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COMPARISON OF THE IMPACT OF THORACIC EPIDURAL ANAESTHESIA ALONG WITH GENERAL ANAESTHESIA VERSUS GENERAL ANAESTHESIA ALONE ON PERIOPERATIVE HEMODYNAMIC CHANGES AND INFLAMMATORY MARKERS IN PATIENTS UNDERGOING OFF PUMP CORONARY ARTERY BYPASS GRAFT SURGERY

Anaesthesiology

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ABSTRACT

Pain in cardiac surgery may originate from the surgical incision, intraoperative tissue stress response, dissection of tissues, location of vessel cannulation, chest tubes, venules harvest sites and rib fractures[1]. After a cardiac surgery, serum levels of stress hormone increases creating a pro-coagulatory state in patients. Thoracic epidural anaesthesia has been used as a sole anaesthetic in patients undergoing off pump coronary artery bypass graft surgery. High thoracic epidural anaesthesia (TEA) as a complementary technique to general anaesthesia provides a thoracic sympatholysis with enhancement of coronary perfusion, decreased heart rate, reduced endogenous stress response, and a decreased possibility for myocardial ischemia[2]. Thus we decided to study the impact of thoracic epidural anaesthesia along with general anaesthesia versus general anaesthesia alone on hemodynamic stability and inflammatory response peri-operatively in patients undergoing off pump coronary artery bypass graft surgery. **Materials And Methods:** A total of 60 patients aged between 18 and 80years of both the sexes belonging to ASA PS III posted for elective off pump coronary artery bypass grafting (CABG) surgery were recruited in this study. Patients were divided into two groups, group E received general anaesthesia plus thoracic epidural while patients in group A received only general anaesthesia. Data was collected for post - operative pain score and inflammatory markers levels were monitored. All tests were evaluated for 95% confidence limits. P <0.05 was considered significant. **Results:** The mean value of the heart rate in both the groups A and E at 1st hour postoperatively was 88.63 and 79.63and their difference was also found to be statistically significant with a p value of<0.05.The mean arterial pressure was found to be lower in both intraoperative period and postoperative period in patients who received thoracic epidural anaesthesia along with general anaesthesia, and the difference was found to be statistically significant (p<0.05) thereby proving the distinct effects of thoracic epidural anaesthesia in maintaining the hemodynamic stability. The difference in CRP values between the groups was found to be statistically significant with a p value of less than 0.05. **Conclusion:** The use of thoracic epidural anaesthesia with general anaesthesia in patients undergoing Off Pump CABG results in better hemodynamic stability throughout the procedure without any remarkable complications.

KEYWORDS

Thoracic epidural anaesthesia, C-reactive protein, Off Pump CABG, Inflammatory markers.

INTRODUCTION

CABG surgery remains the preferred treatment in patients with complex coronary artery disease[3]. Improvements in hemodynamic monitoring, myocardial protection, surgical and anaesthesia technique have led to the improved outcome of these high risk patients leading to shorter hospital stay[4].

The determinants of perioperative myocardial injury in cardiac surgery are disruption of coronary blood flow, reperfusion of ischemic myocardium and myocardial preconditioning. The goals of anaesthesia for cardiac surgery involve avoidance of perioperative cardiac ischemia, tight hemodynamic control, early extubation and avoidance of non-cardiac complications[5].Although general anaesthesia remains the preferred anaesthetic technique there is no ideal induction agent. Various combinations of opioids, benzodiazepines and other intravenous agent can be used. Depth of anaesthesia should be adequate before median sternotomy and it requires supplementation with opioids.

The cause of constant pain after cardiac surgery is multifactorial[3]. Tissue damage, scar creation, rib fracture, sternal wound infection, costo-chondral disconnection, and loss of steel wire sutures may all play roles.Higher doses of opioid administration are associated with a range of side effects including respiratory depression, sedation, lethargy, vomiting, nausea, constipation, urinary retention, pruritus and ileus[6].

High thoracic epidural anaesthesia (TEA) as a supplementary technique to general anaesthesia provides a thoracic sympatholysis with enhancement of coronary perfusion, decreased heart rate, reduced endogenous stress response, and a decreased possibility for myocardial ischemia[5]. It also leads to better hemodynamic stability and postoperative pulmonary function.

The increased sympathetic activity following a cardiac surgery changes the host's hormonal response, immune response and coagulation system. Increased plasma catecholamine level increases the heart rate and left ventricular afterload, while time for coronary perfusion is reduced. Segmental sympathetic block of the cardiac sympathetic nerves not only decreases ischemic pain but also maintains the coronary perfusion.

