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Effects of three different methods of anesthesia on the release of brain natriuretic peptid in patients with cardiac risk undergoing lower extremity surgery

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Aim: To investigate if intra and postoperative thoracal epidural analgesia could decrease plasma concentrations of brain natriuretic peptide (BNP) in patients who were at risk for, or had, coronary artery disease (CAD) and undergoing lower extremity operations.

Materials and methods: Sixty patients with risk of CAD scheduled to undergo lower extremity surgery were divided into 3 groups. Group G was administered general anesthesia followed by intravenous patient-controlled analgesia (I.V PCA) (n = 20). Group L was administered lumbar epidural anesthesia followed by lumbar epidural analgesia (n = 20). Group T was administered general anesthesia combined with intra and postoperative thoracal epidural analgesia as well as I.V PCA (n = 20). Visual analog scale pain scores, hemodynamics, plasma catecholamines, cardiac troponin I (cTnI), atrial natriuretic peptide (ANP), and BNP were measured preoperatively and measurements were extended to 90 min after skin incision, towards the end of surgery, and in the morning of day 1, 2, and 3 postoperation. The data were statistically compared using multiple comparison tests.

Results: Baseline ANP and BNP concentrations were similar in all groups (G: 25.8 ± 4.51 and 25.9 ± 8.52 pg/mL; L: 23.9 ± 3.67 and 20.8 ± 9.8 pg/mL; T: 24.7 ± 4.27 and 23.0 ± 5.98 pg/mL, respectively). The postoperative plasma BNP concentrations of group T were lower than those of groups L and G. and similarly group L was lower compared to group G in terms of postoperative plasma BNP concentrations ($P < 0.05$). Peak plasma concentrations of BNP were 162.4 ± 29.4, 110.6 ± 12.2, and 69.0 ± 6.9 for groups G, L, and T, respectively ($P < 0.05$). However, there was no group difference in peak plasma ANP concentrations. Baseline epinephrine and norepinephrine concentrations were also similar across the groups. Peak plasma epinephrine concentrations of group T were lower than those of groups G and L ($P < 0.05$). Plasma cTnI concentrations were within normal limits (<0.1 µg/L) in all the 3 groups and no difference in plasma cTnI was observed among the groups throughout the study ($P < 0.05$). The plasma cTnI concentration did not correlate with either the ANP or BNP concentration in each group.

Conclusion: Lower plasma BNP level for patients in group T comparing with patients in other groups and in group L compared to group G may suggest that opioids and local anesthetics could contribute to the positive effects of thoracal epidural analgesia and lumbar epidural anesthesia plus analgesia through inhibition of BNP release.

Key words: BNP, thoracal epidural analgesia, lumbar epidural anesthesia

Alt ekstremite cerrahisi uygulanacak kardiyak riskli hastalarda üç farklı anestezi metodunun Brain natriüretik peptid salınımına etkisi

Amaç: İntra ve postoperatif torakal epidural analjezinin (TEA) ve lumbar epidural anestezi (LEA) ve analjezinin koroner arter hastalığı olan veya riski taşıyan ve alt ekstremite cerrahisi uygulanan hastalarda brain natriüretik peptid (BNP) plazma konsantrasyonuna etkisini incelemeyi amaçladık.

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Yöntem ve gereç: Koroner arter hastalığı olan veya riski taşıya alt ekstremite cerrahisi uygulanacak 60 hasta rastgele 3 gruba ayrıldı. Grup G: Genel anesteziyi takiben intravenöz hasta kontrollü analjezi (I.V PCA), Grup L: Lumbar epidural anesteziyi takiben lumbar epidural analjezi, Grup T: Genel anestezi ve torakal epidural analjeziyi takiben IV PCA uygulandı. VAS ağrı skoru, plazma katekolaminleri, kardiyak troponin I, atriyal natriüretik peptid ve BNP değerleri preoperatif, cilt insizyonundan 90 dakika sonra, cerrahinin sonunda postoperative 1, 2, 3. günün sabahı ölçüldü. Verilerin analizi için ANOVA ve Duncan testi uygulandı.

