«Original Articles »

The effects of intrathecal Bupivacaine plus general anesthesia on stress hormones in Coronary Artery Bypass Grafting

Elaheh Peymani Foroushani[1], Seyyed Kamal Tabatabaei[1], Zahra Pourmehdi[1], Mohamad Reza Pipelzadeh[1], Seyyed Ali Mard[2*]

1-*Assistant Professor, Department of Cardiac Surgery Anesthesia, Golestan Hospital, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

2- Assistant Professor, Department of Physiology, School of Medicine, Research Institute for Infectious Diseases of Digestive System, Physiology Research Center (PRC) Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Corresponding Author:
Seyyed Ali Mard, Deptartment of Physiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Tel:09166118532
Email: mard-sa@ajums.ac.ir

Abstract

Background: Activation of stress response during cardiac surgeries such as cardiopulmonary bypass (CPB) can increase myocardial oxygen demand and consumption through induced tachycardia and augmented peripheral vascular resistance. These physiologic consequences may lead to increased morbidity and mortality by putting too great a strain on the already compromised organ systems.

Materials and Methods: This controlled trial study was conducted to evaluate the effect of intrathecal bupivacaine plus general anesthesia on stress response in patients undergoing open heart surgery. Methods In this case, thirty patients undergoing open heart surgery were randomly assigned to receive either intravenous opioid [control group (n=15)] or intravenous opioid plus intrathecal bupivacaine [ITB group (n=15)]. Arterial blood samples were obtained from each patient at five predetermined times to measure plasma levels of norepinephrine and epinephrine and cortisol including: Immediately prior to spinal anesthesia; 5 min after sternotomy; 30 min after initiation of cardiopulmonary bypass (CPB); 30 min after separation from CPB; and 4 hours after separation from CPB.

Results: Administration of intrathecal bupivacaine plus general anesthesia significantly decreased plasma levels of cortisol, adrenalin and noradrenaline in treatment group as compared with control group at 5 min after sternotomy and 30 min after CPB starting and 4 hour after CPB ending, respectively.

Conclusion: the findings showed the application of intrathecal bupivacaine to patients undergoing open heart surgery significantly decreases plasma levels of stress hormones.

Keywords: Intrathecal, bupivacaine, cortisol, adrenaline; noradrenaline, open heart surgery

► *Please cite this paper as:*
Peymani Foroushani E, Tabatabaei SK, Pormehdi Z, Pipelzadeh MR, Mard SA. The effects of intrathecal Bupivacaine plus general anesthesia on stress hormones in Coronary Artery Bypass Grafting.Jentashapir J Health Res 2013;4(5):363-369

Received: 09.07.2013 **Accepted: 14.08.2013**

Introduction

Cardiac surgery cause inflammatory and stress response in patients and cardiopulmonary bypass (CPB) reinforces it [1-3]. The stress response can increase myocardial oxygen demand and consumption through induced tachycardia and augmented peripheral vascular resistance. Moreover, sympathetic stimulation produces coronary vasoconstriction (through α-receptors in the coronary vasculature) which may worsen postoperative myocardial ischemia [4]. These physiologic consequences may lead to an increased morbidity and mortality by putting too great a strain on the already compromised organ systems [5]. Anesthetic techniques that prevent the stress response may reduce morbidity and mortality [4]. High-dose intrathecal bupivacaine, when combined with general anesthesia, results in less beta-receptor dysfunction and a lower stress response during coronary artery bypass graft surgery [6].

To achieve this goal the researchers applied epidural techniques to patients undergoing cardiac surgery, and it was found that application of thoracic epidural opioids or local anesthetics to the patients results in a reliable postoperative analgesia and attenuates the preoperative stress response associated with cardiac surgery. Since the efficiency of this technique is not tested yet and there are concerns on occurrence of epidural hematoma in the patients, the researchers applied spinal anesthesia [7]. This double-blind, randomized, controlled trial study was designed to find if intrathecal bupivacaine decreases the catecholamine stress hormone response to CABG surgery.

