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Combined Thoracic Epidural with General Anesthesia *vs.* General Anesthesia Alone for Major Abdominal Surgery: Anesthetic Requirements and Stress Response

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Abstract

Background: There are two components to the anesthetic state, first component is the loss of consciousness and recall, the second component is obtundation of reflex responses to a noxious stimulus, which occurs below the level of cortex. The problem of unexpected awareness has concerned patients and anesthesiologists since the administration of general anesthesia was first described, the incorporation of paralytic agents into the administration of general anesthetics was associated with an epidemic of cases of awareness.

Aim of the study: To determine the effect of epidural bupivacaine on the requirement doses of propofol, fentanyl, and cisatrcurium and on stress response during major abdominal surgery. Patients and methods: This is a randomized, prospective clinical trial, performed in Assiut university hospital in general surgery theatre and department between April 2010 and October 2014. The protocol of the study was approved by our local ethical committee and informed written consent was obtained from all patients. The study included 80 patients of both genders scheduled for major abdominal surgery, age ranged between 18 and 75 years, with ASA physical status between I and III. Patients were divided equally and randomly into two groups to receive general anesthesia or combined general and epidural anesthesia. The induction and maintenance doses of propofol, fentanyl, and muscle relaxants were calculated in addition to hemodynamic changes, fasting blood sugar, serum cortisol, TSH and interleukin-6 level.

Results: Patients received combined general and thoracic epidural anesthesia showed lower requirements of general anesthetics and muscle relaxants, lower intra and postoperative FBS and serum cortisol levelinterleukin-6 level and higher TSH level.

Conclusion: Combined general and thoracic epidural block decrease the need of general anesthesia and muscle relaxants, decrease stress response more than general anesthesia alone during major abdominal surgery.

Keywords: General anesthesia; Abdominal surgery; Thoracic epidural

Introduction

Surgical injury elicits a well-known stress response involving activation of inflammatory, endocrine, metabolic and immunologic mediators. The surgical stress response is believed to be a necessary and beneficial response. However, exaggerated activation of various components of the surgical stress response result in a hypometabolic period, which lasts about 3 days, followed by a hypermetabolic period. As a result of these changes homeostatic disturbance, hemodynamic instability cellular dehydration, capillary leakage and organ dysfunction may occur, leading to a prolonged convalescence period [1].

General anesthesia may limit the perception of sensations due to injury, but does not abolish the response completely as hypothalamus reacts to the noxious stimuli even in the deeper planes of anesthesia (e.g. rise in HR and blood pressure, during sternotomy). All the intravenous agents and volatile anesthetics in normal doses have minor influence on the endocrine and metabolic functions deep levels of general anesthesia may affect the quality of recovery from general anesthesia.

On the contrary the neural blockade by regional anesthesia with local anesthetics have direct influence on endocrinal and metabolic response [2]. The basic mechanism of neural blockade on stress response to surgery is the total prevention of the nociceptive signals from the surgical area from reaching the central nervous system. The inhibitory effect of neural blockade on endocrine and metabolic response to surgery is involved through both afferent and the efferent pathway but differ among the individual endocrine glands [3], the neural blockade are limited by the hemodynamic changes and respiratory derangements when high level of block is needed.

The simultaneous administration of epidural local anesthetics with general anesthetics (IV or inhaled) is frequently used in major abdominal or thoracic surgery. During combined general/epidural anesthesia (CGEA) the noxious stimulus originating from the surgical site is blocked at the spinal level, reducing the requirements of general anesthetics [4].

Proven advantages of CGEA include early recovery from general anesthesia and postoperative analgesia, together with likely decreases

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in blood loss, cardiac dysrhythmias, or ischemic events and postoperative deep vein thrombosis [5].

The side effects of the technique are related to the dose (hypotension) or site (bradycardia and respiratory distress) of the LA administration and to light general anesthesia, which can result in awareness during surgery [6]. In many settings, the use of CGEA is increasing because of the favorable recovery characteristics that facilitate early hospital discharge [7].

The immunologic and inflammatory responses are largely orchestrated by endogenous mediators referred to as cytokines produced by activated leucocytes, fibroblasts and endothelial cells. Cytokines influence immune cell activity, differentiation, proliferation and survival. They regulate the activity of other cytokines, which may either augment (pro-inflammatory) or attenuate (anti-inflammatory) the inflammatory response. The main cytokines released during surgery are interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α). IL-6 is the main cytokine responsible for production of acute phase proteins in the liver including C-reactive protein, and may activate the hypothalamic-pituitary-adrenal axis [8].

