ISSN 2515-8260 Volume 10, Issue 1, Winter 2023

Comparison of Mixed Venous saturation in Patients Undergoing Coronary Artery Bypass Graft Surgery with High Thoracic Epidural versus Conventional Opioids Anaesthesia: A Randomized Control Study

Running title: Comparing mixed venous saturation in patients undergoing coronary artery bypass graft surgery between two groups: high thoracic epidural anesthesia and conventional opioids

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ABSTRACT

Background: In coronary artery disease (CAD) a mismatch exists between myocardial oxygen consumption and supply. Anesthetic goal targets balance between this supply and demand perioperatively for improved tissue perfusion. Studies show high thoracic epidural anesthesia (HTEA) helps to achieve this goal.

Aims and Objective: To find out the effectiveness of HTEA in achieving improved tissue perfusion as measured by mixed venous oxygen saturation (SvO2) in patients undergoing coronary artery bypass grafting (CABG).

Design of Study: Randomized control study

Material and Method: Prospective randomized control study, where patients undergoing CABG were randomized into 2 groups; Group A: general anesthesia with HTEA and Group B: general anesthesia with conventional opioids. The objectives were to compare SvO2, heart rate (HR), blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], pulmonary artery wedge pressure (PWAP) and blood lactate levels.

Sample size: Sample size was calculated to be 14, seven in each group using WinPepi software. For better evaluation of results, we have taken 28 patients, 14 in each group.

Results: Parameters like SvO2, HR, SBP, DBP, MAP, PAWP, blood lactate levels were better controlled in Group A than B intraoperatively as well as postoperatively.

Conclusion: We conclude that there is better myocardial consumption and supply balance and improved tissue perfusion as measured by SvO2 in patients receiving HTEA in conjunction with general anesthesia as compared in general anesthesia with conventional opioids.

Key Words:

high thoracic epidural anesthesia, mixed venous oxygen saturation, tissue perfusion

Introduction:

The most frequent major surgery for patients with coronary artery disease is coronary artery bypass grafting (CABG). [1] It is a revascularization procedure used to treat coronary artery disease (CAD), which is characterized by the atherosclerotic plaques constricting the arteries transporting oxygen and nutrients to the heart. [1] CABG is the most effective and definitive treatment for ischemic heart disease (IHD), where healthy blood vessels - most frequently the internal mammary artery, is connected distal to the narrowed or blocked portion of the coronary artery to improve blood flow to the heart thus obviating the blockage. [1]

Neuraxial anesthesia in CABG surgeries causes pharmacological sympathectomy, thereby improving the coronary perfusion by balancing the supply and demand of myocardial oxygen, reducing the incidence of postoperative arrythmias and perioperative myocardial infarction. Cardiac sympathetic block also results in improving myocardial perfusion by improving coronary blood flow. [2 – 4]

Epidural analgesia at a high thoracic level improves myocardial oxygen balance, decreases the severity of myocardial infarctions, reduces the perioperative stress response, and maintains hemodynamic stability; hence produces better analgesia which results in better pulmonary functions following cardiac surgery, resulting in decreased morbidity. These factors together may result in early extubation, ambulation, and discharge. [5]

While perioperative volume management has been found to improve outcomes for patients undergoing cardiac surgery, improving oxygen delivery can shorten postoperative intensive care unit (ICU) stays. [6]

Mixed venous saturation is an essential factor in determining the overall tissue oxygen balance. It is intently related to the cardiac output and arterial oxygen content. [7] Measurement of mixed venous oxygen saturation (SvO2) as the best marker of tissue perfusion, is done through correctly positioning the Pulmonary Artery Catheter (PAC). SvO2 has been proposed to be more sensitive indicator for improved tissue perfusion than other parameters namely ScvO2 and lactate. [8]

Material and Methods:

This prospective randomized study was carried out in the department of cardiac anesthesia, Dr. D. Y. Patil medical college and hospital after Institutional Ethics Sub-Committee approval. Patients with ASA grade II and III, patients undergoing CABG with ejection fraction > 30%, INR < 1.5 were selected. Exclusion criteria were patients with deranged left ventricular function, any neurological and psychiatric disorders, patients with any contraindications for neuraxial blockade, patients posted for emergency procedures, history of allergy to any of the drugs being used under study.

