Comparison of Three Different Epidural Solutions in Cardiac Surgery for Stress Protection

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Abstract: *Background*: Different solutions are possible for thoracic epidural analgesia in cardiac surgery. So far, local anesthetics alone or in combination with either clonidine or opioids have been used.

Aims: To determine the stress protection provided by different epidural solutions throughout cardiac surgery.

Study Design: A randomized, prospective, double blind study in patients undergoing off-pump coronary artery bypass grafting (OPCAB), randomized in three different groups. Thoracic epidural analgesia was installed more than 1 h before application of heparin at levels of T2 to T4; analgesia was provided by 8 ml of bupivacaine 0.25% 15 min prior to surgery and extubation, and 10 ml/h during and up to 72 h after surgery using one of the following regimens: bupivacaine 0.125% solely, bupivacaine 0.125% with fentanyl 3 μg/mL or bupivacaine 0.125% with clonidine 0.6 μg/mL. Patients were block-randomized for one of the three treatments. Cortisol and glucose values were determined before surgery, at extubation and 1h and 3h after surgery. Pain scores were assessed up to 48 h after surgery. Hemodynamic stability was also recorded in form of heart rate, systolic and diastolic blood pressure. Multi-comparison ANOVA and Chi-square test were used to compare the data, presented as mean (SD) or median (25th and 75th percentile), $P < 0.05$.

Study Setting: A cardiac surgery unit at a tertiary university hospital.

Participants: Forty-two patients undergoing OPCAB were enrolled.

Main Results: All patient data as well hemodynamic stability were not different between the three groups. All patients were successfully extubated in theatre immediately after surgery. Pain control was good and not significantly different between the groups. Mean glucose concentrations ± SD before surgery and (significantly higher) 3h after surgery were 5.4 ± 1.0 mmol l^{-1} and 8.4 ± 1.6 mmol l^{-1} for bupivacaine alone, 5.2 ± 0.5 mmol l^{-1} and 8.5 ± 2.2 mmol l^{-1} for bupivacaine plus fentanyl and 5.5 ± 1.6 mmol l^{-1} and 9.5 ± 2.1mmol l^{-1} for bupivacaine and clonidine, respectively. The mean cortisol values ± SD in the pre-operative period and 3h after surgery were 413 ± 162 nmol l^{-1} and 562 ± 173 nmol l^{-1} for bupivacaine alone, 393 ± 107 nmol l^{-1} and 581 ± 265 nmol l^{-1} for bupivacaine and fentanyl and 409 ± 159 nmol l^{-1} and 570 ± 160 nmol l^{-1} for bupivacaine and clonidine, respectively. There were no significant differences between the groups.

Conclusions: We conclude that short-term stress protection with TEA is equally effective with solely bupivacaine, bupivacaine with fentanyl or clonidine.

Keywords: OPCAB, TEA, stress protection.

INTRODUCTION

Thoracic epidural analgesia (TEA) has been advantageous in providing superior analgesia and better respiratory function in comparison to opioid based techniques in different types of surgery [1]. Because of these advantages, TEA has gained popularity in cardiac surgery despite the possible risks of epidural hematoma formation. Some studies showed particular advantages of epidural analgesia in cardiac surgery: TEA provides good hemodynamic control [2,3], allows early extubation times [3,4] with better pulmonary function and very little postoperative pain [5]. Thoracic epidural analgesia also reduces morbidity by reducing respiratory complications like atelectasis and pneumonia and possibly supraventricular arrhythmias [6].

Cardiac surgery like any type of surgery triggers an inflammatory reaction. The stress response initiates a catabolic state reflected by muscle breakdown, hyperglycemia [7-9], altered substrate utilization [10] and altered immune function [11]. The cytokine response may also promote end organ dysfunction and may have an impact on cardiac surgery outcome [12-14].

If it is true that TEA with a sole local anesthetic agent reduces the stress response after cardiac surgery, it would be

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interesting to see whether the addition of clonidine or opioid– in our case: fentanyl – could add further to the efficacy to reduce the inflammatory process after cardiac surgery.

In this study, we investigated three different epidural solutions assuming that the addition of either clonidine or fentanyl to bupivacaine might improve the stress protection compared to bupivacaine solution alone.