Aim of the Study

To determine the effect of thoracic epidural bupivacaine on the requirement doses of general anesthetic agents and muscle relaxants during major abdominal surgery guided by AAI index and to determine the effect of thoracic epidural block on the stress response to surgery.

Patients and Methods

This study is a randomized, prospective clinical trial, performed in Assiut university hospital in general surgery theater and department between April 2010 and October 2014.

The protocol of the study was approved by our local ethical committee and informed written consent was obtained from all patients.

Patients

The study included 80 patients of both genders scheduled for major abdominal surgery, age ranged between 18 and 75 years, with ASA physical status between I and III.

Exclusion criteria included severe cardiovascular diseases, neuropsychiatric disorders, severe metabolic diseases, drug abuse, any contraindications to neuraxial blockade as hypersensitivity to amide local anesthetics, bleeding or coagulation disorders, infection at injection site…etc.

Study design

Patients fulfilling the inclusion criteria were allocated randomly into two equal groups each of 40 patients.

- The combined group (Group I) received combined total intravenous general anesthesia (TIVA) with thoracic epidural as maintenance anesthesia.
- The general anesthesia group (Group II) received only TIVA as maintenance anesthesia.

All patients were premedicated with ranitidine 150 mg and midazolam 5 mg at the night of the surgery and 2 h before surgery with sips of water. All patients were monitored non-invasively for heart rate, non-invasive blood pressure, electrocardiogram and oxygen saturation. All Patients were preloaded with 10 mL/kg normal saline (NS). In group I, an epidural catheter was placed between T9-10. Ten mL of bupivacaine 0.1% was administered as a bolus via the epidural route 20 min before induction of anesthesia and then infusion was maintained at 6 mL/h of the same drug concentration.

Patients in both groups received the same technique for induction of anesthesia, bolus dose of fentanyl 2 μg/kg were given intravenously followed by infusion of propofol 1% at a rate of 4 mg/sec. for about 15-20 seconds till the AAI index reached 15-25. Intubation is then performed after I.V cisatracurium 0.15 mg/kg. Ventilation was controlled with a tidal volume of 10 mL/kg and respiratory rate adjusted to maintain end-tidal carbon dioxide between 30-35 mmHg.

After endotracheal intubation, propofol 1% infusion was titrated to maintain AAI index between 15-25 using continuous A-Line ARX index (AAI index) monitoring (AEP monitor/2, Danmeter A/S, Kildemosevej 13, DK-5000 Odense C).

For administration of top-up doses of cisatracurium, one-fifth of the initial dose of cisatracurium was administered once the recovery of T1/T0 of electromyographic response of adductor pollicis muscle to train of four of the ulnar nerve reached 10%.

Inadequate intraoperative analgesia was defined as an increase in SBP and/or HR by >20% of baseline value for >5 min in response. In this case, patients were given bolus doses of fentanyl 0.5 μg/kg.

Fasting and maintenance dose of I.V. crystalloids were calculated as 4 ml/kg for first 10 kg body weight, then 2 ml/kg for the next 10 kg of body weight and 1ml/kg thereafter, blood loss was replaced with 3 ml crystalloid for every 1 ml blood, third space loss were calculated as 6 ml/kg/hour. Packed red blood cells were administered only when hematocrit becomes <24%.

Bradycardia was defined as HR <40 bpm and hypotension as a decrease in SBP <40% of baseline. Hypotension was treated by infusion of NS and, and if necessary, 5 mg ephedrine was given intravenously.

Data collection

Operative date including duration of operation measured from the skin incision to skin closure, blood loss, volume and type of fluid infused were recorded.

At the end of operation, dose requirements of propofol, fentanyl, and cisatracurium were calculated; dose requirements of each drug were calculated by dividing the total amount of the individual drug used by duration of the operation and patient's weight in kilograms, thus giving the individual drug consumption in $mg.kg^{-1}.h^{-1}$[9].

Venous blood sample (5 ml) was withdrawn at baseline, 30 minutes after skin incision and 24 hours postoperatively for detection of fasting blood sugar (FBS), serum cortisol, TSH. Sample for assessment of interleukin 6 was withdrawn at baseline, 6 hours and 24 hours postoperatively.