Materials and Methods

In total, 30 patients scheduled for elective coronary artery bypass grafting (CABG) participated in the study from July 2009 to Nov 2010. The study was approved by the University Hospital and Ahwaz Jundishapur University of Medical Sciences Ethics Committees, and all subjects granted informed consent to participate. Patients with an age greater than 80 yr; and those suffered from or experienced pretreatment with clonidine or corticosteroids; cardiac emergency surgery; previous cardiac surgery; contraindications to neuraxial blockade (including patient refusal; patient's inability to maintain stillness during the needle puncture, raised intracranial pressure; intrinsic and idiopathic coagulopathy; skin or soft tissue infection at the proposed site of needle insertion; severe hypovolemia), serum Creatinine concentration greater than 2 mg; systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 110 mmHg; known or anticipated difficult airway and addiction or tolerance to narcotics were all excluded. Patients had their cardiac medications continued until the morning of surgery. Prior to arrival to the operating room, each patient was premedicated with 0.07 mg/kg intramuscular Midazolam randomized to receive either intrathecal morphine (ITB) group or general anesthesia (GA) Group.

Preoperative technique and management: After placement of an intravenous catheter, patients received a bolus of 10 ml/kg normal saline and an arterial catheter was inserted into radial artery. Patients were placed in the sitting position, and the skin was prepared and draped in an aseptic fashion. Patients in the control group received only local infiltration of the skin with 1 ml of 1% lidocaine with a 25-gauge needle. In the ITB group, the intrathecal space at the L3-4 level was entered with a 25-gauge Quinkc spinal needle. A maximum of three attempts to successfully locate the subarachnoid space were allowed before the patient was removed from the study. If there was blood on the spinal needle, the spinal anesthetic

technique would stop and the patient would be removed from the study. When a clear cerebrospinal fluid was attained 20 mg bupivacaine 0.5% was injected into the intrathecal space. All patients were placed in 15° Trendelenburg position for 5 min.

Physicians and nursing staff receiving the patients intraoperatively and postoperatively were blinded to treatment group. The same anesthetics medicine, were administered to induce anesthesia in all patients (a combination of intravenous fentanyl (5-7 micro/ kg), midazolam (15 mg/kg), and thiopental (4 mg/kg), Atracurium (0.5-0.6 mg/kg). Mean arterial pressure (MAP) kept between 60-90 mmHg and heart rate between 60-100 beat/min during operation time. If required, inhaled isoflurane, intravenous nitroglycerin or ephedrine were used.

Postoperative technique and management: At the end of CABG, patients were transported to the intensive care unit. Postoperative care was similar for all patients and contained intravenous morphine and midazolam at the discretion of the intensive care unit nurse for sedation prior to tracheal extubation the next morning. Administration of morphine and midazolam prior to extubation was not dictated by a rigid protocol. However, the intensive care unit nurse was instructed to initially administer morphine incrementally until a total of approximately 20 mg was given and then to administer Midazolam incrementally if further sedation was required. Indications for morphine and midazolam administration included hypertension, tachycardia, and / or excessive patient movement. After tracheal extubation, each patient exclusively received intravenous morphine. Patients were assessed on a daily basis until discharged from hospital. In general, the Foley catheter was removed the day after extubation.

Hormone assays: Arterial blood samples were obtained from each patient at five predetermined times to measure norepinephrine and epinephrine, cortisol levels include: 1) Immediately prior to spinal anesthesia; 2) 5 min after sternotomy; 3) 30 min after initiation of CPB; 4) 30 min after separation from CPB; and 5) 4 hours after separation from CPB. The blood samples were collected into heparinized glass tubes, centrifuged at 4°c, 3000 g for 10 min and stored at -80°C until hormones were measured using ELIZA kits (IBL, GmBH Hamburg, Germany).

Statistical Analysis:

Data are shown as mean ± S.E.M. Statistical analysis was performed by one-way ANOVA and followed by post hoc Tukey's test. Significance was set at a $P<0.05$ level.

Results

30 patients participated in the study were randomly divided into two groups (n=15).Demographic and clinical characteristics of the patients are listed in Table 1. There were no significant differences in the preoperative patient characteristics.

No patients were removed from the study once enrolled. No bloody tap occurred in any patient, the only intraoperative difference between the two groups was that the ITB group received significantly less pre-CPB isoflurane. The total fluid balance did not differ between groups. Preoperative atropines for bradycardia were required for one patient in ITB group. There was no difference between postoperative hospital length of stay, with mean times of 5.6± 0.07and 4.9 ± 0.15 days for the control and ITB groups, respectively. Plasma cortisol, epinephrine, and norepinephrine concentrations were measured at five time points (Fig. 1). In the ITB group the plasma cortisol concentrations were significantly lower at 5 min after sternotomy ($P<0.05$). Norepinephrine concentrations were lower

in the ITB group at 30 min post-CPB time (P =0.05). Epinephrine concentrations were significantly lower in the ITB group 4 hours after separation from CPB.