Sample size (n) calculation by WinPepi application was 14 (Group A = 7, Group B = 7). For better evaluation of results, we have taken 28 patients (Group A = 14, Group B = 14). Patients were randomized into two groups using computer generated numbers. Group A patients received general anesthesia with high thoracic epidural anesthesia (HTEA) and Group B received general anesthesia

with conventional opioids.

On arrival in operation theatre, American Society of Anesthesiologists (ASA) standards of monitoring was connected to the patient. Baseline vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), pulse oximetry (SpO2) and respiratory rate were recorded.

Under aseptic precautions epidural catheter was inserted in Group A patients at T4-T5 or T5-T6 intervertebral space. Bolus of 10 ml 0.5% bupivacaine with 3 mg morphine was given in aliquots of 2 ml monitoring the blood pressure. Any hypotension during boluses was treated with 50-100 mcg boluses of inj. phenylephrine. Later infusion of 0.25% bupivacaine was started at the rate of 4ml/hr.

General anesthesia was induced in supine position. Premedicated with Inj. Midazolam 0.05 mg/kg IV and Inj. Fentanyl 2 mcg/kg IV, patient was preoxygenated for 3 mins with 100% oxygen. All vital parameters were recorded, Inj. Propofol 2 mg/kg IV was given slowly to induce the patient. Any hypotension during induction was prevented by giving boluses of Inj. Phenylephrine. Inj. Vecuronium 0.1 mg/kg was given to facilitate the intubation. Proper placement of endotracheal tube was confirmed by capnography. Periodic monitoring of vital parameters was carried out at 1, 2-, 3-, 5- and 10-minute intervals post intubation. Pulmonary artery catheterization was done after induction. Anesthesia was maintained with oxygen and air with FiO2 60% and sevoflurane, along with intermittent boluses of muscle relaxant inj. vecuronium 0.1 mg/kg IV and when required throughout the surgery. No opioid was repeated after induction.

In Group B (general anesthesia with conventional opioids), Inj. Midazolam 0.05 mg/kg IV and Inj. Fentanyl 2 microgram/kg IV was given as premedication. Baseline vitals were recorded. Same induction protocol was followed as Group A. Vitals were recorded at same intervals as done in Group A. 5 microgram/ kg Inj. Fentanyl IV was given before sternotomy. 2 microgram/kg Inj. Fentanyl IV was added while on bypass. Inj. Fentanyl 2 microgram/kg IV was given after coming out of bypass. Additional 2 microgram/kg inj. Fentanyl was administered as and when needed in response to tachycardia.

Mixed venous oxygenation was monitored at different intervals after placing catheter as baseline values, 30 mins from baseline, on pump, post bypass, 12 hours after shifting to ICU. Arterial blood gases were taken before induction, before bypass, 10 mins, 30 mins and 50 mins on bypass; 10 mins, 30 mins and 50 mins post bypass and 8, 16, 24, 36, 48 hours postoperatively. Vitals were recorded at intervals of baseline, immediately after induction, 5 mins, 10 mins, 30 mins, 45 mins, at sternotomy, on bypass, post bypass, after shifting to ICU, 2, 8, 16, 24, 36, 48 hours postoperatively, before and after extubation.

Patient was shifted to cardiac surgical intensive care unit and was extubated 4-6 hours after surgery or next day when the patient is fit for extubation. Most of the patients were extubated within 12 hours and shifted from ICU within 48 hours.

Statistics:

The effect of epidural anesthesia on SvO2 levels was found to be 81.7 ± 0.4 and with conventional opioids was found to be 65.2 ± 10.1 at 60 minutes after induction. Entering this data in WinPepi software, total sample size (to begin with) is 14, seven in each group. However, for better validity of results, a greater number of participants were taken in each group.

All the cases were completed in stipulated time and tabulated. SPSS software was used for analysis of data. Komolgorov- Smirnov's one-sample test was used to assess the normality of distribution of the continuous data. Categorical variable is expressed in terms of frequency and percentage and continuous variables in terms of mean and standard deviation (SD). Student t-test is used to test the significance of mean of two groups with $P<0.05$ as statistically significant at 95% confidence level.

