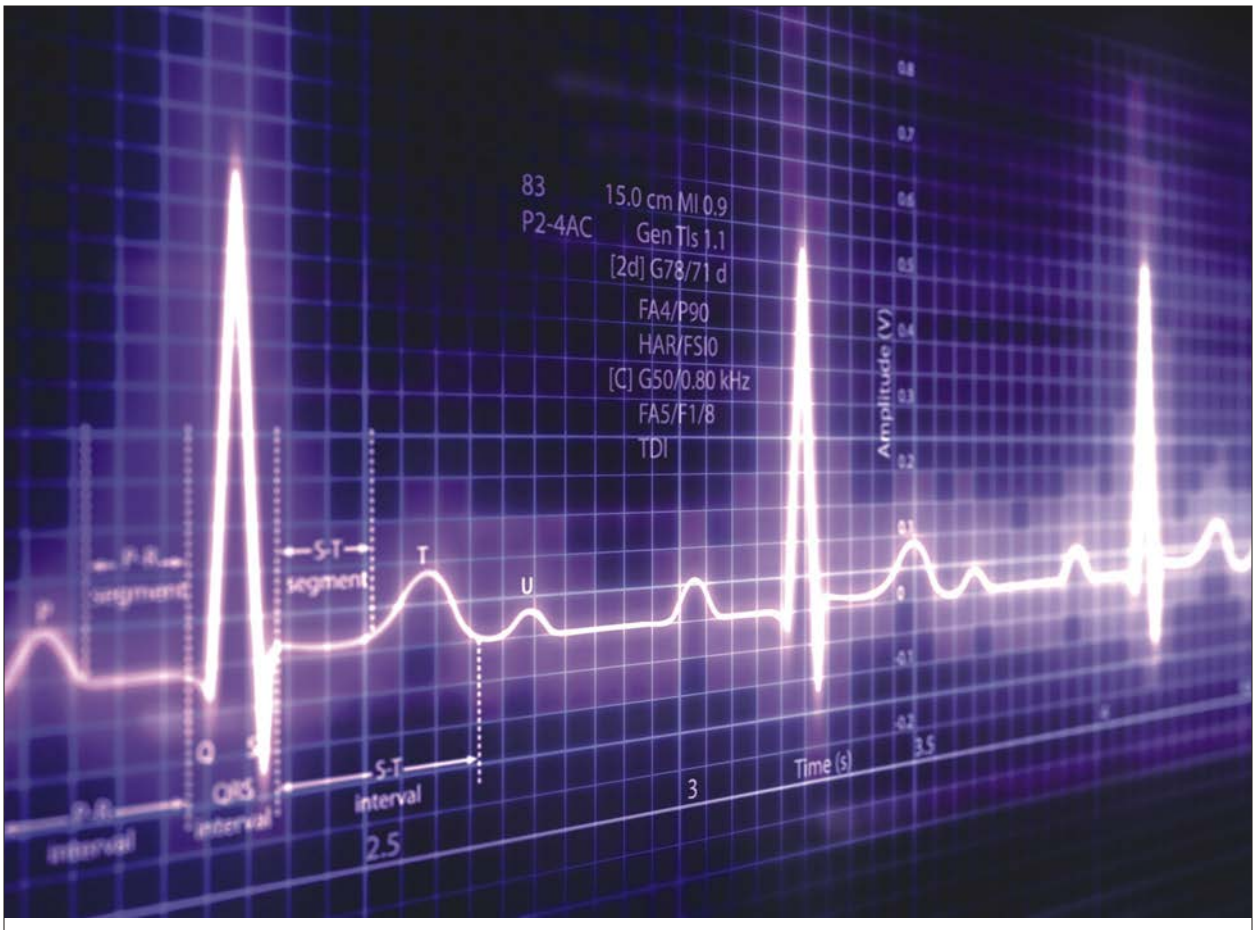

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Effect of High Thoracic Epidural Analgesia on Left Ventricular Function in Patients with Coronary Artery Disease Undergoing Elective Non-cardiac Surgery