Data analysis

Statistical analysis was conducted with SPSS 21 for Windows. Data were summarized as mean and SD and number of patients. The sample size was calculated based on that 20% difference in anesthetic doses is significant. Thirty four patients per group were required to demonstrate a 20% difference in anesthetic doses at α=0.05 and power of 90%. To exclude and dropouts, Six more patients were added to each group. The statistical comparisons between groups were analysed with independent t test and Mann- Whitney U, test. P<0.05 was recognized as statistically significant in all the analyses.

Results

Group characteristics

Patients' general characteristics and other pre-operative data were summarized in Table 1. Both groups were comparable to each other as regard age, weight, height, sex, BMI, ASA status, duration of operation, crystalloids and blood infused.

	Group I	Group II	p-value
Sex (male/female)	24/16	27/13	0.485
Age	57.72 ± 9.34	59.92 ± 6.71	0.230
Height	168.42 ± 7.86	169.62 ± 8.01	0.501
Weight	73.07 ± 13.57	75.05 ± 9.2	0.449
ASA (I/II/III)	11/26/3	7/28/5	0.481
Duration of operation (min.)	160.4 ± 40.74	164.72 ± 40.3	0.634
Fluid infused (ml.)	3153.75 ± 326.67	3232.5 ± 293.2	0.260
Blood infused (ml.)	262.5 ± 277.06	337.5 ± 346.91	0.288
Data were represented as mean ± SD unless otherwise indicated			

Table 1: Group characteristics.

Pre- and post-intubation AAI index

Before intubation, induction dose of propofol titrated to a value of AAI index between 15 and 25. Mean pre- and post-intubation AAI index showed no significant differences between both groups (Table 2).

	Group I	Group II	p-value
Pre-intubation AAI index	16.97 ± 1.45	17.5 ± 1.64	0.135
Post-intubation AAI index	21.1 ± 1.75	21.8 ± 1.52	0.06
Data were represented as mean ± SD			

Table 2: Pre- and post-intubation AAI-index.

Hemodynamic Variables

Mean arterial blood pressure: Both groups showed the same pattern as regard mean arterial blood pressure changes. After induction of general anesthesia and before endotracheal intubation mean arterial blood pressure in both groups was significantly lower than baseline value. Immediately after intubation and after skin incision mean arterial blood pressure increased significantly in both groups compared to baseline values (Figure 1).

Mean arterial blood pressure at 1st, 2nd, and more than 2 hours and at the end of operation were significantly lower than baseline values.

Only at skin incision, mean arterial blood pressure was lower in group I compared to group II.

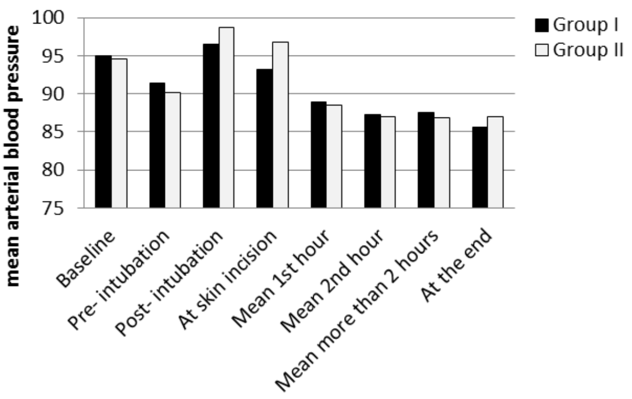

Figure 1: Mean arterial blood pressure changes in both groups.

Heart rate: Heart rate showed higher mean values compared to baseline at after induction, pre and post-intubation and at skin incision in both studied groups (time effect).

Heart rate showed persistently significant lower values in epidural group compared to general anesthesia group after the skin incision till the end of operation (group effect) (Figure 2).