Thoracic epidural anaesthesia has been used as a sole anaesthetic in patients undergoing off pump coronary artery bypass graft surgery, commonly known as conscious off pump coronary artery bypass graft. But opening of left pleura during left mammary artery dissection may lead to left lung collapse with respiratory distress which may require CPAP. This leads to surgical difficulty due to exaggerated diaphragmatic movements[7].

Thus we decided to study the impact of thoracic epidural anaesthesia along with general anaesthesia versus general anaesthesia alone on hemodynamic stability and inflammatory response peri-operatively in patients undergoing off pump coronary artery bypass graft surgery.

MATERIALS AND METHODS:

After obtaining IEC approval and written informed consent, patients aged 18-80 years of both sexes with American Society of Anaesthesiologists physical status class II and above ,undergoing elective off pump CABG with adequate left ventricular function , left ventricular ejection fraction more than 50% and who had discontinued antiplatelet agents (Aspirin, Clopidogrel, Ticagrelor, Prasugrel) seven days preoperatively were included in the study. This study was conducted in the department of anaesthesia and intensive care from August 2018 to October 2019. A prospective randomized parallel group double blinded clinical trial study was conducted. Patients with infection at puncture site, patients with coagulation abnormalities like APTT>45seconds, PT INR>1.5 and platelets less than one lakh, patients on antiplatelet agents within 7 days of procedure or those

undergoing On pump CABG, patients with left ventricular dysfunction EF<50%, patients with chronic inflammatory disease, patients who have undergone recent surgical procedures(less than two weeks) and those who refused to participate in the study were excluded. Patients were divided into one of two groups, Group E which included patients who received general anaesthesia plus thoracic epidural and Group A which included patients who received only general anaesthesia by computer generated random numbers.

All patients were premedicated with fentanyl 1.5mcg/kg intramuscular 30min before shifting to ICU. Peripheral intravenous line was secured and all standard ASA monitors were applied for patients in group E. Patients were explained about the procedure and they were shifted to Intensive Care Unit four hours prior to induction. After positioning, under strict aseptic precautions thoracic epidural catheter placement was performed at T1-T2, T2-T3 with 16G tuohy needle under loss of resistance technique. A test dose of 3ml of Inj.lignocaine was given and then the patients were monitored in ICU for next four hours, before shifting to operating room.

Patients in group A received only general anaesthesia. All patients in the groupA were induced with Inj.fentanyl5mcg/kg, Inj.midazolam 0.05mg/kg, Inj.thiopentone 5mg/kg, Inj.loxicard 1.5mg/kg, Inj.vecuronium 0.1mg/kg. Patients were intubated with endotracheal tube of appropriate size and they were connected to anaesthesia machine. Anaesthesia was maintained with oxygen and air at a ratio of 1:1with isoflurane at 0.6 to 1MAC and infusion of Inj.vecuronium 0.1mg/kg/hour, Inj.midazolam 0.05mg/kg/hour and Inj.fentanyl 2mcg/kg/hr.

Patients in group E received general anaesthesia along with thoracic epidural anaesthesia. Patients in the group E were induced with Inj.fentanyl 5mcg/kg, Inj.midazolam 0.05mg/kg, Inj.thiopentone 5mg/kg, Inj.xylocard 1.5mg/kg, Inj.vecuronium 0.1mg/kg. The patients were intubated with endotracheal tube of appropriate size and were connected to anaesthesia machine. Anaesthesia was maintained with oxygen and air at a ratio of 1:1 with isoflurane at 0.6 to 1MAC, and Inj.vecuronium infusion was started at a rate of 0.1mg/kg/hour. Patients received an initial bolus of Inj. ropivacaine 0.5% 5ml followed by 5ml after five minutes through the epidural catheter. Then infusion of Inj.ropivacaine0.375% at 5ml per hour was started.

Heart rate(HR), Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure(MAP), central venous pressure(CVP) were continuously monitored just before induction and at 1 min, 5min , 30min, 60, 90 min, 120, 150, 180, 210, 240 min post induction. The hemodynamic parameters were monitored hourly for 4hours during postoperative period.

The inotropic requirements (Inj.dopamine 5mcg/kg/min or Inj.noradrernaline/ inj adrenaline 0.05mcg/kg/min) and onset of new arrhythmic changes both intraoperatively and postoperatively was noted.The inflammatory markers C-reactive protein and fibrinogen levels were monitored preoperatively before induction, intra operatively post sternotomy and post skin closure followed by 4hrs postoperatively.The epidural catheter was removed postoperatively after 4hours in patients belonging to group E before starting oral antiplatelet therapy.