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ABSTRACT

Coronary artery disease is a major risk factor for perioperative myocardial infarction. In patients with Coronary Artery Disease (CAD), vasoconstriction is induced through activation of the sympathetic nervous system. Both α1-and α2-adrenergic epicardial and microvascular constrictions are potent initiators of myocardial ischemia. But, there is still controversy whether High Thoracic Epidural Analgesia (HTEA) improves left ventricular function. The main aim of this study was to assess anti-ischemic effect of high thoracic epidural analgesia in patients with coronary artery disease undergoing elective non-cardiac surgery and to investigate the effects of sympathetic blockade by HTEA on systolic and diastolic LV function. Forty eight patients were randomized to receive either general anesthesia (control group n=24) or general anesthesia with high thoracic epidural analgesia(HTEA group n=24) . Patients were subjected to ambulatory Holter monitoring to assess the effect of HTEA in myocardial ischemia. Left ventricular systolic/diastolic function were assessed by echocardiography using the fractional area change. Echocardiographic and hemodynamic measures were recorded before and after institution of HTEA. There was no significant difference between the two groups regarding the heart rate and mean arterial blood pressures ($p>0.05$) in the baseline values. However, a significant reduction in heart rate and mean arterial blood pressure($p<0.05$) was observed till 48 h post operatively in HTEA group as compared to the control group. The post operative cardiac troponin I increase was significant in control group versus HTEA group ($p = 0.0001$). The incidence of myocardial ischemia was significantly low in HTEA group than in control group. The S-T segment changes were noted in 8% of patients in HTEA group as compared to 38% of patients in control group ($p = 0.016$). There were no significant changes in left ventricular systolic function EF and fractional area change FAC in both groups (FAC 55.4±6.3 to 54.22±6.8 (p-value = 1.00)). Also the improvement in LV diastolic function was significant in HTEA group than the control group. In conclusion, the high thoracic epidural analgesia reduced the incidence of myocardial ischemia and improved the diastolic function in patients with coronary artery disease undergoing elective non-cardiac surgery. Therefore, its use might decrease the cardiac morbidity particularly in patients with preoperative ST ischemic changes and in patients with pseudo-normalization, or restrictive diastolic dysfunction.

Key words: High thoracic epidural analgesia, ischemic heart disease, left ventricular function, diastolic, systolic

INTRODUCTION

Perioperative Myocardial Ischemia (MI) in patients with Coronary Artery Disease (CAD) or risk factors for CAD is common (Mangano, 1990; Haggmark *et al*., 1989). Because the MI at each of the three perioperative (pre-, intra- and postoperative) stages is associated with cardiac morbidity and mortality (Raby *et al*., 1989, 1992; Mangano *et al*., 1990). Approximately 20-40% of patients at high risk of cardiac related morbidity develop myocardial ischemia perioperatively (Flood and Fleisher, 2007). Mortality from intraoprative MI varies between 40-70%, especially because the MI is frequently undiagnosed (Thygesen *et al*., 2008). Myocardial Ischemia (MI) of sufficient severity or prolonged duration may result in reversible (e.g., stunning) or irreversible (e.g., infarction) damage, malignant ventricular arrhythmias, or cardiogenic shock (Warner, 2000). Prevention of perioperative Myocardial Ischemia (MI) is essential to avoid the mechanical, metabolic and electro-physiologic changes associated with acute imbalance in the relationship between myocardial oxygen supply and demand (Warltier *et al*., 2000). Epidurally applied local anesthetics targeted to the T1-5 segments produce sensory blockade, motor blockade (depending on concentration) and blockade of the cardiac sympathetic fibers (Blomberg *et al*., 1989). Thoracic Epidural Anesthesia (TEA) has beneficial effects on the major determinants of myocardial oxygen demand, as it reduces heart rate, preload and after-load without affecting coronary perfusion pressure. Also it increases the luminal diameter of stenotic epicardial coronary arteries (Nygard *et al*., 2005). Thus, HTEA is assumed to alleviate myocardial ischemia by improving global myocardial oxygen balance and by redistributing myocardial blood flow to vulnerable regions. Both effects of HTEA may result in an improvement of overall systolic and diastolic left ventricular function (Schmidt *et al*., 2005). Despite several previous clinical and experimental studies, questions remain about the effect of HTEA on systolic LV function, which has variably been reported to be unchanged (Saada *et al*., 1992), impaired (Goertz *et al*., 1993), or even improved (Blomberg *et al*., 1990) in healthy individuals and in patients with Coronary Artery Disease (CAD). Moreover, there have been few studies published on the effect of HTEA on diastolic function in CAD patients, although it is well appreciated that a change in diastolic function is the first hemodynamic manifestation of myocardial ischemia and that subclinical ischemia can alter LV relaxation, filling and distensibility in the presence of normal systolic function (Bonow *et al*., 1985). The aim of the present study was to assess anti-ischemic effect of high thoracic epidural analgesia in patients with coronary artery disease undergoing elective non-cardiac surgery and to assess the effect of HTEA on LV systolic and diastolic function.