Bulgular: Bütün gruplarda bazal ANP ve BNP konsantrasyonları benzerdi (G: 25,8 ± 4,51 ve 25,9 ± 8,52 pg/mL; L: 23,9 ± 3,67 ve 20,8 ± 9,8 pg/mL; T: 24,7 ± 4,27 ve 23,0 ± 5,98 pg/mL sırasıyla). T grubu postoperative BNP konsantrasyonu diğer iki gruptan, L grubu ise Grup G'den düşüktü (P < 0.05). BNP pik plazma konsantrasyonu G grubunda 162,4 ± 29,4 pg/mL; L grubunda 110,6 ± 12,2 pg/mL; ve T grubunda 69,0 ± 6,9 pg/mL idi. ANP pik plazma konsantrasyonunda önemli farklılık yoktu (P < 0,05). Bazal epinefrin ve norepinefrin konsantrasyonu tüm gruplarda benzerdi. Epinefrin pik plazma konsantrasyonu Grup T de diğer iki gruba gore düşüktü. (P < 0,05). Plazma cTnI konsantrasyonu her üç gruptada normal sınırlar içindeydi (<0,1 μgmL-1) ve çalışma süresince gruplar arasında farklılık gözlenmedi. Plazma cTnI konsantrasyonu ANP ve BNP konsantrasyonları ile önemli bir korelasyon göstermedi (P < 0,05).

Sonuç: BNP düzeyi intra ve postoperatif torakal epidural analjezi uygulanan grupta diğer iki gruba göre, Lumbar epidural anestezi ve analjezi uygulanan grupta da genel anestezi grubuna göre azaldı. Biz opioid ve lokal anesteziklerin pozitif katkısı olduğunu düşünüyor ve kardiyak riskli hastalarda torakal epidural analjezi kullanılmasını öneriyoruz.

Anahtar sözcükler: BNP, torakal epidural analjezi, lumbar epidural anestezi.

Introduction

Coronary artery disease (CAD) constitutes the majority of cardiac diseases. Perioperative myocardial ischemia is known to be the single most important predictor of the cardiac outcome, such as (unstable angina, myocardial infarct, and sudden death) in patients with CAD or those at risk for CAD (1,2). Surgical and anesthesia techniques for major operations are continuously being improved to minimize these fatal outcomes, reduce the cost, and help patients return to their normal activities as soon as possible. The role of postoperative epidural analgesia in reducing perioperative risk is controversial (3). Thoracic epidural analgesia (TEA) however provides various benefits including myocardial ischemia reduction (3-5). In addition to pain relief, TEA may decrease cardiac morbidity through correcting the myocardial oxygen balance and modulating the sympathetic response (3,4). Both lumbar epidural anesthesia (LEA) and analgesia reduce pulmonary and cardiac complications, and improve myocardial oxygenation and tissue reperfusion (6).

The majority of patients with perioperative ischemia remain asymptomatic, and serum markers of myocardial ischemia, such as CK-MB and cardiac troponins, usually do not increase (4,7). The ischemic heart disease without myocyte necrosis is characterized by activation of the natriuretic peptide system (7,8). Natriuretic peptides are synthesized by the heart and regulate arterial blood pressure, electrolyte balance, and fluid volume (9,10). The diagnostic and prognostic value of these cardiac hormones in non-surgical patients with or without symptomatic cardiac disease has been confirmed by several studies (11,12). However, studies on the role of epidurals on the release of cardiac natriuretic peptides in patients undergoing major surgery and anesthesia are limited (4,8).

We conducted this study to determine if the supplementation of general anesthesia with intra and postoperative thoracal epidural analgesia could decrease plasma concentrations of brain natriuretic peptide (BNP) in patients with CAD or those at risk for CAD scheduled to undergo major lower extremity surgery.

Materials and method

The study was approved by Atatürk University Ethics Committee, and written informed consent was obtained from each patient. Additionally, all patients were given a comprehensive explanation of the anesthetic techniques, informed about the benefits of optimal pain management, and instructed to notify the attending physician or nurse in case of any pain.