Table 1. Preoperative patient characteristics

P-value	ITB(n=15)	Control(n=15)	Characteristic
NS	65.3±1.8	63.5±1.5	Age, yr
NS	13	12	Sex(male),n
NS	75.0±1.8	79.4±2.3	Weight,kg
NS	23.4±0.53	25.3±0.44	BMI,kg/m²
NS	0.8±0.15	0.7±0.2	Creatinine
NS	6	8	Smoking history
NS	22.0±6.0	20.0±5.0	Smoking, pack/ yr
Coexisting disease,n			
NS	7	6	Diabetes
NS	10	12	Hypertension
NS	0	1	Atrial fibrillation
Medications, n			
NS	13	14	β-Blockers
NS	5	7	Calcium channel blockers
NS	6	8	Long-acting nitrates
NS	2	1	Digoxin
NS	0	1	Other antiarrhythmics
NS	6	8	Diuretics
NS	14	13	ACE inhibitors

Results are expressed as mean ± SEM. ACE=angiotensin converting enzyme; BMI=body mass index; ITB= intrathecal bupivacaine; NS=not significant.

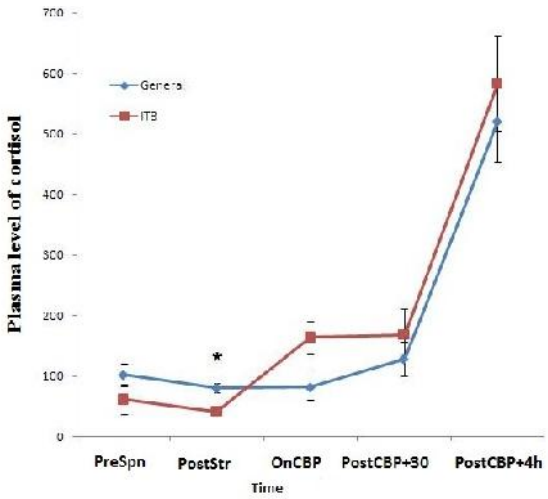

Figure 1. Effect of intrathecal bupivacaine on the plasma level of cortisol. *P <0.05; PreSpn=pre-spinal anesthesia; PostStr=post sternotomy; OnCPB=on cardiopulmonary bypass pump; PostCPB+30=30 min after termination of cardiopulmonary bypass; PostCPB+4h=4 hour after termination of cardiopulmonary bypass.

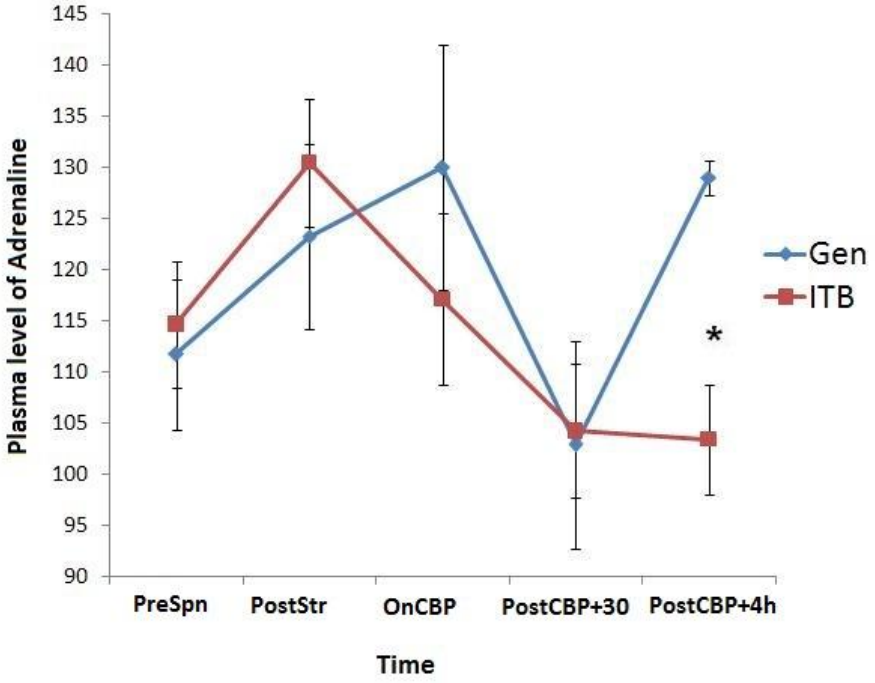

Figure 2. Effect of intrathecal bupivacaine on the plasma level of adrenaline (*P <0.05).