MATERIALS AND METHODS

After the approval of local ethics committee, 48 successive patients (24 control; 24 HTEA) with age ranging between 40 to 60 years with Ischemic Heart Disease (IHD) scheduled for elective non-cardiac surgery (thoracic, orthopedic, abdominal and vascular surgery) were enrolled in this study. After obtaining written consent, patients were divided into two groups i.e., control group and HTEA group. Patients having IHD were included in the study if they had documented coronary artery disease or risk factors for CAD according to Mangano *et al*. (1990). Patients considered were to have documented CAD if they had cardiac angiographic evidence of significant coronary stenosis, a positive exercise stress test, a thallium imaging study suggestive of CAD or a previous myocardial infarction. Patients were not considered for inclusion with electrocardiographic evidence of left ventricular hypertrophy, with repolarization abnormalities, complete bundle branch block, significant left ventricular dysfunction (left ventricular ejection fraction 35%), abnormal coagulation profile, neurological deficits and thoracic spine deformity or previous surgery. All the

patients received their ordinary cardiac medication at 6 am on the day of operation. In addition to that, high thoracic epidural catheter was inserted before operation in the HTEA group to block sympathetic innervations of the heart.

The preoperative investigations such as Complete Blood Count (CBC), liver and kidney function tests, blood sugar, lipid profile, coagulation profile (PT, PTT and INR) and tropinin I Level, Electrocardiogram (ECG) and Trans Thoracic Echocardiography (TTE) were performed in both groups of patients. Plasma concentrations of troponin I were measured pre-operatively and at 6, 12, 24 and 48 h, postoperatively. All the patients were monitored with standard monitors: oxygen saturation, heart rate, noninvasive arterial blood pressure, end tidal carbon dioxide and five leads ECG with ST segment analysis. A three-channel Amplitude Modulated Holter ECG (Philips Digitrak XT, Koninklijke Philips Electronics N.N) was attached to patients at least 30 min before entry to operating room and continued for 24 h postoperatively.

Holter monitor tapes were analyzed for myocardial ischemia based on the criteria of horizontal or down-sloping ST segment depression of ≥1 mm below the baseline, lasting for at least 1 min. Events were separated by at least 5 min without ECG ischemia (Urban *et al*., 2000). ECG changes included new ST-T changes, T inversion, Q waves and/or a bundle branch block.

Standard transthoracic two-dimensional, pulsed, color-flow and color M-mode Doppler echocardiographic examinations were performed with a System Vivid 7 ultrasound machine (GE Medical Systems, Milwaukee, WI) equipped with a multi-frequency phased-array transducer. Three consecutive beats were measured and averaged for each two-dimensional and Doppler variable by two independent investigators.

