



EFFECTS OF CAUDAL ANALGESIA ON OXIDATIVE STRESS RESPONSE IN PEDIATRIC CARDIAC SURGERY

**Betül Kocamer
Şimşek***

Ass. Prof Sanko University, Medicine Faculty; Anesthesiology and Reanimation Dept. Turkey. *Corresponding Author

Senem Koruk

Asc. Prof Gaziantep University, Medicine Faculty; Anesthesiology and Reanimation Dept. Turkey.

Gökhan Gökaslan

Asc. Prof Sanko University, Medicine Faculty; Cardio-Vascular Surgery Dept. Turkey.

ABSTRACT

OBJECTIVE: During congenital heart surgery in pediatric patients, factors such as pain, anxiety, hypoxia and hypercarbia those increase the sympathetic nervous system activity and consequently myocardial oxygen consumption, should be avoided. Therefore, it is important to provide effective perioperative analgesia. In this study we aimed to evaluate the effects of caudal analgesia on oxidative stress response, analgesia status, extubation time and CHIPPS scores.

MATERIAL AND METHODS: After Ethics Board approval from Gaziantep University Medical Faculty, 47 childhood patients (aged 2 to 14 years) undergoing surgical ASD and VSD closure operation were enrolled in this study. Patients randomly divided into two groups, in 24 patients (group G), only routine general anesthesia was performed and in 23 patients (Group C) general anesthesia was performed with caudal anesthesia. In group C, caudal anesthesia was achieved with administration of 1 mL/kg levobupivacaine % 0.25 and morphine 0.1 mg/kg mixture in to caudal epidural space just after intubation. Perioperative MAP, SpO₂, HR, arterial blood gas values, the amount of drug consumption, duration of CPB and ACC, TAS, TOS, OSI and glucose values, extubation time, intensive care and hospital stay and CHIPPS scores were recorded.

RESULTS: There was no difference between groups in terms of demographic data. Perioperative hemodynamics, arterial blood gas values, duration of anesthesia, CPB and ACC times were similar in two groups. Also preoperative TAS, TOS, OSI and glucose levels were showed no difference. After CPB, TAS value was significantly higher, glucose and TOS values were lower in group C, but OSI values showed no statistically significant difference. Although it was not statistically significant ($p = 0.051$), TAS level was higher in the postoperative period in group C. TOS, OSI and glucose values were significantly lower in group C. Glucose values were ranging in normal values in both groups. Extubation time, ICU stay and hospital stay were significantly lower in group C ($p < 0.05$). In all patients any serious adverse events due to anesthesia strategies were not encountered.

CONCLUSION: In pediatric patients undergoing cardiac surgery, caudal analgesia in addition to general anesthesia reduces the stress response and suppresses oxidative stress. Therefore it does not only shorten the duration of extubation time, length of intensive care unit and hospital stay but also reduces the CHIPPS scores.

KEYWORDS : Open Heart Surgery, Pediatric, Caudal Anesthesia, Oxidative Stress Early Extubation, CHIPPS score

INTRODUCTION:

The aim of the anesthesia strategies in congenital heart surgery is to provide an uneventful perioperative course with preventing devastating factors such as pain, anxiety, hypoxia and hypercarbia that increase the sympathetic nervous system activity and consequently myocardial oxygen consumption. Therefore it is important to provide effective perioperative analgesia with high fentanyl doses and suppression of the stress response.

The use of regional anesthesia in adult patients undergoing open heart surgery is incrementally increasing due to many of its benefits such as reduction of postoperative complications and significantly decrease in morbidity and mortality (1). Besides, regional anesthesia in pediatric cardiac surgery gained popularity in recent years and many benefits were reported such as in adults (2).

Purpose of the regional analgesia is to prevent the surgical stress-induced neuroendocrine response. Stress response to surgical trauma is characterized by hypermetabolism and alterations in the endocrine function. Not only pain, but also factors such as temperature alterations, hypovolemia, ischemia, acidosis, infection, type and duration of surgery may lead to stress response too. Increase in sympathetic activity due to pain, give rise to tachycardia and increase at peripheral vascular resistance which results with increase at cardiac load.

Although epidural anesthesia is more effective than caudal anesthesia in suppressing stress hormones and catecholamines in adults undergoing cardiac surgery (3-6), caudal anesthesia with bupivacaine, showed significant decrease in serum cortisol and glucose compared to iv fentanyl in infants (7). Furthermore Christen et al reported increased serious oxidative stress during cardiopulmonary bypass in children undergoing cardiac surgery (8).