METHODS

This is a randomized double-blind controlled trial. Institutional and review board approved this investigation. Forty-two consenting patients undergoing off-pump coronary artery bypass (OPCAB) grafts by two surgeons were included and randomized to receive one of three epidural solutions. Those three epidural groups were:

- Bupivacaine 0,125% alone (B)

- Bupivacaine 0,125% and clonidine 0,06% (BC)

- Bupivacaine 0,125% and fentanyl 3 µg/ml (BF)

Before surgery, patients were familiarized with the insertion of the thoracic epidural catheter and ultra-fast-track protocol (immediate extubation in the operating room). All patients consented for the insertion of the epidural catheter immediately before surgery and immediate extubation after the surgery.

We included patients aged between 18 and 90 and having an ejection fraction of at least 30%. Exclusion criteria were patient refusal to participate in the study or use of epidural analgesia, pregnant women, patients with contraindication for the installation of the epidural catheter such as site infection or coagulopathy. We also excluded diabetic patients.

Routine monitoring included 5-lead electrocardiography, invasive blood pressure monitoring *via* femoral artery catheter, central venous pressure monitoring *via* right subclavian venous catheter, pulse oximetry and BIS monitoring (A-2000 Bispectral Index monitoring system, Aspect Medical System, MN, USA). Anesthesia was performed in the same fashion for all patients: At arrival in the operating theatre, an epidural catheter was inserted at T2-T4 under local anesthesia. Verification of correct placement was performed using 2-3 ml of lidocaine 1,5% with epinephrine 1:200000. Correct functioning of the catheters were tested with ice.

Anesthesia was then induced by fentanyl 3 µg/kg, followed by propofol 1-2 mg/kg. After mask ventilation using 100% oxygen for 3 min, endotracheal intubation was facilitated by rocuronium 0.6 mg/kg. After the trachea was intubated, a right sub-clavian central venous catheter and a right femoral artery catheter were inserted.

Intraoperative anesthesia was maintained by sevoflurane titrated to maintain a BIS around 50, analgesia by epidural analgesia according to group assignment in a blinded way.

In all groups, a bolus of 4-8 ml of bupivacaine 0.25% was given 15 min before skin incision and 20 min before extubation in the operating theatre. The solutions under study were started after the initial bolus of bupivacaine and kept for three days after the surgery at a rate of 10 ml/h. Active temperature control was achieved with forced air warming therapy and increased room temperature (22°C or more). Forced air warming therapy was ascertained by using two BAIR Huggers (Augustine medical company, Eden Prairie, MN, USA). The first one was attached to a modified plastic cover to provide warm air around the patient's head and was started immediately after induction of anesthesia. The second one was attached to a sterile lower body cardiac warming blanket (Augustine medical company, Eden Prairie, MN, USA, Model 630 cardiac blanket) applied after saphenous vein harvesting.

During the ischemic period, treatable bradycardia was defined as a heart rate lower than 40 min^{-1} and was treated with increment doses of iv ephedrine 5 mg. Hypotension was defined as a systolic blood pressure inferior to 70 mm Hg and was treated with increments of iv phenylephrine 50 µg. Heparin 150 IU/kg was given 5 minutes prior to ischemia for all patients and at least one hour after epidural catheter placement.

Extubation criteria were: a cooperative and alert patient; recovery of neuromuscular function assessed by train-of-four (TOF) > 0.8 at the adductor pollicis muscle, pulse oxymetry superior to 96%, P_{ETCO2} less than 45 mm Hg, stable hemodynamics and bladder temperature superior to 35°C. Temporary pacing, intra aortic balloon pump assist or vasopressive medications were not considered to be a contraindication to extubation as long as blood pressure remained stable.

After extubation in the operating room, the patients were transferred to the post-anesthesia care unit (PACU) for a short-term stay of 2 h followed by overnight treatment in the ICU.

We recorded patient demographics data, pre-operative medical status, current medications, left ventricular function as well as operative data (number of grafts, time of ischemia, hemodynamic data), any surgical complications and time to extubation.

Glucose and cortisol levels were measured immediately after installation of the femoral artery catheter (immediately after intubation), immediately after extubation, at 1h and 3h after surgery.

Each blood sample was immediately transferred to a heparinized tube and centrifuged at 4°C (at 3000 rpm for 15 minutes). The obtained supernatant was stored at –70°C until analysis. Plasma glucose levels were measured using a glucose analyzer (model GM7; Analox Instruments Ltd UK, London, England). Plasma cortisol concentrations were analyzed using double-antibody radioimmunoassay (Amersham International, Bucks, England).