In patient selection, presence and/or risk for CAD as well as planned lower extremity surgery were considered. Presence of CAD was ascertained by history of myocardial infarction and diagnosis of typical angina or atypical angina with a positive stress test. Risk for CAD was based on age (65 years old), blood pressure, smoking habit, blood cholesterol (>240 mg/dL), and diabetes. Moreover patients were excluded from the study if they met the following conditions: 1) severe impairment of left ventricular function (ejection fraction <35%-40%), 2) severe symptomatic mitral or aortic valve disease, 3) decompensated congestive heart failure, 4) symptomatic arrhythmias, 5) liver dysfunction (alanine aminotransferase and aspartate aminotransferase > 40 U/L), 6) renal failure requiring hemodialysis, 7) known allergies to the drugs used in the present study, 8) contraindications to dural perforation (chronic back pain or previous lumbar spinal surgery in the area of puncture, localized infection, and use of an antiplatelet drug within 3 days before the surgery), and 9) unusual blood coagulation tests (activated partial thromboplastin time > 40 s, international normalized ratio > 1.25, fibrinogen concentration < 1 g/L, platelet count < 150×10^9/L) (4).

A total of 60 patients who met the selection criteria were randomly allocated to 1 of the 3 groups. Group G (n = 20) received general anesthesia followed by IV patient-controlled analgesia (IV PCA), group L (n = 20) received lumbar epidural anesthesia followed by lumbar epidural analgesia, and group T (n = 20) received general anesthesia combined with TEA and IV PCA. To avoid the risk for epidural hematoma, anesthesia personnel and nurses were also informed about the study groups and no patient was subjected to a sham epidural insertion. A routine clinical examination including a detailed medical history, physical examination, laboratory tests, chest radiography, and 12-lead electrocardiogram (ECG) was performed for all patients before the operation. Preoperative cardiac medications were used until the day of surgery. All patients received intramuscular midazolam (3.5 mg) 1 h before surgery.

For group L, an epidural catheter was placed between L4 and L5 through the median approach using the hanging drop technique. A test dose of 3 mL of lidocaine 1.5% was injected to exclude the intrathecal placement of the epidural catheter. Epidural blockade was achieved by an initial 10-15 mL bolus of 5 mg/mL of bupivacaine and 5 μg/mL of fentanyl, depending on patient size and catheter placement. Somatosensory blockade was checked by evaluating the cold sensitivity of the skin with ice and the pinprick test. Surgery was allowed if the level of block was ensured to be below Th_{10}. Every 1-2 h, 10 mL of the same solution was administered. For postoperative analgesia 10-12 mL of 1.25 mg/mL bupivacaine + 2 μg/mL fentanyl mixture was delivered from the epidural catheter when VAS score was greater than 3.

For group T, an epidural catheter was inserted between a replace T2 and T5 before the induction of general anesthesia. A test dose of 3 mL of lidocaine 1.5% was injected to exclude the intrathecal placement of the epidural catheter. Epidural blockade was achieved by an initial bolus of 10-12 mL of 1.25 mg/mL bupivacaine and 2 μg/mL fentanyl depending on patient size and catheter placement. The extent of the epidural blockade was recorded. The same dose of the same solution was administered at every hour throughout the operation. For TEA, the same dose of the same solution was administered every 3 h during the postoperative period.

Anesthesia of the patients in groups G and T was induced using weight-adjusted doses of thiopental (3 to 5 mg/kg), fentanyl (2 μg/kg), and rocuronium bromide (0.6 mg/kg). After intubation of the trachea, the lungs were ventilated with 40% O_2 + 60% N_2O. Ventilation was set to a tidal volume of 10 mL/kg. The ventilation rate was adjusted to keep the end tidal CO_2 between 35% and 45%. Anesthesia was maintained with sevoflurane and additional bolus injections of rocuronium bromide. Additional bolus injections of fentanyl (0.1 mg, i.v.) were used to sustain intraoperative analgesia in both groups by the order of the attending anesthesiologist. Doses of anesthetics were titrated to provide optimal anesthesia as reflected by lacks of movement, lacrimation, and sweating and surgical state, while maintaining hemodynamic stability.

IV-PCA was started in both groups G and T for postoperative analgesia. After i.v. bolus of injection of 3 mg morphine initially, patients were connected to a

PCA pump (Abbott Pain Management Provider, North Chicago, IL, USA) delivering a continuous infusion of 0.3 mg/h and 1 mg i.v. bolus of morphine on demand with a 15 min lock-out interval and 8 mg of 4-h limit. Fluid balance was monitored. It would be invalid to replace the evaporative loss, which is the loss of free water, with the lactated Ringer's solution. Perioperative monitoring included pulse oximetry, continuous monitoring of leads II and V5 of the ECG with automated ST segment analysis, and continuous invasive measurement of mean arterial pressure (MAP) and central venous pressure (CVP).