In this study we aimed to evaluate the effects of caudal analgesia in addition to general anesthesia on oxidative stress response in

childhood patients undergoing cardiac surgery; as well as the analgesic consumption, hemodynamic response, extubation time, ICU and hospital stay and CHIPPS (Child and infants postoperative pain scale) scores were investigated.

MATERIAL AND METHODS:

After Ethics Board approval from Gaziantep University Medical Faculty and receiving approval from families, 47 children patients aged 2 to 14 undergoing surgical ASD (Atrial septal defect) and VSD (Ventricular septal defect) closure operation at Cardiovascular Surgery Department were enrolled in the study. The night before the surgery and 1 hour prior to surgery, children were premedicated with midazolam 0.1 mg / kg iv and morphine 0.1 mg / kg im (Morphine 0.01gr/ml, Osel Pharmaceuticals, İstanbul, Turkey). Midazolam 0.1 mg / kg (Dormicum, Deva, İstanbul, Turkey) and ketamine 1mg/kg (Ketalar, Pfizer, New York, USD) were given again while patient taken to the operation room.

The patients were computerised randomly divided into 2 groups, Group G (General anesthesia, n = 24): routine induction with propofol 2 mg/kg (Propofol %1, Fresenius Kabi, Uppsala, Sweden), atracurium 0.5 mg/kg (Glaxo Smith Klein, Brentford, Great Britain) and fentanyl 1 mcg/kg. Group C (General anesthesia and Caudal, n = 23): in addition to routine induction, just after intubation levobupivacaine 0.25% 1 ml/kg (Chirocain, AbbVie, Queenborough, England) and morphine 0.1 mg /kg mixture was administered as single shot in to the caudal epidural space.

Arterial cannulation and a central vascular access via internal jugular vein were applied. In each patient, after arterial cannulation 1 cc arterial blood was drawn for blood gas and 3 cc arterial blood was drawn to a plain tube for measurement of Total Antioxidant status (TAS) and Total oxidant status (TOS), also blood glucose was detected with a drop of blood with glucose meter-per-views and recorded (Accu-Chek Performa Nano, Roche). Air / oxygen mixture was %50/ %50.

According to hemodynamic response anesthesia were maintained with Sevoflurane (Sevorane®, AbbVie, Queenborough, England) and fentanyl (Fentanyl, Johnson & Johnson, Glaxo Smith Kline Manufacturing S.p.A./Italy).

Arterial blood gases were recorded and evaluated as follows: after arterial cannulation, after intubation, after the sternotomy, before CPB (Cardiopulmoner bypass), at 5th and 30th minutes of CPB, at 1st minute after CPB, after sternum closure, just then admitted to intensive care unit and after extubation. At the entrance in the operating room, just after CPB established and after extubation 3cc blood was drawn to evaluate TAS and TOS. At the same time blood glucose was checked and recorded.

The mean arterial pressure, heart rate and SpO₂ were recorded preoperatively and intraoperatively, also intraoperative Sevoflurane consumption (as MAC value) were recorded.

Duration of CPB and ACC (aortic cross-clamp) time, the amount of prime fluid, the amount of cardioplegia, urinary output, time to extubation, length of ICU and hospital stay, postoperative analgesic consumption were recorded.

Postoperatively Children's and Infant's Postoperative Pain Scale (CHIPPS) (9) score, respiratory rate and hemodynamic parameters were recorded at the admitting to ICU and then 30th min, 1, 2, 4, 6, 12, 24th hours.

Total antioxidant status (TAS) and total oxidant status (TOS) measurement:

Total antioxidant and oxidant status measurement were performed by using Relassay brand commercial kits (Megatip; Gaziantep-Turkey) with Erel method as previously described (10).

Statistical analysis:

The data were evaluated in the operating system Windows 7 Ultimate with SPSS statistical program (Statistical Package for Social Sciences) for Windows 16.0. Comparisons between groups analysed with non-parametric tests, "Mann-Withney-U" test and intra-group comparisons analysed with Wilcoxon matched test. Chi Square test was used for analysis of ASA and gender. P <0.05 was considered significant. For power analyze we used SPSS program. We calculated the value of TOS after CPB as our primer outcome. The difference between mean values was 6 and the standard deviation was 6.4. For α= 0.05 and power= %80 it was calculated minimum 20 person per group.

RESULTS:

There were no difference between groups in terms of demographic data (p>0.05) (Table 1).