LV dimensions were measured at the mid-ventricular level from two-dimensional images obtained in the parasternal short-axis view. LV End-Diastolic Area (EDA) and Fractional Area Change (FAC) were determined according to the criteria published by Clements *et al*. (1990):

$$FAC = \frac{(EDA\text{-}ESA)}{EDA} \times 100$$

where, FAC indicates Fractional Area Change; EDA, End-diastolic area and ESA, End-Systolic Area.

Conventional Doppler variables of transmitral inflow velocity curve were also measured. On the basis of mitral E/A ratio (peak early filling velocity to peak velocity at arterial contraction) and Deceleration Time (DT) of mitral E velocity (Nishimura and Tajik, 1997). Patients were divided into four groups according to the grade of diastolic dysfunction: normal, impaired relaxation, pseudo normal and restrictive filling. These different patterns correspond to increasing LV stiffness.

In HTEA group, an 18 gauge portex epidural catheter was inserted 3-4 cm into the epidural space through a Touhy needle via one of the second to fifth thoracic vertebral interspaces, employing the median approach and the loss of resistance technique with minimal amounts of normal saline. In the supine position, a test dose of 3 mL of 2% lidocaine was injected to exclude intradural administration of the local anesthetic. Five minutes later, 6-8 mL bolus of 0.25% bupivacaine was injected into the epidural space to block the somatosensory level T1-T5 vertebrae for reversible cardiac sympathectomy. The extent of the block was evaluated after 10-15 min by assessing both temperature and pinprick discrimination. Epidural infusion of bupivacaine 0.125% at a rate o f 4-6 mL h^{-1} was continued for 48 h, postoperatively. In both groups general anesthesia was induced after 5 min pre oxygenation, 1-1.5 μg kg^{-1} fentanyl, 4-6 mg kg^{-1} thiopental and 0.6 mg kg^{-1} rocuronium and suitable size cuffed endotracheal tube was inserted, anesthesia was

maintained using 1-2% sevoflurane delivered in approximately 50% NO_2/O_2 mixture and rocuronium was given in incremental doses. Intermittent Positive Pressure Ventilation (IPPV) with tidal volume 7-10 mL kg^{-1} and respiratory rate 10-12 min^{-1} was adjusted to maintain end tidal CO_2 between (32-35 mmHg). Post operatively all patients were monitored in an intensive care unit setting for 48 h. Pain management in both groups, visual analogue scale ≥4 out of 10 was treated with morphine 4 mg interavenously as needed .

Data analysis: All the data were described as Mean±Standard Deviation (SD). Using Student's t-test compared data of both groups and the categorical variables were compared by chi-square test. The level of significance was set at $p<0.05$. The statistical analysis of data was done by using the software package SAS version 9.2 (SAS Institute, 2003).

RESULTS AND DISCUSSION

Forty-eight patients, who satisfied the admission criteria for the current investigation, were included in the study. There was no significant difference in the base line characteristics of both groups. However, angina was significantly frequent in patients with HTEA than control group (p-value = 0.08). Twenty one patients of control group had Diabetes Mellitus (DM) as compared to 16 patients of HTEA at p = 0.08 (Table 1).

Out of 48 patients, 23 had 3-vessel disease and 16 had 2-vessel disease, 13 had previous myocardial infarction, 10 had previous coronary angioplasty and 4 had previous coronary artery bypass surgery. There was no significant difference between the two groups regarding heart rate and the mean arterial blood pressure in the baseline values. However there was significant reduction in heart rate and mean arterial blood pressure (p = 0.0001) in HTEA group than the control group after the induction and up to 48 h post operative (p = 0.0001) (Fig. 1). A troponin I levels were non significant before induction in both groups (p = 0.1), serial troponin I levels 6, 12, 24 and 48 h post-operatively were significantly higher in control group than HTEA group

