared to Group 2 (3.2±0.6 vs. 2.7±0.6 day, respectively; p=0.0202). Patients in Group 1 also received a higher level of rescue analgesia (n=22, 73%) (p<0.0017) (Table 2). In addition, urine free cortisol levels were higher in Group 1 than in Group 2 (631±505 h and 401±297 μg at 24 h, respectively; p=0.0362) (Table 2).

When the groups were evaluated in terms of PIS during intubation, no significant difference was found between the groups at four h, while PIS scores were higher at two h in Group 1 than Group 2 (p<0.05) (Table 3). When the groups were compared in terms of VAS scores after extubation, the scores in Group 1 were higher than those in Group 2 at all time points, except at 24, 36, and 48 h (p<0.05). Similarly, when the groups were compared in terms of VAS scores during coughing and breathing exercises, scores were higher in Group 1 than Group 2 at all time points, except at 6, 24, 36, and 48 h (p<0.05) (Table 4).

In addition, we found no significant correlation between 24-h urine cortisol levels in all patients and all VAS and PIS scores, although a positive correlation was observed between 24-h cortisol levels and length of stay in the ICU (Spearman r= 0.4847, 95% confidence interval: 0.2560 to 0.6621, p<0.0001) (Figure 1). Correlation between 24-h urine cortisol levels and length of hospital stay was lower (Spearman r= 0.4131, 95% CI: 0.1703 to 0.6086, p=0.0010). The probable reason for the low level of correlation between urine cortisol and hospital stay is that length of hospitalization is dependent on the length of stay in the ICU. Also, we found a moderate correlation between the length of stay in the ICU and hospital in all patients (Spearman r= 0.5698, 95% CI: 0.3625 to 0.7233 p<0.0001). It is not, therefore, possible to conclude that the correlation between the urine cortisol levels and length of hospital stay is based on a direct correlation.

Table 3. Intra- and postoperative data

	All patients			Group 1			Group 2			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p
Cross-clamp time (min)			47.8±15.1			47.6±16.1			47.9±14.3	0.9262†
Duration of pump (min)			79±17			78±17			80±17	0.6425†
Number of surgical drains			2.5±0.5			2.5±0.5			2.5±0.5	0.8272‡
TLAR (mg)		50	69±91		73	108±103		27	29±55	0.0017‡*
Operating time (min)			261±21			260±19			262±24	0.8096†
DE-ICU (min)			304±98			302±103			305±94	0.8824‡
D-ICU (hour)			72±14			78±12			66±13	0.0004†*
NN	31	52		16	53		15	50		0.8272‡
NV	16	27		10	33		6	20		0.3643‡
Length of hospital stay (day)			6.9±0.7			6.9±0.7			6.9±0.6	0.8743‡
Urinary free cortisol level (µg/24h)			516±424			631±505			401±297	0.0362†

SD: Standard deviation; * p value is less then 0.05, comparison between group 1 and group 2; † Unpaired t test; ‡ Mann-Whitney test; TLAR: Total leak analgesia rate; DE-ICU: Duration of extubation in intensive care unit, D-ICU: Duration of intensive care unit; NN: Number of patients with nausea; NV: Number of patients with vomiting.

Table 4. Pain scores of patients

	Group 1	Group 2	Difference	
	Mean±SD	Mean±SD	%	*p**
PIS-WIICU				
Pain at zero h	1.0±0.0	1.0±0.0	-	-
Pain at 2 h	1.8±0.9	1.2±0.4	33	0.0259*
Pain at 4 h	2.4±0.8	2.1±0.8	12	0.2002
VAS-ETWCBE				
Pain at zero h	3.4±1.1	1.1±0.6	68	<0.0001**
Pain at 2 h	2.9±1.0	1.4±0.7	52	<0.0001**
Pain at 4 h	2.6±0.9	1.6±0.9	38	<0.0001**
Pain at 6 h	2.2±0.6	1.8±1.1	18	0.0470*
Pain at 10 h	2.1±0.8	1.4±0.6	33	0.0018*
Pain at 16 h	2.0±1.0	1.3±0.7	35	0.0041*
Pain at 24 h	1.3±0.9	0.8±0.6	38	0.0661
Pain at 36 h	0.8±0.8	0.6±0.6	25	0.4448
Pain at 48 h	0.6±0.9	0.6±0.6	0	0.9342
VAS-ETCBE				
Pain at zero h	3.9±1.1	1.9±0.8	51	<0.0001**
Pain at 2 h	3.5±1.1	2.2±1.0	37	<0.0001**
Pain at 4 h	3.1±1.0	2.1±1.1	32	0.0004*
Pain at 6 h	2.7±0.7	2.4±1.2	11	0.0584
Pain at 10 h	2.5±0.9	1.9±0.7	24	0.0101*
Pain at 16 h	2.1±0.9	1.6±0.8	24	0.0436*
Pain at 24 h	1.6±1.1	1.1±0.6	31	0.0507
Pain at 36 h	1.3±1.2	0.8±0.6	39	0.2230
Pain at 48 h	1.0±1.1	0.6±0.7	40	0.3653

SD: Standard deviation; *,** Mann-Whitney U test; PIS: Pain intensity scale; VAS: Visual analog scale; WIICU: While intubated in intensive care unit; ETWCBE: Extubation times without cough-breathing exercise; ETCBE: Extubation times with cough-breathing exercise.