Statistical Analysis:

Data was recorded in Microsoft excel sheet. Statistical analysis was carried out using the SSPS statistics 20 software.The numerical data was analyzed using independent t-test, repeated measures ANOVA and Mann-Whitney U -test. Chi-square test and fisher's exact test was be used to find out association between the categorical variables. $p<0.05$ was considered statistically significant.

RESULTS:

Statistical analysis done and results interpretedSixty patients satisfying the inclusion criteria were recruited in the study and divided into two groups of 30 by randomization. They were followed-up and analysed. Both the groups were comparable in terms of clinical and demographic factors such as age, gender, height, weight, BMI, ASA physical status and duration of surgery.

The mean heart rate was compared between Group A and Group E using t test and Mann Whitney test and the highlighted values are the ones in which there was a difference in each time point. The difference was also statistically significant i.e., $p<0.05$.

Table 1 Comparison Of Heart Rate Between The Groups At Each Time Point

Heart Rate (Group A Vs Group E)	p-value
Before induction	0.8360*
1min induction	<0.0001u
5min induction	0.0006u
30min induction	0.0012u
60min induction	<0.0001*
90min induction	0.0180*
120min induction	0.0050*
150min induction	0.0932*
180min induction	0.0075*
210min induction	0.2219*
240min induction	0.0045*
60min Post OP	0.0102u
120min Post OP	0.0163u
180min Post OP	0.0001*
240min Post OP	0.0040*

The SBP, DBP, MAP and CVP were compared between Group A and Group E and the highlighted values are the ones in which there was a difference in each time point. The difference was also statistically significant i.e., $p<0.05$.

Table 2 Comparison Of SBP, DBP, MAP, CVP Between The Groups At Each Time Point

Time intervals (Group A Vs Group E)	Comparison of p value of SBP	Comparison of p value of DBP	Comparison of p value of MAP	Comparison of p value of CVP
Before induction	0.0076u	0.0040*	0.0016*	0.0912u
1min induction	0.4778u	0.2099*	0.4568*	0.2511u
5min induction	0.4177t	0.6245*	0.0219*	0.7239*
30min induction	0.2195t	0.2099*	0.1851*	0.3813u
60min induction	0.0572u	0.6074*	0.8458*	0.6683*
90min induction	0.5382*	0.3441*	0.2095*	0.2216u
120min induction	0.7900u	0.0006*	0.2135*	0.2629u
150min induction	0.9403*	0.2431*	0.0702*	0.9102u
180min induction	0.0419*	0.0003*	0.0101*	0.2879u
210min induction	0.9017*	0.0132*	0.0033*	0.2233u
240min induction	0.1742*	0.0224*	0.050*	0.6057*
60min Post OP	0.0002u	0.0001u	0.0010*	0.4551*
120min Post OP	0.0052u	0.0001u	0.0044*	0.4923*
180min Post OP	0.0002*	<0.001*	0.0187*	0.7816*
240min Post OP	0.5784*	0.0209*	<0.001*	0.5228*

Table 3 Comparison Of Fibrinogen At Baseline And Follow Up In Each Group:

Fibrinogen	Group A p-value	Group E p-value
Before induction Vs Post OP Sternotomy	0.0557w	<0.001p
Before induction Vs After skin Closure	0.0483w	0.0002w
Before induction Vs 240min Post OP	0.0956w	0.0719p

In the above table the Fibrinogen levels were compared between baseline and different follow-up durations using W-Wilcoxon sign rank test and paired t-test. The highlighted values say that there was a difference between the baseline and the respective follow up period in each group. The difference was also statistically significant i.e., $p<0.05$.

Table 4 Comparison Of Fibrinogen Between The Groups At Each Time Point

Time intervals	P value of Fibrinogen between both groups	P value of CRP between both groups
Before induction	0.0127u	0.0072u
Post OP Sternotomy	0.0130u	0.0422u
After Skin Closure	0.0363u	0.0035u
240min Post OP	0.0183u	0.0005u

In the above table the Fibrinogen and CRP levels were compared between Group A and Group E using u-Mann Whitney U test. There was a statistically significant difference in each time point.

Table 5 Comparison Of Onset Of New Arrhythmias Between The Groups

	GROUP A	GROUP E
YES	4(13.4%)	2(6.6%)
NO	26(86.6%)	28(93.3%)

In the above table onset of new arrhythmias was compared between Group A and Group E. The onset of new arrhythmias was found to be higher in patients who received general anaesthesia only when compared with patients who received general anaesthesia with thoracic epidural anaesthesia but this difference was statistically insignificant.