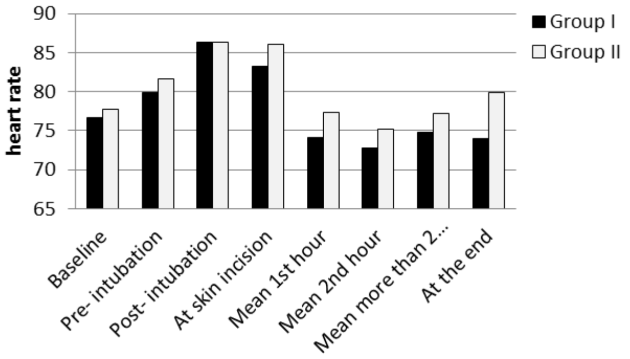

Figure 2: Heart rate changes in both groups.

Induction and maintenance doses of anesthetic agents

In both groups general anesthesia was induced with bolus dose of IV fentanyl 2 μg/kg then propofol was infused at a rate of 4 mg/sec for about 15 to 20 seconds targeting AAI index of 15-25. The total induction dose of propofol required for this AAI index target was significantly lower in epidural group (1.82 ± 0.53 mg/kg) than general anesthesia group (2.94 ± 0.56 mg/kg).

In the same context propofol doses required to maintain the same level of anesthesia were also significantly lower in epidural group compared to general anesthesia group (Table 3).

Increased MAP or HR by more than 20% of the baseline was treated with 0.5 μg fentanyl. Total dose of fentanyl was significantly lower in epidural group compared to general anesthesia group.

Cisatracurium was given at a dose of 0.15 mg/kg to facilitate endotracheal intubation, then top up doses were given guided by the train of four. Maintenance doses of muscle relaxants were significantly lower in epidural group than general anesthesia group.

	Group I	Group II	p-value
Propofol induction dose(mg)	1.82 ± 0.53	2.94 ± 0.56	0.000*
propofol maintenance dose (mg/kg/hr)	4.65 ± 1.21	5.54±1.3	0.002*
Fentanyl (µg)	0.43 ± 0.21	1.09 ± 0.22	0.000*
Cisatracurium maintenance dose (mg/kg/hr)	6.27 ± 2.4	7.83 ± 2.44	0.005*
Data were represented as mean ± SD *Significant difference between both groups			

Table 3: Propofol, fentanyl, and cisatracurium doses.

Fasting blood sugar, cortisol and TSH interleukin 6 levels

Baseline values in both groups were comparable to each other. Thirty minutes after skin incision fasting blood sugar, cortisol rose significantly from the baseline while TSH level decreased significantly from the baseline in both groups. After 24 hours significant rise in FBS and cortisol and significant decrease in TSH level still exist.

	Group I	Group II	p-value
Fasting blood sugar			
baseline	93.82 ± 18.74	99.2 ± 16.64	0.181
after 30 minutes	106.94 ± 17.82	119.35 ± 18.42	0.003*
after 24 hours	115.89 ± 16.21	123.15 ± 17.69	0.061
Cortisol level			
baseline	11.96 ± 5.15	13.2 ± 5.96	0.324
after 30 minutes	15.06 ± 5	21.88 ± 5.67	0.000*
after 24 hours	17.81 ± 5.86	25.44 ± 6.14	0.000*
TSH level			
baseline	2.14 ± 0.51	2.01 ± 0.63	0.319
after 24 hours	1.43 ± 0.61	1.14 ± 0.59	0.035*
Interleukin 6 level			
Baseline	7.32 ± 2.04	6.6 ± 2.81	0.193
After 6 hours	11.87 ± 3.99	15.81 ± 4.4	0.000*
After 24 hours	58.01 ± 16.59	66.93 ± 20.06	0.033*
Data were represented as mean ± SD *Significant difference between both groups			

Table 4: Fasting blood sugar, cortisol and TSH level.

FBS was significantly higher after 30 minutes of operation but not after 24 hours, while serum cortisol level was significantly higher in the later two times in general anesthesia group compared to combine group. TSH was lower in general anesthesia compared to combined group only after 24 hours.

Interleukin-6 level was significantly higher in group II compared to group I at both postoperative samples (Table 4).

Discussion

We compared the effect of general anesthesia alone or in combination with thoracic epidural block on the consumption of anesthetics and muscle relaxants. Our results showed reduction in induction and maintenance dose of propofol, maintenance dose of fentanyl and atracurium in combined group compared to general anesthesia group.