Patients were extubated in the intensive care unit (ICU). From day 1 to 3 postoperation days (PODs), all patients were evaluated at least twice a day to adjust the dose of analgesics, to avoid insufficient analgesia, by a physician in the acute pain department. The analgesic demand in all groups was supplied to obtain a VAS pain score < 3 during rest and a dynamic pain score (i.e., scoring the pain during movement, coughing, or taking deep breaths) of < 5 (0 = no pain; 10 = worst pain)). Analgesic use in both groups was further reviewed during the daily visits by the physicians in the acute pain department in order to optimize the analgesia while minimizing side effects, such as sedation, respiratory depression, nausea, pruritus, and hemodynamic instability. Venous blood specimens were obtained preoperatively, 90 min after skin incision, towards the end of surgery, and in the morning of the PODs 1, 2, and 3 ; and stored at -40 °C until analysis. The following variables were determined using commercially available laboratory kits: BNP (Triage BNP test, Biosite Inc., France), a result >80 pg mL^{-1} was considered an indication of neurohormonal activation in patients with acute coronary syndromes [10]; atrial natriuretic peptides (ANP) (ANP Eliza kit, Biosupply, UK), with a reference value in the range of 10-70 pg/mL in healthy men under 65 years of age [10]; and cardiac troponin I (cTnI) (Troponin I Enzyme Immunoassay; Biosite, Germany) with levels up to 0.1 μg/L as normal. The plasma concentrations of epinephrine and norepinephrine were measured by reverse-phase high-performance liquid chromatography (HPLC).

We considered any decrease in BNP with thoracal epidural analgesia as a primary outcome. To achieve 30% reduction in BNP, power analysis at an alpha error of 0.05 with a power (beta error) of 0.80 revealed a sample size of 19 patients in each group. The data were analyzed by ANOVA and Duncan test was used for group difference (SPSS 11.5 for Windows, Chicago, IL, USA). All data were expressed as either mean ± SD or quartiles and statistical significance was declared at $P < 0.05$.

Results

A total of 60 patients were included in the study. Table 1 shows similarity of the patients, with respect to cardiac risk factors preoperative medication, and surgery type across the groups. There were no differences in the anesthesia, surgery, and ICU durations, blood loss, urine output, fluid and blood amounts administered perioperatively, and hospital stay among the study groups (Table 2). Hemodynamic measurements did not differ among the patients in none of the groups, except the heart rate, which was the lowest among patients in group T (Table 3). The postoperative dynamic VAS scores were similar across the study groups. The baseline ANP and BNP concentrations were also similar among the groups (25.8 ± 4.51 and 25.9 ± 8.52 pg/mL for group G, 23.9 ± 3.67 and 20.8 ± 9.8 pg/mL for group L, 24.7 ± 4.27 and 23.0 ± 5.98 pg/mL for group T (Figures 1and 2). The variables changed over time; increased toward the end of surgery and remained high, regardless of the study groups. The postoperative BNP plasma concentrations for group T was the lowest, followed by groups L and G ($P < 0.05$; Figure 1); and group L was lower compared to the G group. The BNP peak plasma concentrations were 162.4 ± 29.4, 110.6 ± 12.2 and 69.0 ± 6.9 pg/mL for patients in groups G, L, and T, respectively ($P < 0.05$; Figure1). There was no group difference in the peak plasma ANP concentrations. It was 64.0 ± 4.48, 60.4 ± 2.4, and 58.1 ± 3.11 pg/mL patients in group G, L, and T, respectively ($P < 0.05$; Figure 2). The baseline epinephrine and norepinephrine concentrations were similar in all groups (Figures 3 and 4). Plasma concentrations of epinephrine at the end of surgery and 90 min after surgery were lower among patients in group T than those among the patients in groups G and L ($P < 0.05$; Figure 3). The plasma cTnI concentrations were within normal limits (<0.1μg/L) in all patients throughout the study period without a

Table1. Patient data, medication, and type of surgery.