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

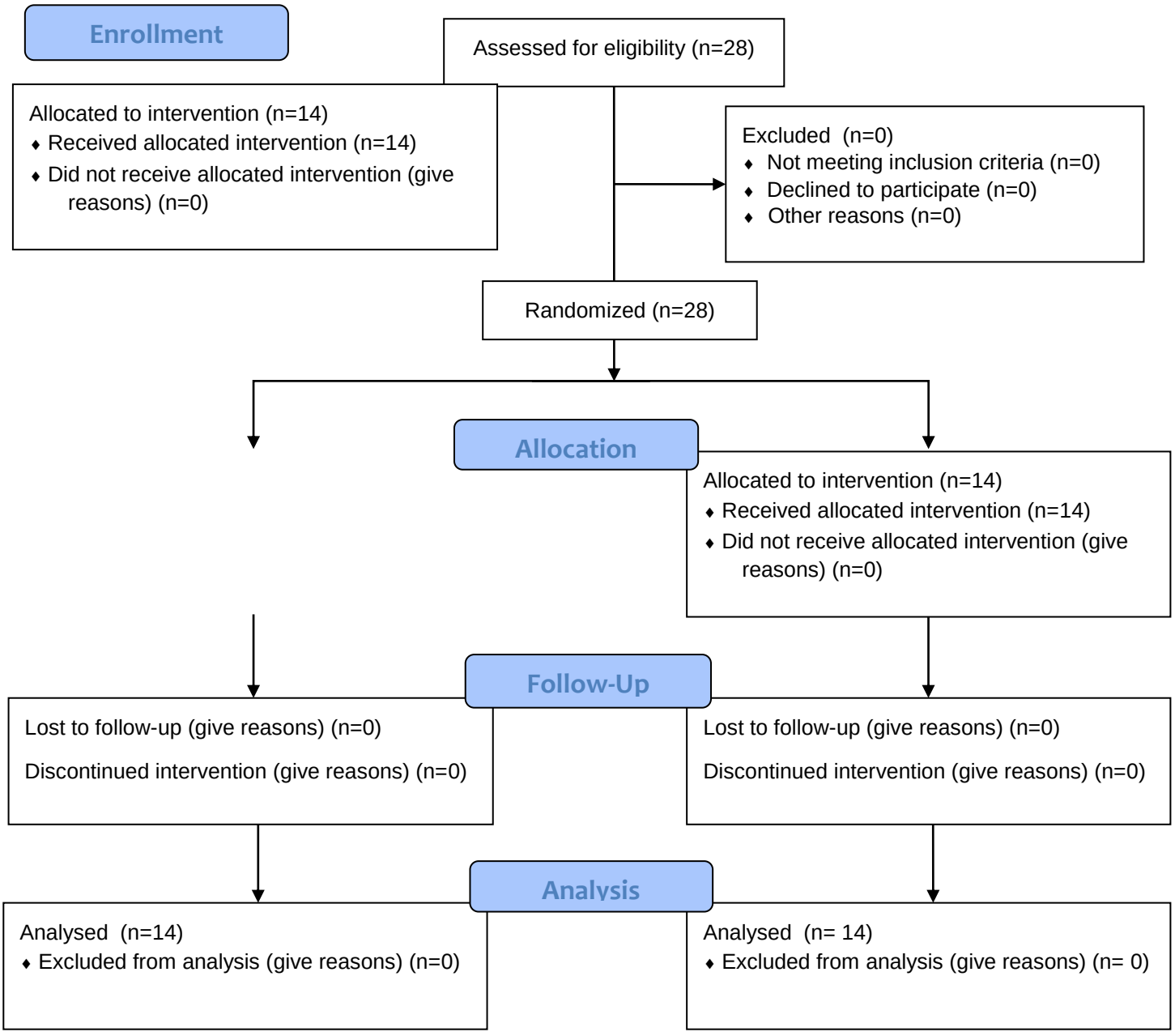


Figure 1: Consort diagram

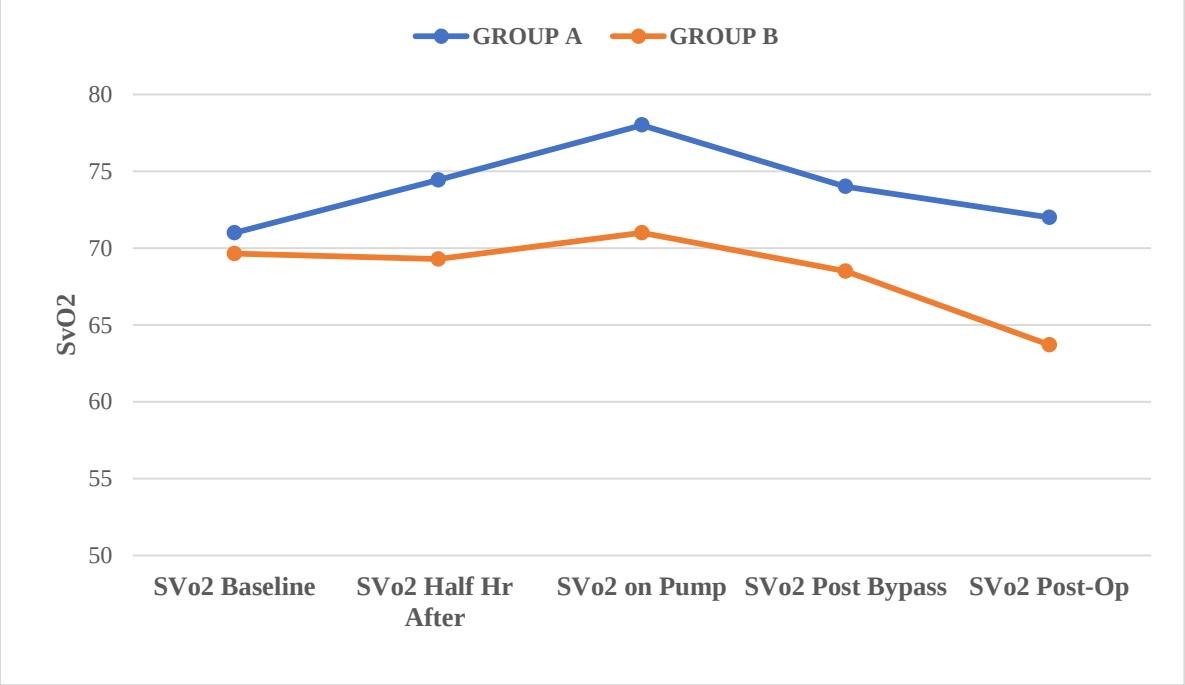
Results:

Table 1: Graph showing demographic variations

Variables	Group A N = 14 Mean±SD	Group B N = 14 Mean±SD	*P value*
Age (in years)	58.79±08.98	62.07±8.64	0.33
Weight (in kg)	65.79±11.66	62.71±8.79	0.44
Height (in cm)	150.00±11.99	151.00±10.86	0.68
Gender	M- 8 | F- 6	M-9 | F-5	0.84
Ejection Fraction	46.64±10.67	45.71±9.17	0.81