Table 6 Comparison Of Requirement Of Inotropes Between The Groups

	GROUP A	GROUP E
YES	2(6.6%)	2(6.6%)
NO	28(93.3%)	28(93.3%)

In the above table requirement of inotropes was compared between Group A and Group E. The requirement of inotropes was found to be the same in both the groups. The p value for the above data is 0.1 and was found to be statistically insignificant.

DISCUSSION:

In this study the impact of thoracic epidural anaesthesia along with general anaesthesia on the hemodynamic and inflammatory markers on patients undergoing off pump coronary artery bypass graft surgery was studied. Hemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, central venous pressure, requirements of inotropes and new onset of arrhythmias were studied at specific intervals. C-reactive protein and fibrinogen were the inflammatory markers which were noted at four specific time intervals.The patients in both the groups were comparable in respect to demographic profile and duration of surgery.

The heart rate variation between two groups at each point of time was found to be statistically significant. The heart rate of the patients receiving thoracic epidural anaesthesia was found to be on the lower side, both intraoperatively and post operatively and the difference was found to be statistically significant. In a study by Ahmed E Salem et al[4], intraoperative hemodynamics were non-significantly lower in group receiving thoracic epidural anaesthesia till 30 min after induction of general anaesthesia, then the difference became significantly lower in thoracic epidural group till end of the surgery. The mean heart rate in our study in the general anaesthesia group 30min post induction was 75.8 beats/minute and in patients receiving thoracic epidural anaesthesia group was 73.3beats/minute. In a study done by Michael J.barringtonet al[8], there was no significant hemodynamic difference between general anaesthesia and high thoracic epidural group expect that post sternotomy mean arterial pressure was lower in the high thoracic epidural group. Thus it was evident from our study that thoracic epidural anaesthesia provides a stable heart rate peri-operatively.

In our study we studied the impact of thoracic epidural anaesthesia on hemodynamic parameters in terms of systolic blood pressure. The mean value of systolic blood pressure was low in patients who received thoracic epidural anaesthesia along with general anaesthesia. The first 30 minutes post induction in cardiac surgery is considered as a time at which patients are prone for hemodynamic fluctuations because of the stress responses such as intubation, skin incision, sternotomy. From our study it is noted that the systolic blood pressure of patients who has received thoracic epidural anaesthesia maintained a lower value when compared with patients who received general anaesthesia alone during first 30min of the surgery. The intraoperative systolic blood pressure values at 90th, 120th, 150th min post induction were on the lower side for the thoracic epidural group. Thus thoracic epidural anaesthesia along with general anaesthesia reduces the systolic blood pressure because of lesser sympathetic stimulation, by which it reduces the myocardial oxygen demand. The systolic blood pressure in the postoperative period was also on the lower side explaining the superior analgesic property of the thoracic epidural analgesia.

In a study conducted by Ahmed E Salem et al[1] the systolic blood pressure was lower in patients with thoracic epidural group but the difference was statistically insignificant till 30-min after induction of general anaesthesia; then the difference became significantly lower in group receiving thoracic epidural till end of the surgery. The systolic arterial pressure post induction in general anaesthesia group was 116 and in thoracic epidural group was 115.7. The systolic arterial pressure at 30th min, 60th min was found to be 107.5mmHg and 105.8mm Hg when compared to general anaesthesia group, systolic arterial blood pressure of 111.9 mm Hg and 122.2mm Hg.

In a study conducted by Gamal et al[(9)]mean arterial pressure was recorded at the following intervals , before induction, after skin incision, post sternotomy, five minutes before initiation of pump, after closure of sternum, and postoperatively for next 24 hours in ICU. The mean arterial pressure was found to be lower in both intraoperative period and postoperative period in patients who received thoracic epidural anaesthesia along with general anaesthesia, and the difference was found to be statistically significant ($p<0.05$) , thus by proving the distinct effects of thoracic epidural anaesthesia in maintaining the hemodynamic stability.

Regional anaesthetic and analgesic technique may reduce surgical stress- induced alterations of organ function thereby contributing to accelerated recovery following surgery. The systemic inflammatory response induced during coronary artery bypass graft surgery will subsequently contribute to the development of postoperative complications such as myocardial dysfunction, respiratory insufficiency, renal impairment, neurological dysfunction. The inflammatory markers such as interleukines, cytokines, C- reactive protein, and fibrinogen are found to be high in patients undergoing cardio thoracic surgery. Formulating the anaesthetic techniques to reduce the levels of inflammatory markers will give a better perioperative outcome following these major surgeries. The administration of local anaesthetics at the epidural level inhibits the inflammatory response brought about by surgical insult.