	Group L (n = 20)	Group G (n = 20)	Group T (n = 20)
Age	67 ± 3	66 ± 2	67 ± 2
Sex (M/F)	9/11	8/12	9/11
Weight (kg)	75 ± 11	74 ± 13	72 ± 9
Typical angina	3	2	4
Diabetes	5	6	7
Smoker	11	11	13
Hypercholesterolemia	9	8	6
Hypertension	10	11	12
Preoperative medications			
ACEI	6	8	13
Diuretics	5	6	4
β- Blockers	11	9	6
Type of surgery			
Total hip arthroplasty	11	10	12
Hip arthroplasty	9	10	8

Values are expressed as mean ± SD or number of patients (n). ACEI: angiotensin-converting enzyme inhibitor. There were no group differences ($P < 0.05$).

Table 2. Perioperative data

	Group L (n = 20)	Group G (n = 20)	Group T (n = 2 0)
Duration of surgery (min)	180 ± 67	175 ± 50	160 ± 63
Duration of anesthesia (min)	224 ± 65	238 ± 55	230 ± 50
Intraoperative blood loss (mL)	398(250-875)	410(275-978)	400(280-985)
intraoperative urine output (mL)	320(210-570)	325(240-630)	315(250-625)
intraoperative volume infusion (mL)	3500(3000-4000)	3600(3100-4300)	3550(3000-4250)
POD1	3200(2200-4250)	3000(2100-4000)	3250(2250- 4275)
POD2	3100(2100-4200)	2950(2100-4150)	3150(2200-4200)
POD3	2500(2000-3500)	2550(1900-3250)	2550(1800-2950)
ICU length of stay (days)	2 (1-3)	2 (1-3)	2(1-3)
In-hospital mortality (%)	0	0	0
Postoperative hospital stay (days)	10 (9-11)	12 (9-16)	9 (8-10)

Values are expressed as mean ± SD, number of patients (n) or median. POD = postoperative day, ICU: intensive care unit. There were no group differences ($P < 0.05$).

Table3. Hemodynamic variables.

Time and Group	HR	MAP (mmHg)	CVP (mmHg)
Baseline			
G	79.4 ± 7	84.9 ± 12	10 ± 3
L	78.7 ± 6	85.3 ± 9	11 ± 2
T	77.5 ± 5	85.2 ± 9	11 ± 2
90 min			
G	80.1 ± 5	83.2 ± 8	12 ± 4
L	80.5 ± 8	84.1 ± 12	11 ± 2
T	68.2 ± 4*†	80.7 ± 5	10 ± 1
End of surgery			
G	82.4 ± 8	83.7 ± 6	13 ± 3
L	84.5 ± 7	85.2 ± 9	13 ± 4
T	65.2 ± 7*†	82.2 ± 7	12 ± 3
POD 1			
G	80.4 ± 7	84.5 ± 14	14 ± 4
L	79.6 ± 10	84.1 ± 11	13 ± 3
T	78.2 ± 4	83.3 ± 9	12 ± 3
POD 2			
G	77.7 ± 6	85.4 ± 10	12 ± 3
L	75.2 ± 8	83.2 ± 10	13 ± 4
T	76.5 ± 5	82.4 ± 6	12 ± 5
POD 3			
G	75.3 ± 10	84.4 ± 9	11 ± 4
L	73.4 ± 9	83.1 ± 13	12 ± 3
T	72.4 ± 3	82.5 ± 10	12 ± 4

Values are expressed as mean ± SD. They are reported at baseline (induction of anesthesia), 90 min after skin incision, end of surgery and PODs 1, 2, and 3. HR = heart rate, MAP = mean arterial blood pressure, CVP = central venous pressure in both groups. * $P < 0.05$ compared to other groups. † $P < 0.05$; significantly different from baseline.

group difference (Table 4). The plasma cTnI concentration was correlated with neither the ANP nor BNP concentration in each group.

Discussion

The perioperative stress is associated with hypercoagulability and the release of proinflammatory cytokines into the circulation caused by excessive activity of the neuroendocrine systems, particularly due to insufficient pain control in the postoperative period (3). Vasospasm caused by this stress response impairs the coronary blood flow and consequently increased contractility of the myocardium disturbs the balance between the supply and the need for oxygen that may lead to outcomes ranging from myocardial ischemia to severe cardiac injury (2,4,8).