Pain intensity was measured by a numeric pain score at rest (0= no pain, 10= worst pain imaginable) and recorded 2h, 6h, 24h and 48h after surgery. Post-operative blood pressure and heart rate were documented continuously for the first 6 hours after surgery. Complications such as bleeding, hemodynamic problems, arrhythmias and respiratory dysfunctions (with arterial PO_2 and PCO_2 for the first 12 hours) were also noted. Side effects such as drowsiness, nausea, pruritus, paresthesia as well as neurological symptoms such as unexplained muscle weakness in the legs or arm were noted and led to discontinuation of TEA, followed by neurological investigations.

Data are presented as mean and standard deviation and median (25th, 75th percentile, min, max) for glucose and cortisol. Comparison of all continuous data was performed between the three groups using multi-comparison ANOVA and of all categorical data using Chi-square test, $P < 0.05$ was considered to show significant difference. Since this was a pilot study, no Power calculation was performed prior to the study.

RESULTS

Baseline characteristics are shown in Table **1**. There were no significant differences between the three groups for age, sex, weight, ejection fraction, number of grafts and ischemic time (Table **1**). The incidence of past myocardial infarction or stroke, hypertension, diabetes, chronic obstructive pulmonary disease and renal insufficiency was also similar. Room temperature, body temperature at the beginning of the surgery and at the moment of extubation was not different. Thoracic epidural catheter insertion was successful in all patients. There was no difference between groups for the incidence of nausea or vomiting. All patients experienced good analgesia after surgery with pain scores below 4 in the vast majority of patients (Table **2**). There were no differences between the three groups. None of the patients required supplementary analgesia for leg pain. The incidence of paresthesia in dermatoma higher than T1 was not different between the three groups. There was no patient with any drowsiness or reduced vigilance due to any of the three solutions. Blood pressure and heart rate remained stable throughout surgery by using phenylephrine in 12 patients in the bupivacaine and clonidine and bupivacaine and fentanyl group, respectively, and in 9 patients in the bupivacaine group. This was not different between the groups.

Glucose concentrations before surgery and (significantly higher, $P < 0.01$) 3h after surgery were 5.4 ± 1.0 and 8.4 ± 1.6 for bupivacaine alone, 5.2 ± 0.5 and 8.5 ± 2.2 for bupivacaine plus fentanyl and 5.5 ± 1.6 and 9.5 ± 2.1 for bupivacaine and clonidine, respectively (Fig. **1**). These values were not statistically significant between the groups.

The cortisol values in the pre-operative period and 3h after surgery were 413 ± 162 and 562 ± 173 for bupivacaine alone, 393 ± 107 and 581 ± 265 for bupivacaine and fentanyl and 409 ± 159 and 570 ± 160 for bupivacaine and clonidine, respectively without significant differences throughout the measurement period or between the groups (Fig. **2**).

DISCUSSION

Our findings show that the addition of clonidine or fentanyl does not create better stress protection than the sole use of bupivacaine for TEA in OPCAB. All three solutions provided equal stress protection with moderate increases in blood glucose and circulating cortisol concentration. Regardless of the type of epidural analgesia all patients were extubated in the operating room and showed good postoperative pain control. There was no drowsiness or nausea and vomiting associated with any of the three solutions.

Inflammatory and Catabolic Responses, TEA and Outcome in Cardiac Surgery

Hyperglycemia is a prominent feature of the metabolic alterations induced by surgical tissue trauma. During cardiac surgery the disturbance of glucose homeostasis is particularly severe with blood glucose values frequently exceeding 15 mmol/L in non-diabetic [15,16] and 20 mmol/L in dia-

Table 1.   Demographic Data

	Bupivacaine 0.125%	Bupi + Fentanyl 3µg/ml	Bupi + Clonidine 0.6µg/ml
Age (y)	65 (7)	66 (11)	66 (8)
Weight (kg)	72 (15)	77 (13)	72 (15)
Sex (m/f)	11/3	9/5	9/5
Ejection fraction (%)	63 (9)	65(11)	55 (11)
Operative time (min)	105 (30)	114 (14)	112 (36)
Number of grafts	3 (1)	3 (1)	3 (1)
Ischemic time (min)	17 (7)	17 (6)	17 (5)
PO_2 (mmHg)	189 (60)	138 (65)	142 (53)
PCO_2 (mmHg)	47 (4)	48 (4)	45 (4)