Table 1: Baseline characteristics of HTEA and control groups

Parameters	HTEA g (n = 24)	Control g (n = 24)	p-value
Age (years)	49.16±7.6	50.79±4.98	0.37
Weight (kg)	77.33±9.06	79.45±10.44	0.45
Height (cm)	165.83±7.97	166.79±8.9	0.69
Gender (male, female)	13/11	14/10	0.77
Hypertension	18	15	0.35
Diabetes mellitus	16	21	0.08
Angina	16	10	0.08
Myocardial infarction	8	6	0.52
Hospitalized for CHF	2	6	0.24
Smoker	11	7	0.23
Peripheral vascular disease	2	2	1
Cerebral vascular accident	2	1	1
Chronic B-blockade	10	12	0.56
Calcium channel blocker	4	5	1
Angiotensin ACEI	6	6	1
Statin therapy	23	22	1
Duration of anesthesia (min)	159.4±10.8	155.9±12.11	1

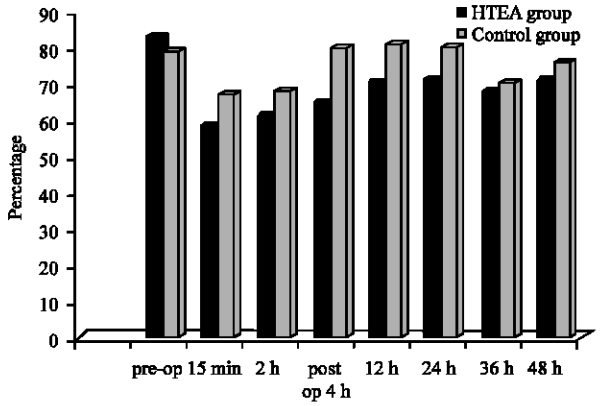

Fig. 1: Heart rate in HTEA group vs control group (p = 0.0001)

Table 2: Serial tropinin I in HTEA and control groups (Meas±SD)

	T I (ng dL^{-1})		
Time of measure	HTEA group	Control group	p-value
Preoperative	0.05+0.03	0.06+0.0	0.10
Postoperative			
6 h	0.06±0.05	0.39±0.12	<.0001
12 h	0.12±0.30	0.81±0.39	<.0001
24 h	0.10±0.17	1.54±0.91	<.0001
48 h	0.06±0.03	1.05±0.00	<.0001

(1.54±0.91 vs. 0.10±0.17 p-value = 0.0001) (Table 2). The Holter monitoring revealed significant myocardial ischemia with new T wave inversion and ST depression in 9 (38%) patients of control group as compare to 2 (8%) patients of HTEA group postoperative p = 0.016 (Table 3). No significant changes were observed after HTEA in Fractional Area Change (FAC) and LV Ejection Fraction (EF) (FAC 55.4±6.3 to 54.22±6.8 p = 1.00 non significant, EF 55.4±5.4 to 56.9±5.8 p = 1.00 non significant). There were no significant changes in LV systolic function in both groups.

The Doppler transmitral flow velocity profile at baseline exhibited different grades of diastolic dysfunction in 15 patients (63%) of HTEA and in 14 patients (58%) of control. The Doppler transmitral flow was categorized as normal in 9 (38%) patients of HTEA and 10 (42%) patients of control group. Abnormal relaxation in 13 (54%) patients of HTEA vs. 8 (33%) patients of control and as a pseudo-normalized pattern in 2 (8%) of patients of HTEA vs. 6 (25%) of control for the baseline study. Out of the total patients with an abnormal relaxation pattern in HTEA, the transmitral flow curve changed to normal in 6 patients. There was significant improvement of abnormal relaxation pattern to normal pattern in HTEA group (from 9 (38%) patients to 15 (63%) patients p = 0.08) and 7 patients remained in an abnormal relaxation. In the 2 patients with a pseudonormalized pattern at baseline, the transmitral velocity profile changed to an abnormal relaxation pattern in 1 patient (Table 4).

In control group, 4 patients changed from the normal pattern to abnormal relaxation pattern. Post-operatively 10 (42%) patients had abnormal relaxation and 6 had pseudo-normalization pattern while 2 of them were in abnormal relaxation peri-operatively. Two (8%) patients of pseudo normalization changed to restrictive pattern (Table 5).