Group A-epidural on pump, Group B-opioids on pump, M-male, F-female

Figure 2: Line graph showing the comparison between two groups on SvO2 readings

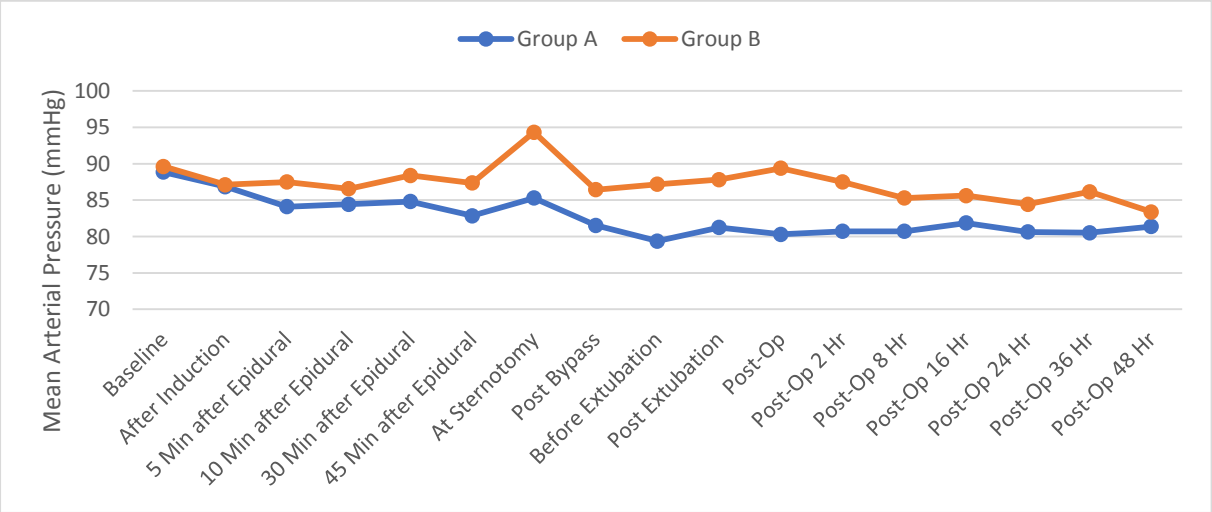


Group A-epidural on pump, Group B-opioids on pump, SvO2-mixed venous saturation during baseline: prior to induction, 30 mins after giving epidural or opioids, on pump, post bypass and 12 hours post operatively

Figure 3: Line graph showing comparison between two groups in heart rate

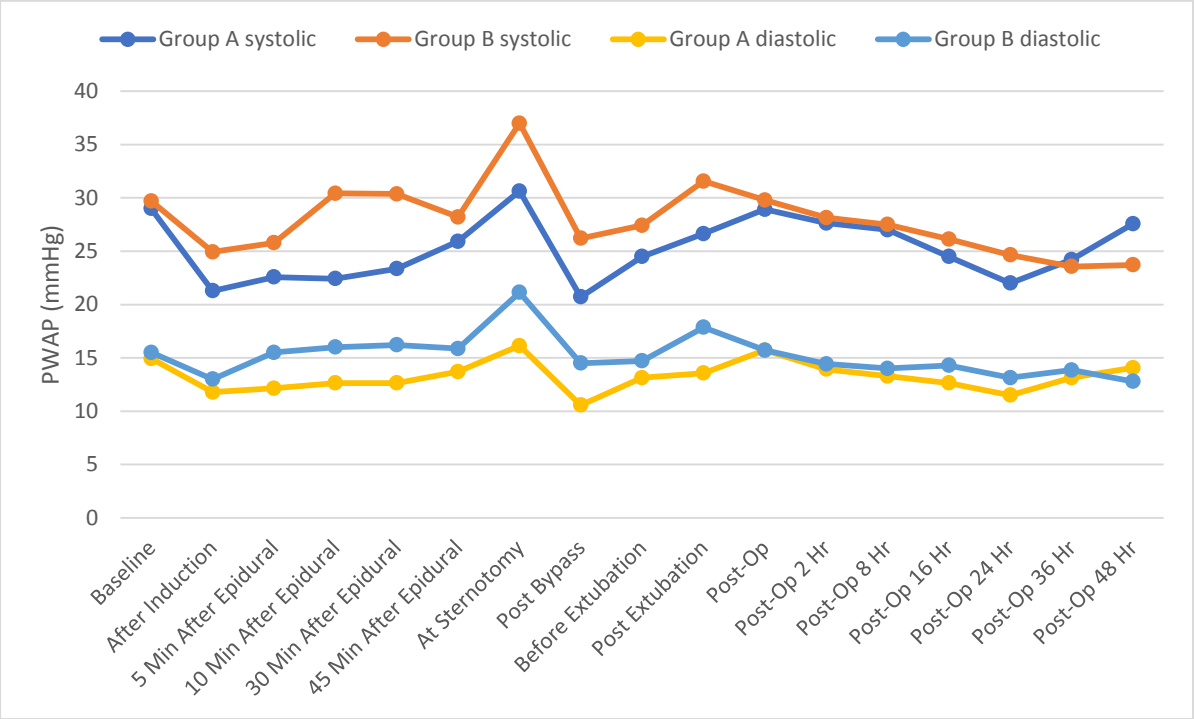
Group A-epidural on pump, Group B-opioids on pump, HR-heart rate measured from baseline till postoperatively 48 hours