Table 2.   Pain Scores at Forced Inspiration/Expiration

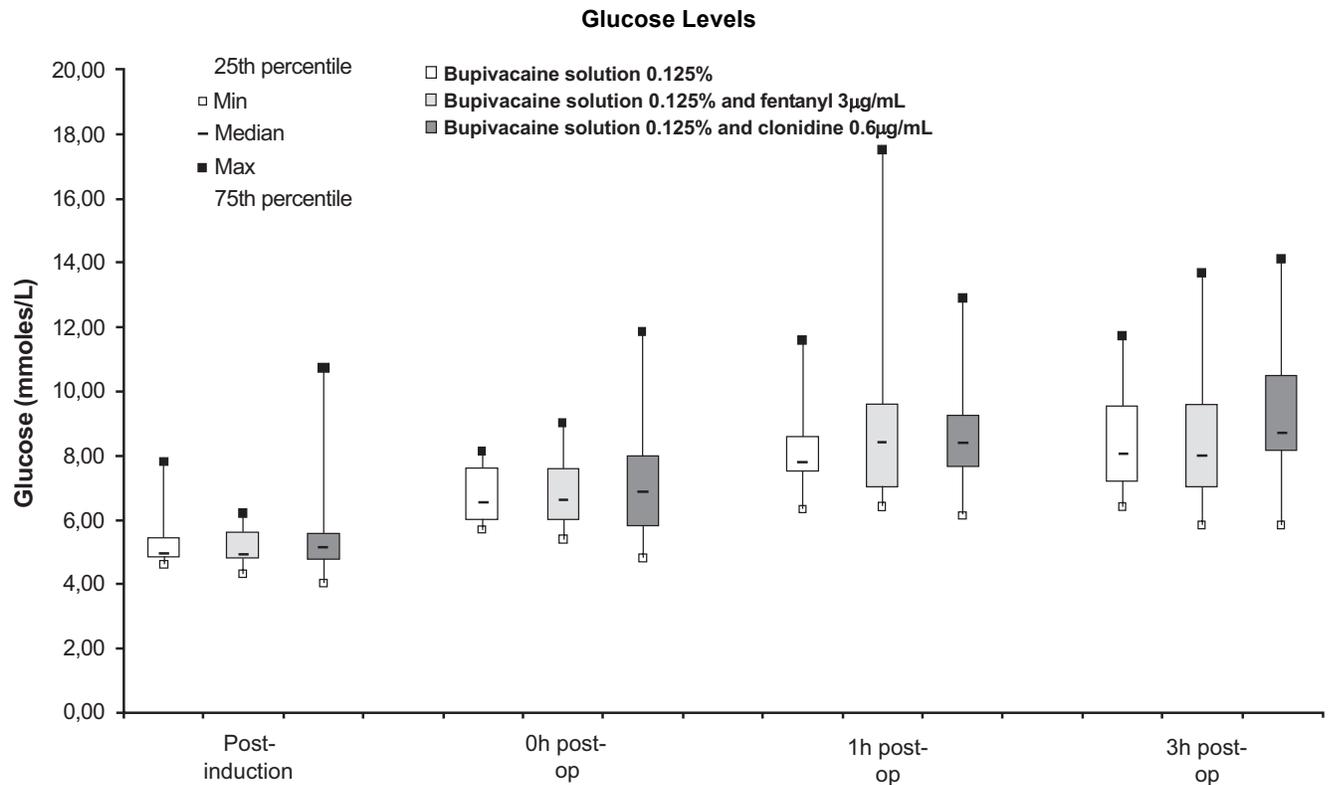| Pain Score (0-10)	Bupivacaine	Bupi + Fentanyl	Bupi+ Clonidine
0h po.	1.5 (2.4)	0.8 (2.4)	1.1 (2.3)
2h po.	1.7 (1.4)	0.6 (1.5)	0.8 (1.5)
6h po.	1.1 (1)	0.3 (0.9)	0.2 (0.6)
24h po.	0.9 (1)	0.6 (1)	0.1 (0.3)
48h po.	0.6 (0.9)	0.2 (0.6)	0.3 (0.7)

Glucose Levels

Fig. (1). Glucose levels immediately after intubation, immediately after extubation and 1h and 3h after surgery.

betic subjects [17].