Table 3: Incidence of ischemic ECG changes perioperatively in the two groups

	HTEA group		Control group		
Ischemic changes	No.	%	No.	%	p-value
Pre-operative	5	21	6	25	0.731
Intera-operative	6	25	10	42	0.220
Post-operative	2	8	9	38	0.016

Table 4: The effect of high thoracic epidural analgesia on LV systolic and diastolic function

Parameters	Baseline	Postoperative after HTEA	p-value
LVESD (mm)	29.70±3.0	30.50±3.91	0.44
LVEDD (mm)	50.27±4.0	50.20±4.73	1.00
EDA (cm_2)	23.50±3.9	23.07±3.8	0.87
LVEF (%)	55.40±5.4	56.92±5.8	1.00
FAC (%)	55.40±6.3	54.22±6.8	1.00

	Baseline		Postoperative after HTEA		
Trans mitral flow	No.	%	No.	%	p-value
Normal	9	38	15	63	0.08
Abnormal relaxation	13	54	8	33	0.14
Pseudo-normalization	2	8	1	4	1.00
Restrictive pattern	0		0		

Figures in parenthesis are the percent values

Table 5: Changes of LV systolic and diastolic function in control group

Parameters	Baseline	Control after GA	p-value
LVESD (mm)	30±4.7	32.08±3.65	0.08
LVEDD (mm)	50.2±4.73	52.09±4.73	0.16
LVEF (%)	60.57±3.44	57.96±4.14	1.00
FAC (%)	4	51.67±5.25	1.00
	53.96±7.3		

	Basline		Control after GA		
Transmitral flow	No.	%	No.	%	p-value
Normal	10	42	6	25	0.22
Abnormal relaxation	8	33	10	42	0.55
Pseudo-normalization	6	25	6	25	1.00
Restrictive pattern	0	0	2	8	0.48

Figures in parenthesis are the percent values

DISCUSSION

In patients with ischemic heart disease, High Thoracic Epidural Analgesia (HTEA) has been proposed to improve myocardial function. This study was designed to evaluate the effects of High Thoracic Epidural Analgesia (HTEA) on LV systolic and diastolic function and on perioperative coronary risk in patients with CAD undergoing elective non cardiac surgery.

The key finding of this study was that diastolic, but not systolic, LV function improved in patients with CAD after HTEA. The observed improvement in diastolic function was reflected by a change of the pattern and grades of diastolic dysfunction. The effects of HTEA on LV function

are thought to be produced by blockade of cardiac sympathetic efferent nerve fibers that have their origin in segments T1-T5 (Magnusdottir *et al*., 1999). Activation of these fibers results in stimulation of both α_1-and B_2-adrenergic receptors. Stimulation of B_2-receptors leads to increased inotropy, chronotropy and blood pressure, whereas stimulation of α_1-adrenergic receptors induces vasoconstriction of epicardial coronary arteries (Young and Vatner, 1986). Similar findings were reported in a study using quantitative coronary angiography that HTEA significantly increased the diameter of stenotic coronary artery segments without causing any changes in the tone of the coronary resistance vessels (Blomberg *et al*., 1990). HTEA-induced loss of sympathetic drive to the myocardium, the epicardial coronary arteries and the small resistance vessels may thus influence LV function. LV function can be analyzed according to systole and diastole. With respect to HTEA, much more attention has been devoted to the assessment of systolic function, but the results remain controversial. In CAD patients, HTEA preserved (Berendes *et al*., 2003) or even improved (Goertz *et al*., 1993; Kock *et al*., 1990). LV systolic function. In this study global systolic LV function was not altered by HTEA and there were significant changes in diastolic dysfunction in HTEA group as well as in the control group with significant improvement of diastolic function with the use of HTEA. It was reported that a change in diastolic function is the earliest hemodynamic manifestation in CAD (Castello *et al*., 1990). Because diastolic function can be modified reversibly by subclinical myocardial ischemia, even in asymptomatic patients (Bonow *et al*., 1985). For that reason, diastolic function is considered to be the most sensitive variable of ischemic injury (Apstein and Grossman, 1987). TEE is a highly sensitive ischemia monitor and demonstrates development of new regional wall motion abnormalities, decreased systolic wall thickening and ventricular dilation as a result of ischemic events. Usually, a transgastric cross-sectional view of the left ventricle is imaged because this view displays the myocardial perfusion territories of the three major coronary arteries. The use of TEE has become increasingly common in the operating room for cardiac surgery but is less frequently used in non-cardiac surgery (Statinder *et al*., 2007). Berendes *et al*. (2003) reported that global left ventricular function as assessed by fractional area change was comparable in all patients independent of the existence of reversible cardiac sympathectomy by high TEA during the study period. Postoperatively, however, global left ventricular wall motion was significantly improved in patients with additional reversible cardiac sympathectomy. They also reported that peak cardiac troponin I concentrations were significantly lower in patients who received additional high TEA compared with those who received general anesthesia only. His results were similar to our findings.