Figure 4: Line graph showing the comparison between two groups in mean arterial pressure



Group A-epidural on pump, Group B-opioids on pump, MBP-mean blood pressure measured from baseline till postoperatively 48 hours

Figure 5: Line graph showing the comparison between two groups on readings of systolic and diastolic PAWP



Group A-epidural on pump, Group B-opioids on pump, PWAP-pulmonary artery wedge pressure measured from baseline till postoperatively 48 hours

In our study, the two groups were found to be comparable in terms of age, weight, height, gender, and ejection fraction (Table 1).

- In our study, levels of SvO_2 were found to be significantly lower in group B than in group A at all intervals except for baseline values. (Figure 1)

- In our study heart rate in Group A is significantly less in comparison to Group B at different intervals. (Figure 2)
- We have measured SBP, DBP, MAP of patients starting from before induction (baseline values) to 48 hours postoperatively at different intervals (Figure 3). There was a significantly higher SBP, DBP and MAP noted in group B (Figure 3). There was a decrease in the SBP, DBP and MAP on bypass in both the groups ensuring MAP of 65 mmHg maintained by aliquots of vasopressor like Inj. Phenylephrine 100 mcg. On weaning from bypass, SBP, DBP and MBP till 48 hours post-op, was restored which further however remained same with mild rise of SBP in Group A. This was found to be similar and comparatively higher in group B from the level of post bypass to 48 hours post-op.
- It was found that, there was significant change noted in Systolic PAWP and similarly of Diastolic PAWP with reduction in its levels from induction to of at post op of 48 hours in Group A, a similar finding was noted in Group B but relatively higher levels were found since induction to post op of 48 hours.
- On intragroup analysis, it was found from our study that among the Group A there was no significant difference between HR, MAP, PWAP and SvO2 based on different timelines. Amongst the Group B there was a significance difference between HR, MAP and PAWP at sternotomy and no significant difference in HR, MAP, PWAP and SvO2 at other timelines.

Discussion:

CABG is one of the most frequent cardio-surgical procedures. Many healthcare centers perform CABG surgery without cardiopulmonary bypass (CPB), called as off-pump coronary artery bypass grafting (OPCAB). [9,10] The off-pump method allows coronary revascularization while the heart is still beating, without the use of CBP thereby lowering the risk of CPB related complications. [11,12]

Sympathetic activity causing hypertension, tachycardia, and an increase in metabolism leads to impaired platelet activation, peripheral blood flow, and peripheral oxygen saturation. This causes paradoxical ischemia despite a high FiO2 level. Determining the balance between oxygen delivery (DO2) and consumption (VO2) in CABS is therefore crucial. [13,14] SvO2 is a crucial factor in determining the overall tissue oxygen balance and it is closely related to cardiac output and arterial oxygen levels.

Patients undergoing surgical procedures may benefit from thoracic epidural anaesthesia (TEA). [15] Because TEA decreases sympathetic nervous system activity during surgery, its benefits in cardiac surgery include faster regaining of consciousness and spontaneous ventilation, hemodynamic stability, better analgesia, decreased oxygen demand, optimal redistribution of coronary blood flow, decreased risk of depression and post-traumatic stress, improved pulmonary function and quicker extubation. [16]

Comparison of stress responses:

A) Comparison of Heart Rate

Heart rate should be well controlled in patients having CAD. In our study, heart rate in Group A is significantly less compared to Group B from 30 mins after induction till post op 48 hours. There was no significant increase or decrease in HR at different intervals

intraoperative from baseline till postoperative period in Group A, whereas there was a spike in HR at sternotomy in Group B. It can be inferred that the heart rate was in the lower limit and better controlled in epidural group similar to a study conducted by **Liu SS, Block BM, Wu CL et al (2004),** [17] where they studied the effects of preoperative central neuraxial analgesia on outcome after coronary artery bypass surgery and found that that use of regional anesthesia in conjunction with general anesthesia leads to better control of hemodynamic parameters including heart rate and blood pressure.

