

Thoracic Epidural Analgesia Lessens Inflammatory Response to Coronary Artery Bypass Grafting Surgery

Ahmed E Salem^{1*}, Maha M Hagra², Mohamed Amr³ and Manal Hassaan⁴

¹Department of Anaesthesia & ICU, Tanta University, Egypt

²Department of Clinical Pathology, Tanta University, Egypt

³Department of Cardiosurgery, Suez Canal University, Egypt

⁴Department of Medical Biochemistry, 6 October University, Egypt

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*Corresponding author: AE Salem, Department of Anesthesia & ICU, Faculty of Medicine, Tanta University, Tel: 01001802978; Email: essamahmed20016@gmail.com

Abstract

Objectives: To evaluate the effects of preoperative thoracic epidural analgesia (TEA) on inflammatory response of patients undergoing on-pump coronary artery bypass graft (CABG) surgery under general anesthesia (GA).

Patients & Methods: Eighty-eight patients were divided into two groups; Group TEA received TEA and GA and Group GA received GA alone. Blood samples were collected preoperatively (T₀), 4-hr (T₁), and one (T₂) and two (T₃) days after surgery for ELISA estimation of serum interleukin (IL)-1 β , IL-6, IL-10 and tumor necrosis factor (TNF)- α . Intraoperative (IO) and postoperative (PO) data were collected.

Results: Patients of group E had significantly lower IO hemodynamic measures, shorter time for hemostasis and wound closure and less IO blood loss than patients of group G. Amount of 1st PO day wound drainage was significantly less, and durations of mechanical ventilation (MV), ICU stay and PO hospital stay were significantly shorter in group TEA. Patients of group E had significantly lower individual and collective pain scores. All patients showed significantly higher levels of estimated cytokines compared to preoperative levels. Patients of group E showed significantly lower serum IL-1 β , IL-6 and TNF- α with significantly lower serum IL-10 levels compared to patients of group GA.

Conclusion: TEA provided significantly better control on inflammatory response during on-pump CABG in favor of anti-inflammatory arm. Continuous epidural analgesia during ICU stay significantly shortened duration of MV and ICU stay with reduction of need for opioid. Pain control provided by TEA allowed PO early ambulation, rehabilitation and short hospital stay.

Keywords: Thoracic epidural analgesia; Inflammatory response; CABG

Introduction

Coronary artery bypass grafting (CABG) surgery remains the preferred treatment in patients with complex coronary artery disease [1]. However, CABG has inherent impacts on multiple organ systems that could be attributed to altered inflammatory system functions [2]. Cardiopulmonary bypass (CPB) procedures are thought to activate systemic inflammatory reaction syndrome [3] and comparative studies found off-pump surgery could attenuate the CABG-associated inflammatory response [4,5].

Various drugs administered during anesthetic procedure were tried to reduce inflammatory response during on-pump CABG. Desflurane anesthesia induced lower concentrations of interleukin (IL)-8 and IL-6 [6], methyl-prednisolone [7] and dexamethasone [8] decrease levels of IL-6 and increase anti-

inflammatory activity through IL-10 [7]. Also, dexmedetomidine reduced circulating IL-1, IL-6, tumor necrosis factor- α (TNF- α), and interferon- γ levels after mini-CPB [9].

Epidural anesthesia is a central neuraxial block technique with many applications. It is a versatile anesthetic technique that can be used as an anesthetic, as an analgesic adjuvant to general anesthesia, and for postoperative analgesia [10].

The current prospective comparative study aimed to evaluate the effects of preoperative thoracic epidural analgesia (TEA) on inflammatory response of patients undergoing CABG surgery under general anesthesia (GA).

Patients & Methods

The current prospective study was conducted at Departments of Anesthesia and Cardiovascular Surgery at Nasser Institute.

The study protocol was approved by Local Ethical Committee. Patients signed fully informed written consent were randomly; using sealed envelopes prepared by blinded assistant and chosen by patients, allocated into two equal groups: Group TEA included patients will receive TEA as adjuvant to inhalational GA and Group GA included patients will receive inhalational GA alone.