DISCUSSION

Uncontrollable pain occurring after CABG associated with the splitting of the sternum is one of the most important factors adversely affecting mortality and morbidity. The major component of postoperative pain is median sternotomy-related sternum pain. Other important components include the incision region, intraoperative tissue retraction and dissection, vascular cannulation areas, vein extraction areas, chest tubes and pain related to traumatic events, such as fractures in the thoracic cage. Inflammatory response induced by a surgical trauma is also implicated in the pathophysiology of postoperative pain. Chemical mediators released by peripheral tissue associated with the inflammatory response are thought to lower the threshold of nociceptors and thus make these receptors more susceptible to painful stimuli. In addition, an increase in the level of nociceptors responding to a specific stimulus following trauma may also increase the response to pain.[12] Visceral and somatic stimuli occurring in the periphery and perceived through nociceptors reach the central nervous system via the dorsal horn neurons in the medulla spinalis and are perceived as pain in the central nervous system.[2,13]

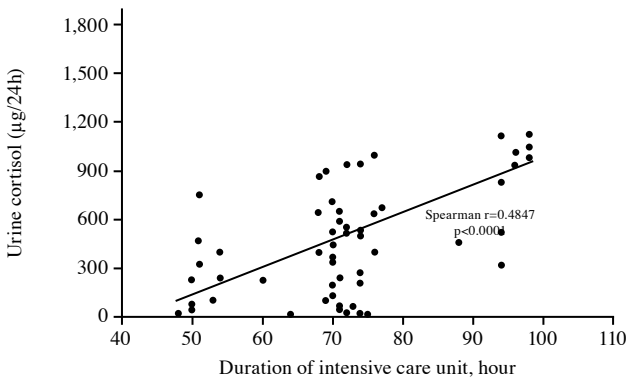

Figure 1. A graph showing correlation between urinary free cortisol levels and the length of intensive care unit stay.

The stress mainly related to the severing of the sternum can significantly increase the heart rate and blood pressure, since it is a powerful stimulus for the sympathetic nervous system. It may also lead to severe problems, such as cardiac ischemia and heart failure, as a cause of arrhythmias. Indeed, in addition to the cardiac system, pain can even adversely affect the immune, hormonal, hematological, and respiratory systems. Patients may experience lung problems, since they are unable to perform sufficient respiratory exercises due to sternum pain arising after sternotomy.[14] On the basis of these facts, the objective of the present study was to treat pain associated with the severing of the sternum, the major component in other words, to reduce patient discomfort in the treatment of postoperative pain to a minimum. Bupivacaine infusion to the sternum region was employed for this purpose. As a result, pain associated with sternum incision was controlled more effectively. Reduction of pain following bupivacaine infusion facilitated respiration and led to higher PO_2 levels at 10 and 16 h during the postoperative ICU stay. This finding is also supported by the PCO_2 levels at 24 h in the group receiving bupivacaine infusion to the sternum region, compared to those receiving fentanyl. Shapira et al.'s[15] study in which they reported that median sternotomy was associated with severe, but brief pulmonary dysfunction represents a guide to the local anesthetic approach directed toward the splitting of the sternum, the major component in postoperative pain in cardiac surgery.

In their study, Friedrich et al.[16] reported that the length of stay in the ICU increased with age, thereby, increasing mortality. The lack of any significant difference in terms of the mean ages of the patients in the two groups in our study suggests that the difference in terms of length of stay in the ICU is not dependent on the age variable. In addition, there was no significant difference between the groups in terms of gender, BMI, WC, LVEF, smoking status or biochemical parameters. The decrease in the length of stay in the ICU in the patients receiving bupivacaine infusion is probably due, not to the characteristics of the patients, but to the method applied being directed toward the primary source of pain (splitting the sternum) and to its ability to provide better analgesia.

Postoperative pain is an undesired side effect of operations intended to improve morbidity and mortality. Good postoperative pain control is associated with rapid improvement in heart, respiratory and gastrointestinal functions, decreased thromboembolic complications, increased arterial graft survival, decreased septic shock complications, less postoperative pain, a decrease in mortality in high-risk patients, and lower health costs.[17] A shorter stay in the ICU in the group receiving bupivacaine infusion, compared to the group receiving intravenous fentanyl citrate, was interpreted as the result of overcoming pain-related adverse outcomes following heart surgery, which is a powerful stressor. To put it another way, a short stay in the ICU shows that patients were not sufficiently comfortable following administration of intravenous fentanyl citrate, but that this was achieved with bupivacaine. The number of patients using rescue analgesia being higher in the intravenous fentanyl citrate group, compared to the bupivacaine group, supports this idea. Methods that increase the administration of rescue analgesia are also questionable in terms of costs. Recent studies have shown that, when stressors such as pain and agitation are appropriately controlled, ventilation support requirement of the patient decreases, stay in the ICU is shortened, and morbidity and mortality rates decline significantly.[9,18] These findings support our hypothesis that a better result can be achieved with an appropriate therapeutic approach primarily targeting sternotomy-related pain.