Perioperative hyperglycemia has been demonstrated to be an independent risk predictor after cardiac operations. For each 1 mmol/L increase of blood glucose above 6.1 mmol/L the risk of adverse outcome increased by 17% in diabetic patients undergoing cardiac surgery [18].

Tight glycemic control attenuated the systemic inflammatory response during and after coronary artery surgery [19] and decreased mortality in critically ill patients, most after elective cardiac procedure [20]. Observational studies further suggest that the quality of glycemic control affects morbidity and mortality in diabetic patients undergoing coronary artery bypass grafting [21]. Hence, perioperative maintenance of normoglycemia gains clinical relevance.

In the present protocol, epidural analgesia limited the hyperglycemic and cortisol responses to OPCAB whether fentanyl or clonidine was added to epidural bupivacaine or not. This finding is in agreement with previous observations reporting inhibitory effects of TEA on the metabolic-endocrine responses to cardiac [22-24] and non-cardiac surgery [25]. Studies using stable isotope tracer kinetics during MIDCAB and abdominal surgery showed that thoracic epidural analgesia attenuates the perioperative increase in blood glucose through the inhibition of endogenous glucose production rather than through an increase in glucose utilization [23,26].

There is controversy about the role of TEA in preventing the inflammatory response during cardiac surgery.

Some studies conducted in patients undergoing on-pump coronary artery bypass grafting did not demonstrate a modi-

fying influence of TEA on cytokine production [27] and the circulating cortisol and catecholamine concentrations [28]. Fransen *et al*. [29] investigated in a small number of patients the influence of cardiopulmonary bypass on the systemic inflammation. The release of bactericidal permeability increasing protein was markedly reduced during OPCAB, thus indicating a decreased response of the polymorphonuclear neutrophil protein with possible benefits for outcome after cardiac surgery. Two other studies have also found a reduction in cytokine response during OPCAB [30] and tumor necrosis factor [31]. However, the acute phase response as indicated by interleukin-6 release was the same for OPCAB and OnCAB, indicating that surgery as such is the drive behind the acute inflammatory response. As much as for OnCAB, TEA reduces cortisol and catecholamine release during surgery in OPCAB [25].

Clonidine in Epidural Administration

Clonidine is a α2-adrenergic agonist with analgesic properties and the propensity to potentiate the effects of local anesthetics [32,33]. Concern has been described about the possible effect of clonidine addition in epidural infusions because of the possible effect on the blood pressure. Whereas one recent study [34] showed lower blood pressure when clonidine was added to ropivacaine for epidural analgesia after spinal anesthesia, we could not support these findings in a previous study with the same study setup [35, 36] Although this was not the main focus of the study, perioperative blood pressure and heart rate remained stable and was not different between the three groups.