BNP is recognized as a marker to determine the acute risk of patients with cardiovascular condition ranging from asymptomatic myocardial ischemia without ST segment elevation to acute transmural myocardial infarction (11). We postulated that TEA in addition to general anesthesia would suppresses the neurohormonal response and epidural administration of local anesthetics and opioids attenuated BNP release in patients undergoing lower extremity surgery. In this study, intra- and postoperative TEA

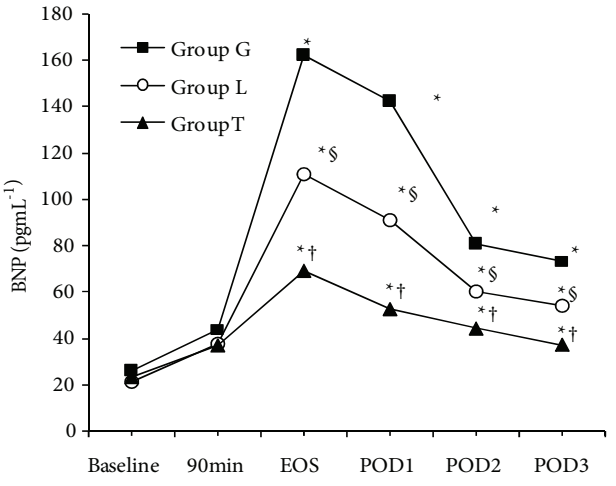

Figure 1. Perioperative changes in brain natriuretic peptide (BNP). Values are expressed as mean ± SD baseline (induction of anesthesia), 90 min (90 min after skin incision), EOS (end of surgery), PODs (postoperative days) * P < 0.05: significantly different from baseline. † P < 0.05 compared to other groups. § P < 0.05 different from G. Group G= General anesthesia + IV PCA, group L = Lumbar epidural anesthesia + analgesia, group T = General anesthesia +Thoracal epidural analgesia + IV PCA.

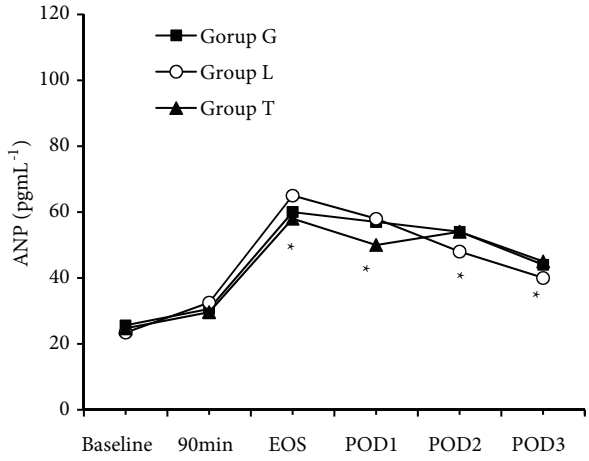

Figure 2. Perioperative changes in atrial natriuretic peptide (ANP). Values are expressed as mean ± SD. Baseline (induction of anesthesia), 90 min (90 min after skin incision), EOS (end of surgery), PODs (postoperative days) * P < 0.05: significantly different from baseline. Group G = General anesthesia + IV PCA, group L = Lumbar epidural anesthesia + analgesia, group T = General anesthesia + Thoracal epidural analgesia + IV PCA.

Table 4. Perioperative changes in cTnI (μgL^{-1}).

	Group T (n = 20)	Group L (n = 20)	Group G (n = 20)
Baseline	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
90min	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.02
EOS	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
POD1	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
POD2	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.02
POD3	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.01

Values are expressed as mean ±SD. Baseline (induction of anesthesia), 90 min (90 min after skin incision), EOS (end of surgery), PODs (postoperative days) Plasma cTnI were not diffrrent among the groups throughout the study period (P < 0.05), no significant difference.