Anesthetic technique

All patients were taken into the operating room unpremedicated and after standard non-invasive monitoring, Lactated Ringer’s solution was started. In Group E epidural catheter was inserted before induction of anesthesia using the loss of resistance technique. A 20 gauge epidural catheter (Prefix 401, B. Braun, Melsungen AG) was inserted through an 18-gauge Tuohy needle that was placed at the T1–2 interspace and advanced 3 to 5 cm into the epidural space. An initial bolus of 10ml ropivacaine 0.75% was injected and followed by continuous infusion of ropivacaine 2% at rate of 10ml/hr. Sensory block was ascertained by sensory loss to needle prick.

For both groups, general anesthesia was induced with midazolam (0.05mg/kg) as a pre-anaesthetic medication, propofol (1-2mg/kg), fentanyl (1-2µg/kg), and atracurium (0.5mg/kg). After tracheal intubation, lungs were ventilated with 100% O2 using a semi-closed circle system, with a tidal volume of 6-8ml/kg, and the ventilatory rate was adjusted to maintain end tidal CO2 between 35-40mmHg. Anesthesia was maintained by sevoflurane 2% and atracurium injection was adapted to the patient’s physiological reaction to surgical stimuli. Heart rate (HR), systolic, diastolic, mean arterial blood pressure (MAP) and oxygen saturation were invasively monitored throughout the surgery. Patients of group GA received fentanyl infusion (2µg/kg/hr) as intraoperative analgesia. Postoperative (PO) pain was evaluated using the visual analogue score (1-10 points) and rescue analgesia for both groups was given at VAS of ≥4 as intramuscular mepridine (50-100mg).

Collected operative data included number of grafted vessels, aortic cross clamping (CCT), cardiopulmonary bypass (CPB) and total operative times. Duration of ICU stay, amount of chest tube drainage, and the frequency of PO events were recorded.

Table 2: Intraoperative hemodynamic data of studied patients.

Group	Time Measures	Pre-Operative	Post-Induction	30-min	60-min	120-min	180-min	At end of surgery
Group GA	HR	87.8	79.8	75.8	75.4	73.6	73.3	71.8
	SAP	117.8	116	111.9	122.2	120.2	119.4	118.9
	DAP	79	77.8	73.9	82	80.6	80.1	79.7
	MAP	91.9	90.6	86.5	95.4	93.8	93	92.9
Group TEA	HR	84.7	79.2	73.3	71.3*	68.9*	65.3*	63.4*
	SAP	117.5	115.7	107.5	105.8*	102.8*	98.7*	95.6*
	DAP	78.2	77	71.5	70.4*	68.4*	65.7*	63.6*
	MAP	91.3	89.9	83.5	82.2*	79.9*	75.7*	75.3*

Data are presented as mean±SD; HR: Heart Rrate; SAP: Systolic Arterial Pressure; DAP: Diastolic Arterial Pressure; MAP: Mean Arterial Pressure; *: Significance Versus Control Levels

Laboratory investigations

Blood samples were collected from preoperatively (T0), 4-hr (T1), one (T2) and two (T3) days after surgery. Separated serum was stored at -80°C until assayed for ELISA estimation of serum IL-1β (Quantikine ELISA kit from R & D Systems, Inc., Minneapolis, MN, USA) [11], IL-10 (Milenia®, DPC Biermann, Bad Nauheim; Germany) [12], IL-6 [13] and TNF- α (Pelikine™ Inc., Concord, USA) [14].

Statistical analysis

Sample size was calculated using the standard nomogram proposed by Kraemer & Thiemann [15] and a sample size of >40 patients was determined to be sufficient to detect a difference at the 5% significance level and give the trial 80% power (16). Obtained data were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test (X2 test) using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Table 1: Patients’ enrolment data.

Data		Group G	Group E
Age (years)		59±6	56.5±6.3
Male: Female ratio		29:15:00	24:20:00
BMI (kg/m2)		29.3±1.9	29.7±2.1
Smoking	Current: Ex: Non	13:22:09	10:27:07
Clinical findings	ASA grade	II:III	25:19:00
	NYHA class	II:III:IV	10:21:13
	Ejection fraction (%)	50.5±14.6	49±16.7
	Co-morbidities	No: Yes	17:27
		19:25	

BMI: Body Mass Index; ASA grade: American Society of Anesthesiology; NYHA: New York Heart Association

The study included 88 patients assigned for isolated CABG (Table 1). Intraoperative hemodynamic measures were non-significantly (p>0.05) lower in group TEA till 30-min after induction of GA; then the difference became significantly (p<0.05) lower in group TEA till the end of surgery (Table 2 & Figure 1).