Currently, the VAS scores are widely used to evaluate postoperative pain. However, despite its wide use, the minimum difference of clinical significance is still unclear. In a recent study, Myles et al.[19] reported that the administration of analgesia producing a 10 mm change in 100-mm VAS pain scores could be clinically significant, and that a change in VAS less than 33 mm represented acceptable pain control after surgery. The VAS scores were significantly lower in our study in the group receiving bupivacaine infusion, compared to fentanyl citrate group (except at 24, 36, and 48 h). The difference in the VAS scores between the two groups was statistically significant, being generally higher than 30%. This is also consistent with the Myles et al.'s[19] findings. However, although the difference in the VAS scores was higher than 30% during coughing and breathing exercises, there were some patients in whom the difference was not statistically significant. This is probably due to severity of pain varying unpredictably during coughing and respiration exercises and to deviation being greater than normal. Another reason for VAS scores being lower both at rest and during coughing and respiration exercises with bupivacaine infusion can be attributed to the fact that it is more effective on the sensory nerves. Bupivacaine is commonly used as a local anesthetic in the treatment of postoperative pain due to its long-acting effect and to its relatively higher affinity for sensory nerve fibers than motor nerve fibers.[6] These findings all constitute evidence showing why postoperative pain was better

controlled in the group receiving bupivacaine infusion in our study.

Surgical trauma stimulates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system though at least three mechanisms: *(i)* hypovolemic stimulation of baroreceptors; *(ii)* direct afferent stimulation and cytokine release from traumatic tissue; and *(iii)* psychological stress deriving from postoperative pain and fear. These contribute to a rise in cortisol levels.[20] A study investigating the reactions of the HPA, renin-angiotensin and sympathetic systems during controlled surgery and anesthetic stress observed an increase in plasma adrenocorticotropic hormone (ACTH) during and immediately after surgery, and that this raised cortisol levels.[21] Epinephrine levels increased through a separate stress-related mechanism. However, they reported that the essential component in the secretion of ACTH, cortisol and epinephrine was the conclusion of anesthesia, not surgical trauma.[21] Successful anesthesia may probably have a calming effect on acute stress response. We, therefore, believe that the response to stress was lightened through successful anesthesia established through local bupivacaine infusion after anesthesia and that free cortisol levels were lower accordingly.

Free cortisol, rather than the protein-bound fraction, is reported to be the hormone responsible for human physiological functions.[22] Free cortisol in urine, a marker of free cortisol as a response to the pain stressor, was measured in this study. Relatively longer ICU stay and higher urine free cortisol levels were measured in the group receiving intravenous fentanyl. However, this situation was reversed in the patients receiving bupivacaine infusion. In addition, free cortisol levels were found to be correlated with the length of ICU stay. It is natural that the length of the ICU stay and urine free cortisol levels should be related, since they are dependent on the ability to control postoperative pain. However, it needs to be confirmed in further studies.

The stress response after a surgical trauma is thought to be a combination of endocrinological, immunological, and hematological changes and the degree of the response is proportional to the dimension of the wound.[23] Activation of the neuroendocrine axis with perioperative pain contributes to immune changes after surgery. The management of postoperative pain can reduce immunosuppression and inflammation induced by surgery. Pain signals activate the neuroendocrine system (catecholamines and glucocorticoids). A constant feedback between the neural and immune systems produces a positive feedback cycle, increasing production of pro-inflammatory cytokines which contribute to severe pain. In addition, a decrease in pro-inflammatory cytokine levels and an increase in lymphocyte activity have been found in patients with successful analgesia.[24] Hypersecretion of cortisol and catecholamine due to surgical stress is reported to have both anti-inflammatory and immunosuppressant effects.[25] A study investigating pre- and postoperative cortisol response showed a significant rise in cortisol levels in all pediatric cases.[26] The reason for this cortisol elevation was shown to be a stress response to the surgical trauma. These findings explain the elevation in urine free cortisol levels in the patients receiving intravenous fentanyl citrate, compared to those receiving bupivacaine infusion, in our study. An increase in urine free cortisol is a marker of a response to stress developing to reduce postsurgical pain signal transmission or to reduce sensitivity to pain (to increase tolerance). An anti-inflammatory process in which cytokine, histamine, and prostaglandin production is inhibited probably occurred due to this response. In this way, the postoperative pain stressor was kept within tolerable limits for the body.

Limitation of study: Other catabolic hormones (catecholamines, glucagon, aldesterone, ACTH and ADH) expected to increase due to postoperative pain due to trauma or surgery, and anabolic hormones expected to decrease (such as insulin and testesterone) could not be measured due to insufficiency.

In conclusion, the patient-controlled analgesia protocol involving bupivacaine administered between the sternum and subcutaneous tissue is a relatively more useful method which produces improved results in blood gas analysis by reducing the effects of pain and shortens the length of intensive care unit stay. Low levels of free cortisol, a marker of acute stress, also confirm this finding.

Declaration of conflicting interests

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