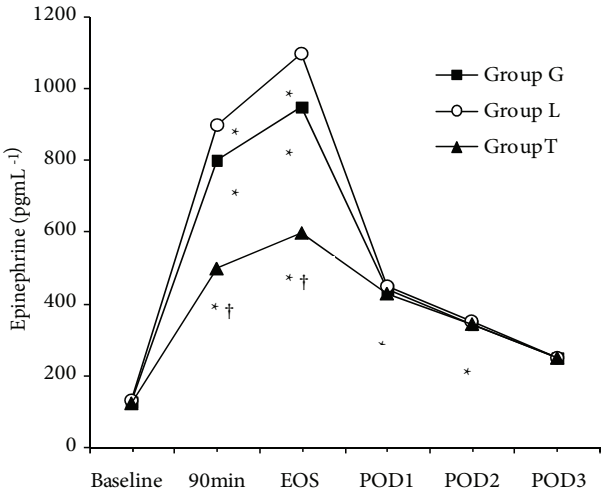

Figure 3. Perioperative changes in epinephrine. Baseline (induction of anesthesia), 90 min (90 min after skin incision), EOS (end of surgery), PODs (postoperative days) * P < 0.05: significantly different from baseline. + P < 0.05: compared to other groups. Group G = General anesthesia + IV PCA, group L = Lumbar epidural anesthesia + analgesia, group T= General anesthesia +Thoracal epidural analgesia+ IV PCA.

used for patients with cardiac risk decrease the release of BNP, and also BNP release was lower in the LEA and analgesia group compared to the general anesthesia and IV PCA group.

The ANP and BNP concentrations are used as markers of myocardial function (11). Increased plasma BNP level reflects the extent and severity of

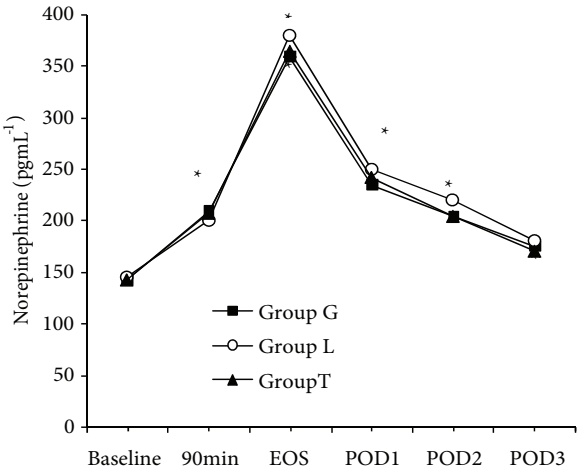

Figure 4. Perioperative changes in norepinephrine. Values are expressed as mean ± SD. Baseline (induction of anesthesia), 90 min (90 min after skin incision), EOS (end of surgery), PODs (postoperative days) * P < 0.05: significantly different from baseline. Group G = General anesthesia + IV PCA, group L= Lumbar epidural anesthesia + analgesia, T = General anesthesia + Thoracal epidural analgesia + IV PCA.

an ischemic insult, as well as the degree of left ventricular dysfunction resulting from myocardial ischemia even when myocyte necrosis has not occurred (8,10). When sympathoadrenal and neurohormonal activation increase in response to ischemic myocardial injury, ANP and BNP act as counter regulatory hormones (4,11). In patients with cardiovascular circumstance, such as unstable angina, acute coronary syndromes, heart failure, or larger concentrations of BNP, are associated with increased cardiovascular and overall mortality (11-14).

The combination of epidural analgesia with general anesthesia is a method employed frequently for major operations. This combination suppresses the hormonal and autonomous response to surgery by inhibiting afferent stimuli (4), suggesting that the use of continuous TEA for perioperative pain management in patients with CAD modulates the neurohormonal pathways to produce anti-ischemic actions and decreases the severity of myocardial ischemia (8,10,12,15). In a study involving 40 patients with unstable angina, lausson et al. performed a blockade of upper 5 thoracal segments by continuous bupivacaine infusion through TEA (16). They concluded that TEA reduced the heart rate without affecting the MAP and coronary perfusion pressure, and therefore exerted a positive effect on the oxygen balance of the myocardium. A meta-analysis study by Beattie et al. (17) demonstrated that pain management with TEA for 24 h after surgery reduced the postoperative myocardial infarction (PMI) rate by 40% and reported that TEA was superior to lumbar epidural analgesia in reducing PMI. Stunner et al. (4) also performed continuous intra- and postoperative TEA in patients undergoing major abdominal surgery and reported that TEA attenuated BNP release.

In our study, intra- and postoperative BNP levels in patients who had received TEA were significantly lower compared to the other 2 groups.