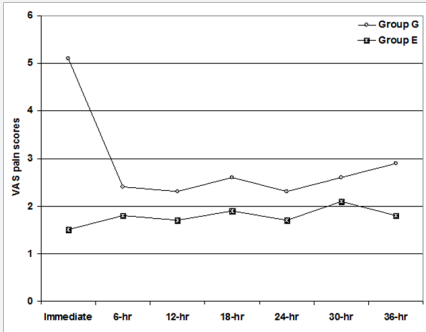


Figure 1: Mean pain VAS scores determined throughout 36-hr after ICU discharge.

Operative data showed non-significant difference between both groups. Patients of group TEA showed significantly lower amount of 1st PO day wound drainage, and durations of mechanical ventilation and ICU stay. Pain scores, determined throughout 1st 36-hr afterward transfer, were significantly lower in patients of TEA group than those of group GA (Fig. 1) with significantly lower collective 36-hr pain score. Mean total duration of hospital stay was significantly shorter in group TEA compared to group GA (Table 3).

Table 3: Operative data of patients of both groups.

Data		Group G	Group E
Operative times (min)	Cross clamping time	60.7±13.1	61.4±13.2
	Cardiopulmonary bypass time	114.1±19.7	106.3±14.7
	Hemostasis & Chest closure	58.2±7.6	53.8±11.6*
	Total operative time	233±27.8	221.5±29.6

Table 4: Mean (±SD) PO serum levels of studied cytokines compared to preoperative levels in patients of both groups.

Cytokine	Time Group	Preoperative	4-Hr	1-Day	2-Day
IL-1β (pg/ml)	Group GA	1.75±0.32	2.05±0.36*	2.32±0.54*	2.66±0.69*
	Group TEA	1.72±0.42	1.87±0.42*†	2.09±0.41*†	2.37±0.48*†
IL-6 (pg/ml)	Group GA	12.6±3.39	35.91±8.8*	41.38±9*	47.9±11.4*
	Group TEA	12.9±3.7	27.7±6.8*†	31.7±6.55*†	38.8±9.33*†
TNF-α(pg/ml)	Group GA	7.04±2.8	21.2±8.17*	29.3±4.81*	38.52±10.78*
	Group TEA	6.76±1.27	17±3.32*†	24.93±6*†	27.5±7.66*†
IL-10 (pg/ml)	Group GA	12±5.06	20.75±8.15*	26.82±14.12*	37.68±21*
	Group TEA	12.5±6.03	27.24±15.7*†	32.5±8.68*†	57.18±15.3*†

Postoperative serum levels of inflammatory cytokines were significantly higher, while levels of anti-inflammatory cytokine were with significantly lower compared to preoperative levels; a finding that illustrates the stress imposed by CABG surgery on immune system and supported that previously reported in literature [17-21]. However, thoracic epidural analgesia (TEA) significantly lessened this effect compared to general anesthesia (GA) alone. These findings illustrated the beneficial effects of epidural analgesia on surgery-induced activation of immune system and supported that previously reported by Bach et al.

Number of vessels	One: Two: Three	7:17:20	11:19:14
	Mean	2.3±0.7	2.1±0.8
Operative blood transfusion	Frequency of blood transfusion	13 (29.5%)	10 (22.7%)
	Number of transfused units	1.5±0.5	1.3±0.5
Amount of 1st PO day tube drainage (ml)		587.5±117	493±134*
Duration of MV(hr)		7.9±1.8	7.2±1.1*
Mean duration of ICU stay (days)		2.8±1.2	2.1±0.6*
PO complications		1.07±0.82	0.7±0.85*
Collective postoperative pain score		2.9±1.3	1.8±0.5
Total PO hospital stay (days)		11±3.3	8.5±1.8*

Data are presented as mean±SD, ratios & numbers; percentages are in parenthesis; *: significant difference versus group GA

Preoperative serum cytokine levels showed non-significant (p>0.05) difference between studied patients. All patients showed significantly (p<0.05) higher PO cytokines levels compared to preoperative levels with significantly higher serum IL-1β, IL-6 and TNF-α and significantly lower serum IL-10 levels in patients of group G compared to patients of group E. This significant difference persisted till 2-day PO (Table 4).