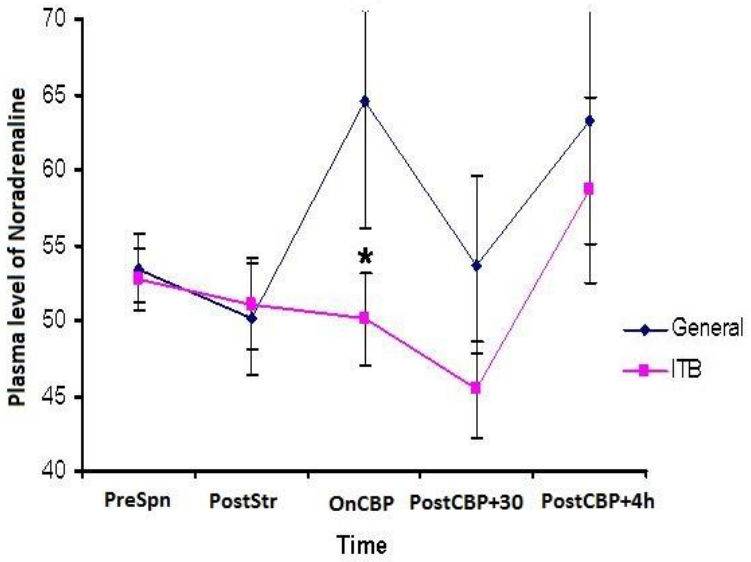

Figure 3. Effect of intrathecal bupivacaine on the plasma level of noradrenaline. Plasma level of noradrenaline in ITB group was significantly lower 30 minutes after separation from the pump compared with the control group (* P =0.05).

Abbreviations: PreSpn=pre- spinal anesthesia; PostStr=post sternotomy; OnCPB=on cardiopulmonary baypass pump; PostCPB+30=30 min after termination of cardiopulmonary bypass; PostCPB+4h=4 hour after termination of cardiopulmonary bypass

Discussion

Surgical stress, particularly during large surgeries, leads to severe metabolic and endocrine responses and increased plasma levels of stress hormones. Since increased levels of stress hormones are usually accompanied by heightened patient morbidity, researches worldwide have been done to reduce stress levels with coronary heart surgery and consequently, lower levels of stress hormones using spinal anesthesia. Chaney et al. conducted a study in which morphine (4 mg) was injected into the spinal cord in patients undergoing coronary surgery and the level of epinephrine and norepinephrine in 12 time points was measured [8]. Consequently, they claimed that analgesia results were reliable in these patients but no reliable reduction in the levels of epinephrine and norepinephrine were present. Hall and co-workers evaluated the effect of intratechal morphine (1-1.5 mg) on plasma concentrations of cortisol and catecholamines before surgery, after sternotomy, at the time of entry to ICU, after extubation, and after ICU admission. They showed that intrathecal morphine administration partially attenuated the stress response after open heart surgery [9]. Since, the effects of intra-spinal opioid on stress hormones were not significant in Lee et al study; they decided to use intra-spinal local anesthetics instead of opioid [6]. They chose dose of 37.5 mg of bupivacaine for spinal injections, then the level of epinephrine and norepinephrine and cortisol in six time points were measured. The epinephrine levels in spinal anesthesia group after sternotomy and during and after CPB were significantly lower than the control group [6]. Consistent with these results, the present study showed the plasma level of cortisol 5 min after sternotomy, the plasma level of epinephrine 30 min after CBP and the plasma level of norepinephrine 4 hours after CBP ending were significantly lower in ITB group than in control group. These findings together suggest that application of intrathecal bupivacaine to patients undergoing CABG could decrease the stress response.