The use of neuraxial block in combination with general anesthesia was extensively studied. Authors studied the effect of this combination on the anesthetic doses, the hemodynamics, the stress response to surgery, post-operative pain, quality of recovery, and length of hospital stay. Different concentrations and different agents were used. Shono et al. in their study compared the hemodynamic effects, dose of sevoflurane and stress hormones with lidocaine 1% and 2% on 33 patients scheduled for lower abdominal surgery under CGEA with BIS kept between 40-50; with similar hemodynamic and BIS values they reported lower sevoflurane requirements and more suppression of stress hormones with lidocaine 2% more than lidocaine 1% [10].

Kanata et al. studied 35 patients scheduled for lower abdominal surgery, they compared the effect of two different concentrations of epidural bupivacaine (0.2% and 1%) on propofol dose, patients in bupivacaine 1% needed less amount of propofol for unconsciousness, noxious stimuli just above the level of block and at C5 level [11].

Casati et al., found that bupivacaine 0.125% to be more effective than 0.0625% in reducing the isoflurane requirements but not induction dose of thiopental. They also found that addition of fentanyl 2 µg/kg to the lower bupivacaine dose produce the same effect of higher doses of bupivacaine with less hemodynamic effects [12].

Agarwal et al. [9] showed that epidural bupivacaine can reduce the dose requirement of the induction and maintenance dose of propofol, fentanyl and vecuronium during general anesthesia. Moharari et al., also showed that epidural bupivacaine decreases the requirement dose of propofol and fentanyl for maintenance of anesthesia [13].

The mechanism behind this effect of local blocks on the needs for general anesthetic agents is still unclear.

Plasma level of local anesthetic agents was thought to affect the anesthetic needs as i.v. lidocaine infusion has a minimal alveolar concentration (MAC)-sparing effect of 10%~28% [14], Senturk et al., reported reduction in the induction and maintenance doses of propofol with intramuscular lidocaine or bupivacaine [15]. This theory was antagonized by the work of Hodgson and Liu [4] who observed decrease in anesthetic requirements despite matched plasma level of local anesthetic agents in general anesthesia alone and combined general and epidural anesthesia. The afferentation theory proposes that excitatory descending modulation of spinal cord motorneurons can be decreased through decreased afferent input to the brain and that tonic sensory and muscle-spindle activity modulate cerebral activity which maintains the state of wakefulness [16-18]. Decreased pain from the surgical site plays a role in decrease anesthetic requirements [19].

The mechanism behind the reduction in the requirement dose of muscle relaxants is thought to be due to small increase in blood level of local anesthetics which depresses postsynaptic potentiation and increases the neuromuscular block of muscle relaxants [20-22].

Metabolic and endocrinal process occurs as a result of surgery which leads to an increase in plasma levels of stress hormones, such as ACTH, cortisol, TSH [23]. The response is manifested through increased serum level of catabolic hormones and decreased serum level of anabolic hormones which is correlated to the severity of surgical injury [24]. Moreover, the depth of anesthesia may affect this stress response to surgical trauma [25]. Stress hormones such as cortisol, adrenocorticotropic hormone (ACTH), epinephrine, and norepinephrine have been validated to evaluate the magnitude of the surgical stress response [26,27].

Evidences are accumulating that attenuation of this stress response may play an important role in a patients' outcome [28,29].

Epidural blocks were also associated with reduction in postoperative cardiac, pulmonary, coagulation, and infection, which may be closely related to blunting of the stress response. For example, Yeager et al. [30] studied epidural block versus standard general anesthesia in 53 high risk patients, and found a significant reduction in cardiac failure, overall postoperative complications and major infectious complications in epidural group of patients which was also correlated with concurrent, significantly lower urinary cortisol excretion in epidural group. The authors suggested that low serum catecholamines level in the epidural group with subsequent effects of tachycardia, hypertension, and increased myocardial oxygen consumption as the probable mechanism. Decreased incidence of infectious complications and wound healing may be explained by hyperglycemia and hypercatabolic state associated with sympathetic overactivity during periods of stress [31].

Limitations of our study may include the effects of hypotensive events on the level of A-line ARX index and therefore the propofol doses in not thoroughly investigated. Another problem is the difficulty in determining the level of thoracic epidural during general anesthesia. Lastly as we did not determine the plasma concentration level of propofol and with the interaction with propofol and fentanyl, we might use more of one of them instead of other.

Conclusion

Combined general and thoracic epidural block decrease the need for general anesthesia and muscle relaxants, decrease stress response more than general anesthesia alone during major abdominal surgery.

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