Jakobsen *et al*. (2009) studied that the effect of HTEA on myocardial function in patients with ischemic heart disease. They demonstrated that 2D measures of left ventricle function improved significantly reflecting an increase in LV global systolic function and longitudinal systolic displacement. The E"/A" ratio increased indicating improved relaxation. They concluded that a 2D-echocardiography in combination with Tissue Doppler Imaging (TDI) indicates both improved systolic and diastolic function after HTEA in patients with ischemic heart disease. His findings are similar to our study regarding the improvement of diastolic function. However, in our study there was no significant improvement in the systolic function. This can be attributed to the use the TDI and tissue tracking for assessment of LV systolic function.

Liu *et al*. (2004) also reported decreased dysrhythmias with TEA (OR 0.52 and 95% CI 0.29-0.93 and $p = 0.03$) although there were no significant and differences in myocardial infarction and mortality. But, Whilst Scott and Turfrey both identified lower incidences of Andatrial Fibrillation (AF) with TEA (Scott *et al*., 2001; Turfrey *et al*., 1997). It was reported that

TEA in combination with general anesthesia results in more rapid extubation and significantly better pain relief. There may also be a lower incidence of respiratory, cardio-vascular renal complications although the length of hospital stay is not affected (Scott *et al*., 2001).

Limitations: Probably, the optimal drug regime has not been and established and the large randomized studies are lacking. The use of tissue Doppler might detect an improvement in systolic function. It was concluded that High Thoracic Epidural Analgesia (HTEA) improved the left ventricular diastolic function and decreased myocardial ischemia during the intra-operative and postoperative periods. Above all, it is a safe procedure with no significant complications. It is, therefore, recommended the use of HTEA combined with general anesthesia in patients with IHD particularly those with pre-operative angina or ECG changes as well as in patients with left ventricular restrictive diastolic dysfunction.

CONCLUSIONS

There was no significant difference in the heart rate and mean arterial blood pressures ($p>0.05$) in the baseline values between the two groups. However a significant reduction in heart rate and mean arterial blood pressure ($p<0.05$) was observed till 48 h post operatively in HTEA group as compared to the control group. The post operative cardiac troponin I increased significantly in control group than HTEA group ($p = 0.0001$). The incidence of myocardial ischemia was significantly low in HTEA group as compared to control group. The S-T segment changes were noted in 8% of patients in HTEA group as compared to 38% of patients in control group ($p = 0.016$). There were no significant changes in left ventricular systolic function EF and fractional area change FAC in both groups, (FAC 55.4±6.3 to 54.22±6.8 (p-value = 1.00)). In conclusion, the high thoracic epidural anesthesia reduced the incidence of myocardial ischemia and improved the diastolic function in patients with coronary artery disease undergoing elective non-cardiac surgery.

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