In Conclusion It is well known that stress hormones reduction improves the patient's post-surgery recovery which per se reduces mortality and morbidity. Thus, reducing the dose of the anesthetic medicine may decrease its complications and may be effective and cost-effective for patients. Therefore, use of low dose of intrathecal bupivacaine (20 mg) can reduce stress hormones such as epinephrine, norepinephrine and cortisol. However, whether or not this decrease in stress hormones can affect the patient's post-surgery recovery need further investigation.

Comments

The ultimate goal of reducing stress hormones during surgery is to improve outcome and to decrease patient morbidity. Since the stress hormones reductions are occurred at various times points, the fundamental question raised is whether this rate of change in stress hormones is sufficient to improve the outcome and reduce morbidity of open heart surgery. Therefore, a study on the short-term and long-term outcomes is recommended.

Furthermore, during on-pump open heart surgery much of stress hormones are due to a heart lung pump that spinal anesthesia cannot affect. So it is recommended to study the effects of spinal anesthesia on stress hormones during off-pump open heart surgery. High concentration of serum catecholamines causes adrenergic receptor desensitization and their dysfunction following the initiation of cardiopulmonary pump. This effect is probably involved in myocardial function reduction. Atrial adrenergic receptor density measured during

surgery can be considered as a sign of hormones stress response being suppressed.
Apart from stress hormones several factors are involved in morbidity after open heart surgery. The most common cause of morbidity after heart surgery is impaired lung function [10-11]. In fact atelectazi is more common than any other postoperative symptoms in heart surgery patients. Therefore, an investigation on the effect of spinal anesthesia on the pulmonary function outcome seems significant. Phenylephrine is an alpha agonist which prolongs the local anesthesia in case of mix with local anesthetics. Thus, the effect of bupivacaine spinal anesthesia through phenylephrine in reducing levels of stress hormones during open heart surgery can be separately studied. Dexmedetomidine is an alpha agonist which decreases dose dependently, the heart rate and plasma catecholamines level, it prevents the hemodynamic instability during induction of anesthesia, and reduces the need for anesthetics. Considering the unique characteristics of this drug, study on its effects on the stress hormone during open heart surgery seems useful and valuable.

Acknowledgements

This paper is issued from thesis of Dr. Elahe Peymani Foroushani in Medical Anesthesiology and financial support was approved by Ahvaz Jundishapur University of Medical Sciences (Grant and registration NO#24/D/P). The authors thank to vice chancellor of research affairs for the financial support.

References

1-O'Brien JE Jr, Marshall JA, Tarrants ML, Stroup RE, Lofland GK. Intraoperative hyperglycemia and postoperative bacteremia in the pediatric cardiac surgery patient. Ann Thorac Surg 2010;89(2):578-83.
2-Jakob SM, Stanga Z. Perioperative metabolic changes in patients undergoing cardiac surgery. Nutrition 2010;26(4):349-53
3-Rassias AJ. Intraoperative management of hyperglycemia in the cardiac surgical patient. Semin Thorac Cardiovasc Surg 2006;18(4):330-8.
4-Malhotra V, Sudheendra V, Diwan S. Anesthesia and the renal and genitourinary system. In: Miller DR, ed. Miller's anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. P. 1962–98.
5-Jezova D, Hlavacova N. Endocrine factors in stress and psychiatric disorders: focus on anxiety and salivary steroids. Ann N Y Acad Sci 2008;1148:495-503.
6-Lee TW, Grocott HP, Schwinn D, Jacobsohn E. High spinal anesthesia for cardiac surgery: effects on beta-adrenergic receptor function, stress response and hemodynamics. Anesthesiology 2003;98(2):499-510.
7-Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. Anesth Analg 2006;102(1):45-64.
8-Chaney MA, Smith KR, Barclay JC, Slogoff S. Large-dose intrathecal morphine for coronary artery bypass grafting. Anesth Analg 1996;83(2):215-22.
9-Hall R, Adderley N, MacLaren C, McIntyre A, Barker R, Imrie D, et al. Dose intrathecal morphine alter the stress response following coronary artery bypass grafting surgery? Can J Anaesth 2000;47(5):463-6.
10-Canver CC, Chanda J. Intraoperative and postoperative risk factors for respiratory failure after coronary bypass. Ann Thorac Surg 2003;75(3):853-7.
11-Hein OV, Birnbaum J, Wernecke KD, Konertz W, Jain U, Spies C. Three-year survival after four major post-cardiac operative complications. Crit Care Med 2006;34(11):2729-37.