[22] and Palomero Rodríguez et al. [23] who reported that TEA as a part of a combined anesthesia attenuated the inflammatory response to cardiac surgery with CPB. Moreover, Caputo et al. [24] detected significantly lower IL-6 and IL-8 levels with significantly higher levels of IL-10 with combined GA and ETA than in GA alone in patients underwent off-pump CABG. Also, Zawar et al. [10] found combined TEA with GA decreased IL-6 at day 2, TNF-α at day 2 and 5 and concluded that TEA decreases inflammatory response to CABG.

Patients received TEA showed significantly lower pain score and rescue analgesia consumption for 36-hr after extubation. This allowed early ambulation and favorable outcome. Such outcome supported that previously documented that TEA provided better analgesia with significantly reduced pain intensity and analgesic consumption in early PO period after CABG (El-Morsy & El-Deeb [25], Gurses et al. [26], Onan et al. [27] and Porizka et al. [28]).

Patients received TEA enjoyed significantly better PO course with significantly shorter duration of MV and ICU stay. This could be attributed to the better control on inflammatory response in favor of anti-inflammatory direction and the perfect control of pain that allowed freer chest movement with subsequent better lung ventilation, thus reducing postoperative MV-induced complications. Additionally, TEA minimized the need for opioid with its sedative and possible respiratory inhibition effects thus allowed earlier weaning of MV and ICU discharge.

These data go in hand with El-Morsy & El-Deeb [25] who reported that in elderly CABG patients, TEA reduced severity of PO pulmonary dysfunction with faster restoration of normal function and significantly higher PaO₂, lower PaCO₂, thus resulting in earlier extubation and awakening. Moreover, Gurses et al. [26] found PO need for vasodilator, transfusion; analgesics, extubation time and duration of stay in ICU were significantly lower in TEA group of CABG patients compared to GA group. Also, Nesković et al. [29] reported that combination of GA with TEA appears to be good choice during synchronous carotid endarterectomy and OPCAB due to advantages of early extubation and early neurological assessment. Recently, in 2016; Porizka et al. [28] and Barbosa et al. [30] reported significantly shorter time to extubation and lower ICU stay of CABG patients received TEA.

Furthermore, patients had combined GA and TEA showed significantly lower amount of mediastinal drainage on 1st PO day; mostly due to better intraoperative hemodynamic control secondary to significantly lower blood pressure so minimizing bleeding and subsequently decreased PO oozing and collection. Similarly, Gurses et al. [26] reported significantly lower intraoperative MAP, need for transfusion, whereas cardiac output and index, hematocrit values were significantly higher; and postoperative MAP, HR, hypertension development were significantly lower with TEA compared to GA.

In addition, patients received TEA showed non-significantly lower frequency of PO events, but had significantly shorter duration of hospital stay. In line with such outcome, Zawar et al. [10], Gurses et al. [26] and Porizka et al. [28] reported significantly shorter duration of hospital stay in TEA group compared to GA group. Also, Barbosa et al. [30], found combined TEA and GA showed lower incidence of arrhythmias and lower ICU and hospital stay and Stenger et al. [31] reported significantly lower frequency of PO dialysis and myocardial infarction and 6-m mortality rate of cardiac surgery patients received supplemental TEA to GA.

In line with outcomes of the current study and in support of the efficacy of TEA for patients undergoing CABG, multiple studies approved efficacy of combined TEA and GA for cardiac surgery in obese patients [32], chronic obstructive pulmonary disease patients [33] elderly cardiac surgery patients [34] and even in high risk cardiac surgery patients [35].

Multiple experimental studies tried to evaluate the beneficial effects of TEA for patients undergoing CABG; Bedirli et al. [36] using a rat model of mesenteric ischemia/reperfusion found TEA significantly decreased cytokine, malondialdehyde, and myeloperoxidase levels and increased antioxidant enzyme levels with significantly decreased intestinal injury score and percentage of apoptotic cells. Onan et al. [37] using immunocytochemistry showed that TEA increased internal thoracic artery free blood flow significantly via increased vascular endothelial growth factor and inducible nitric oxide synthase expressions and recommended the use of TEA as an adjunct to GA as an alternative to vasoactive agents for increasing internal thoracic artery blood flow during CABG surgery.

Conclusion

TEA provided significantly better control on inflammatory response during on-pump CABG in favor of anti-inflammatory arm. Continuous epidural analgesia during ICU stay significantly shortened duration of MV and ICU stay with reduction of need for opioid. Pain control provided by TEA allowed PO early ambulation, rehabilitation and short hospital stay.

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