Very little is known whether the addition of clonidine to a local anesthetic in epidural analgesia improves the stress
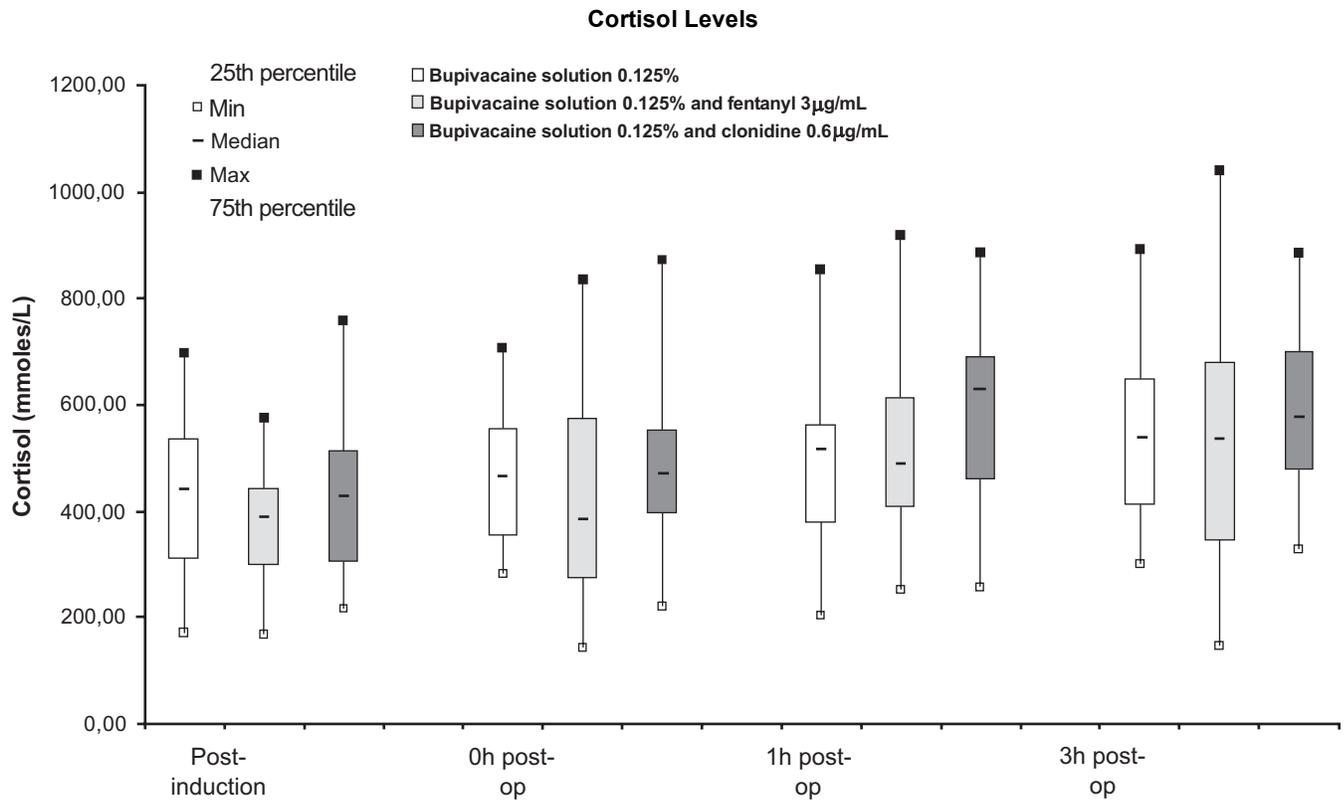
Fig. (2). Cortisol levels immediately after intubation, immediately after extubation and 1h and 3h after surgery.

response [32]. However, some studies in children showed an increase in postoperative sedation when clonidine was added to caudal blockade [37-39]. We did not find any such influence in our study.

Fentanyl as Adjunct to Epidural Analgesia

The fact that sole bupivacaine produced already very good pain scores, might be one of the reasons why the addition of clonidine or fentanyl did not further improve stress protection. Only few studies have shown a beneficial effect of adding fentanyl to an epidural of local anesthetic. The results of a recent study performed in patients undergoing colorectal procedures lend support to the assumption that local anesthetic and opioid must be administered concomitantly to suppress the catabolic responses to surgery [40].

Furthermore Breslow *et al* [41] have shown a diminution of the inflammatory response in surgery of the lower extremities when bupivacaine and fentanyl were used as an epidural solution. However, in that study, no control group with solely bupivacaine was compared. Other studies in adults did not show any adding effect in terms of stress protection with opioids in adults [42,43], nor in children [44]. This is in concordance with our findings. Possibly, the excellent pain control is the confounding factor in optimal stress control.

Epidural Hematoma in OPCAB

The risks of epidural hematoma has been calculated as being lower than 1:1500 in OnCAB [45]. This calculation

was not made for OPCAB, but since the heparinization is less in off-pump surgery, the risk should be lower. The lower doses of heparin used in OPCAB (150 IU/kg) are similar to doses used in vascular surgery where the use of TEA is well established. When calculating the risks, we must considerate the possibility of converting an off-pump surgery to an on-pump CABG. In our institution, nearly 95% of coronary bypass are done off-pump with a very low conversion rate (< 2%) to on-pump surgery. The risk of a hematoma should be significantly lower than 1: 1500.

In conclusion, this study showed that TEA for beating heart surgery prevented raise in cortisol reflecting a perioperative hormonal stress protection. The addition of either fentanyl 3 μg/ml or clonidine 0,06% to bupivacaine 0,125% did not further improve that stress protection.

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