Lumbar epidural anesthesia and analgesia are associated with a lower incidence of reoperation, which may be advantageous for this surgical population (6,18). In several studies comparing epidural analgesia with IV PCA, it has been demonstrated that epidural analgesia is superior in terms of pain relief in orthopedic, general surgical patients when compared with PCA. Additional advantages of epidural analgesia in comparison with i.v opioids for postoperative pain control include reduction of pulmonary and cardiac complications and improvement in myocardial oxygenation and tissue reperfusion (6,19). Cardiac morbidity was shown to be lower among patients undergoing major vascular surgery after the administration of general combined anesthesia and postoperative epidural analgesia compared to the administration of general anesthesia alone and postoperative systemic opioid analgesia (20). A meta-analysis revealed a significant reduction in venous thromboembolism in patients undergoing surgery for hip fracture under regional anesthesia compared with general anesthesia, but resulted in only a marginally better effect on early mortality (21). In our study, intra- and postoperatively, the BNP levels of the group L were significantly lower compared to group G. Christopherson et al. (18) compared epidural and general anesthesia in terms of myocardial ischemia, MAP, and HR in high-risk patients scheduled for lower extremity vascular surgery. Their results showed significantly lower MAP and HR values in the LEA group, and did not show a difference in myocardial ischemia between groups. In our study

MAP and HR values did not show remarkable difference compared to general anesthesia due to administration of below Th_{10} levels and absence of sympathetic blockade in group L.

In non-surgical patients, increased plasma BNP values may be used as diagnostic and prognostic markers to assess asymptomatic myocardial ischemia without ST segment elevation (4,8,11). However, it is unclear whether an increase of ANP and BNP after surgery indicates myocardial ischemia in patients without symptoms. In a meta-analysis it was reported that performance of BNP and NT-pro-BNP were at least equivalent to the best of the traditional preoperative diagnostic tests of cardiac morbidity for vascular surgical patients. Rodseth et al. (8), however, emphasized that the performance of BNP and NT-pro-BNP as pre-operative diagnostic tests may be better than what it was presented in that meta-analysis. ANP and BNP are considered to have different but complementary functions in the regulation of cardiovascular homeostasis (10). BNP is more sensitive for left ventricular damage than ANP (10). The mean concentration of ANP in healthy volunteers was 26.8 ± 9.7 pg/mL., whereas the mean control value for BNP was 15.9 ± 9.6 pg/mL. De Lemos et al (11) studied the prognostic value of BNP in the acute coronary syndrome in 2525 patients with ischemic symptoms. The authors determined that a BNP level above 80 pg/mL was associated with mortality and new or recurrent myocardial infarction more than those with a level of ≤ 80 pg/mL. They thought that cut off point was neurohumoral because at pre, peri, and postoperative periods there was no cardiac complication and death. BNP may also be considered an indicator of reduced cardiac performance rather than structural myocardial damage, because all natriuretic peptides have different release mechanisms. Since some endogenous vasoactive factors, neurotransmitters, proinflammatory cytokines, and hormones may directly stimulate ANP and BNP releases, natriuretic peptides exhibit variable behaviors (10,12). ANP may regulate blood pressure and water-electrolyte balance, whereas BNP may act as a ventricular local regulator for protecting the heart from damage and fibrosis (8). Plasma concentrations of natriuretic peptides may also increase after transient volume load due to perioperative fluid administration (9). Berendes et al. (10) observed that ANP and BNP had variable secretion patterns in cardiac surgery patients. We performed volume replacement according to CVP monitoring. As the ANP values did not exceed the normal limits, no difference was observed among groups. In our study higher plasma BNP values among patients in group G could be related to a possible increase in the left ventricular wall stress secondary to transient myocardial ischemia.

Cardiac specific troponins (cTnI) are common biochemical indicators used for the diagnosis of myocardial infarction and unstable angina pectoris and assessment of the prognosis (22). Although a slight increase in the troponins does not suffice to indicate extensive myocardial damage, high levels may be accepted as an indicator of myocardial damage. In the present study, there was neither ST change nor difference in plasma cTnI concentration among groups. Concentrations of cTnI was independent from ANP and BNP releases.

In conclusion, BNP release was lower upon intra and postoperative TEA group compared to 2 other groups and in LEA + analgesia group compared to the general anesthesia group among patients with or at risk for coronary artery disease undergoing lower extremity operations. We believe that opioids and local anesthetics also contributed to the positive effects of TEA and lumbar epidural anesthesia plus analgesia. For high-risk cardiac patients, epidural anesthesia followed by epidural postoperative analgesia should be preferred.

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