B) Comparison of SBP, DBP and MAP

After 30 minutes of giving epidural and opioid doses to post-op period of 48 hours, there was significantly lesser systolic, diastolic, and mean blood pressure was recorded in Group A as compared to Group B. There was a decrease in the SBP, DBP and MAP on bypass in both the groups ensuring MAP of 65 mmHg maintained by aliquots of vasopressor like Inj. Phenylephrine. On weaning from bypass, SBP, DBP and MBP was restored. Post bypass, SBP and DBP was found to be comparatively higher in Group B at 48 hours post-op. There was no significant increase or decrease in SBP, DBP, MAP at different intervals intraoperative from baseline till postoperative period in Group A, whereas there was a spike in SBP, DBP, MAP at sternotomy in Group B. It can be inferred that the blood pressures were in the lower limit and better controlled in Group A. Corelating with other studies, **Kessler P, Aybek T, Neidhart G et al (2005)** [18] showed the role of different anesthetic techniques in altering the stress response during coronary artery bypass grafting and found that use of regional anesthesia in conjunction with general anesthesia leads to better control of hemodynamic parameters including heart rate and blood pressure (systolic, diastolic and mean).

C) Comparison of SvO2

In our study, levels of SVO_2 were found to be significantly less in Group B than in Group A except for the baseline value, as SvO2 was maintained for better myocardial oxygen consumption and demand by achieving good blood pressures and heart rate. There was no significant increase or decrease in SvO2 at different intervals intraoperative from baseline till postoperative period in Group A and Group B, corresponding to a study done by **J. Holm, E. Hakanson, F. Vanky and R. Svedjeholm et al** (2011) [19] where they studied the association between SvO2 and outcome after coronary artery bypass grafting (CABG) surgery and found that patients with SvO2 <60% had higher 30 day mortality and morbidity including higher incidence of perioperative myocardial infarction, renal failure, stroke, and reoperation for bleeding. ICU stay and ventilator treatment was prolonged in patients with SvO2 <60%. Patients with SvO2 of 60% received inotropic drugs more frequently both intraoperatively and in the ICU.

D) Comparison of lactate levels

In our study, blood lactate levels were lower in Group A as compared to Group B on Arterial Blood Gas (ABG) analysis from 45 mins after induction till post op 48 hours. Hence it can be inferred that use of epidural analgesia led to decrease in the body response to tissue damage which was seen as lower lactate levels. This corresponds to **J. Thorelius, R. Ekroth et al** [20] study which tests the hypothesis that the addition of thoracolumbar epidural blocking can avoid alterations in myocardial lactate metabolism that are produced by increased adrenergic activity in the early stages of coronary surgery and conclude that, in the early stages of

coronary surgery, the thoracolumbar epidural blockade is not clearly advantageous when combined with high dose fentanyl/midazolam anesthesia.

E) Comparison of PAWP (systolic and diastolic)

It was found from the current study that, there was significant change noted in systolic and diastolic PWAP since the induction with reduction in its levels from induction to post op of 48 hours in Group A, a similar finding was noted in Group B but relatively higher levels were found since induction to post op of 48 hours, there was no significant increase or decrease in Systolic PAWP, Diastolic PAWP at different intervals intraoperative from baseline till postoperatively in Group A, whereas there was a spike in Systolic PAWP, Diastolic PAWP at sternotomy in Group B, which was in comparison to study done by **Sebastien Roy, Pierre Couture, Baqir Qizilbash et. al**. [21] who studied and concluded that the a/v ratio measured on the PCWP tracing is a predictor of fluid responsiveness in patients with preserved left ventricular function undergoing coronary artery bypass grafting.

Conclusion:

We can conclude that high thoracic epidural anesthesia shows better myocardial oxygen demand and supply balance and improved tissue perfusion where SvO2 was used as a surrogate to measure this parameter, with good analgesia thereby leading to early extubation and lesser ICU length of stay.

Limitation:

1. Sample size was small for generating the results.
2. Protocols in the two groups like choice of fluids, choice of inotropes may have been different as the study was not carried out by the same anesthetist.

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