In a study conducted by Ahmed E Salem et al[4] the effects of thoracic epidural anaesthesia on the inflammatory markers in patients undergoing CABG was studied. The study quoted that the postoperative serum levels of inflammatory cytokines were significantly higher in general anaesthesia, while levels of anti-inflammatory cytokines were significantly lower when compared to preoperative values in patients who underwent Coronary Artery Bypass Graft Surgery with thoracic epidural anaesthesia. Thus the study proved the beneficial effects of epidural analgesia on surgery-induced activation of immune system.

In a study conducted by Bhanuet al[10] the non-analgesic benefits of combined thoracic epidural analgesia with general anaesthesia in high risk elderly off pump coronary artery bypass graft surgery was studied. In his study serum concentration of interleukin 6, TNF-alpha, cortisol, Troponin – I, CK-MB and HsCRP was compared between the groups. The authors quoted that thoracic epidural anaesthesia along with general anaesthesia attenuates the stress response to cardiopulmonary bypass and coronary artery bypass graft surgery. There was a significant reduction in the levels of plasma epinephrine, cortisol and catechol amines surge, TNF alpha, leukocyte count, and pro calcitonin. It was also noted that epidural analgesia has also been seen to reduce the hypercoagulable response to surgery, improve the myocardial blood flow and reduce postoperative myocardial infarction.

In our study the fibrinogen and C-reactive protein levels were compared between group A and group E. The fibrinogen and C-reactive protein in both the groups were noted after sternotomy, post skin closure, and fourth hour postoperatively. The post sternotomy values of fibrinogen levels in group A and E 316.83 and 266.80 and this difference was statistically significant. The levels of fibrinogen post skin closure and postoperatively in group A and group E were 318.90, 335.63 and 273.83, 303. The difference was found to be statistically significant. The results of the study explain the effect of thoracic epidural anaesthesia in attenuating the inflammation in cardiac surgery and thereby reducing the morbidity and mortality caused by it. The levels of C-reactive protein was monitored at the same intervals that of fibrinogen monitoring. The levels of C-reactive protein were found to be continuously lower in patients who received thoracic epidural anaesthesia.

We compared the requirement of inotropes between the two groups to study the impact of thoracic epidural anaesthesia on it. The requirement of inotropes was the same between the two groups and there was no difference in it. In a study conducted by caputoet al[11] the

intraoperative need of vasoconstrictors differed significantly between two groups; patient who received epidural anaesthesia were likely in need of vasoconstrictors compared to general anaesthesia group.

In a study conducted by caputoet al[11] the incidence of new arrhythmias was significantly lower in patient receiving thoracic epidural anaesthesia. The lower incidence of arrhythmias in thoracic epidural group was contributed to the better hemodynamic stability of the patients receiving thoracic epidural anaesthesia. In a prospective comparative study conducted by Nicolas et al[12] the incidence of supraventricular arrhythmias occurred more commonly in patients who received only general anaesthesia when compared with thoracic epidural group. As a consequence of sympathetic blockade there is a decrease in occurrence of supraventricular arrhythmias. In our study the onset of new arrhythmias was lower in thoracic epidural group when compared to general anaesthesia group. Totally six patients developed arrhythmias, among which four were from general anaesthesia group and two were from thoracic epidural group.

CONCLUSIONS

From the present study it is concluded that using, thoracic epidural along with general anaesthesia in patients undergoing Off Pump CABG results in a hemodynamic stability throughout the procedure without any remarkable complications. It was noted that the strong nociceptive stimulation from the operation field was balanced by thoracic epidural anaesthesia thus providing a optimal control over heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure. There was also a decrease in occurrence of perioperative arrhythmias with no significant difference in requirement of inotropes in patients who received thoracic epidural anaesthesia. Thus the anaesthetic regimen of Thoracic epidural anaesthesia with general anaesthesia in patients undergoing Off Pump Coronary Artery Bypass Graft surgeries provided better hemodynamic stability and resulted in lower levels of inflammatory markers such as Fibrinogen and C reactive protein.

Limitations Of The Study

The study was done with a small sample size, which precluded the generalizability of our results. The use of volume of fluids to maintain hemodynamics is not standardized which could have influenced our hemodynamic changes.

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