Table 1: Demographic Data.

	Group (n = 24)	Group K (n=23)	P value
Age (year)	6,4 ± 3,7 (1-13)	7,2±3,1 (2-12)	NS
Gender: M/F	14/10	14/9	NS
Weight (kg)	20±9,3 (7-42)	23,3±10,6 (10-52)	NS
Operation (ASD/VSD)	15/9	16/7	NS

NS:P value is >0.05, nonsignificant

There was no difference in mean arterial pressure (MAP), SpO₂, and HR preoperatively (p>0.05). Hemodynamic measurements after sedation; MAP was significantly lower only at 5th minute after CPB in group C (Group C: 66.0 ± 2.92 mm Hg vs Group G: 68.8 ± 2.48 mm Hg, p <0.05) (Figure 1). Other measurements were similar to each other. Intraoperative measurements of SpO₂ and HR were similar between groups (p>0.05).

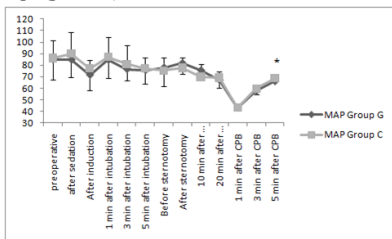


Figure 1. Intraoperative MAP values.

*p<0,05: Significantly lower in group C

HR values, in group C showed a significant reduction after induction, after intubation, 3rd and 5th minutes of entubation, before and after sternotomy at 1st and 10th minutes (p<0.05).

Postoperatively in ICU, HR was significantly higher at 30 th min, 6, 12 and 24 th hours in group G (p <0.05). Also all MAP measurements were significantly higher in group G (p <0.05).

Peroperative arterial blood gas values such as pO₂, pCO₂, pH, BE, HCO₃, K, Ca⁺⁺, Hct did not differ between groups (p>0.05).

Anesthetic drug dose such as midazolam, did not differ between groups significantly but fentanyl and atracurium consumption were significantly lower in group GC. (p <0.05, Table 2). The amount of sevoflurane consumption (in percentage) was significantly higher after intubation, at 3rd, 5th and 10th min, before sternotomy, and 1st, 10th, 20th minutes after sternotomy closure and 5 minutes after CPB in group G (p <0.05, Table 3, Figure 2)

Table 2: Anesthetic Drug Consumption.

	Group G	Group C	P value
Midazolam (mg)	7,2±0,8	7,3±0,9	>0.05
Atracurium (mg)	113,7±40,2*	94,5±20,4	<0.05
Fentanyl (mcg)	185±71*	135±12,2	<0.05

* P<0,05, for comparison of variables caudal vs noncaudal groups within atracurium and fentanyl consumption.

Table 3: Sevoflurane Consumption (%).

	Group G	Group C	P value
Initial	2,7±0,3	2,8±0,4	NS
After induction	2,5±0,4	2,5±0,4	NS
1 min after intubation	2,5±0,4	2,5±0,4	NS
3 min after intubation	2,2±0,4*	1,8±0,5	<0.05
5 min after intubation	2,1±0,3*	1,8±0,5	<0.05
Before sternotomy	2,3±0,3*	1,6±0,4	<0.05
After sternotomy	2,3±0,4*	1,9±0,4	<0.05
10 min after sternotomy	2,2±0,5*	1,8±0,5	<0.05
20 min after sternotomy	2,0±0,4*	1,6±0,5	<0.05
1 min after CPB	0,4±0,1	0,4±0,1	NS
3 min after CPB	0,6±0,1	0,6±0,1	NS
5 min after CPB	1,0±0,1*	0,9±0,9	<0.05

*P<0,05 for difference between caudal and noncaudal groups. NS for p value >0.05, nonsignificant.

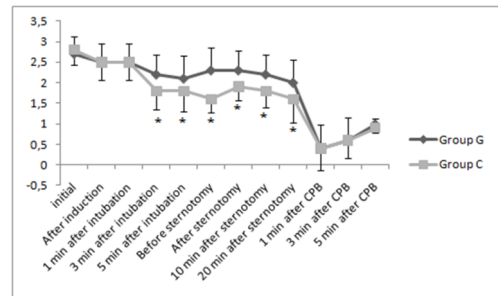


Figure 2: Comparisson of Sevoflurane Consumption between Groups

*p<0,05: Significantly lower in group C

The lowest body temperature during surgery, the amount of cardioplegia, the total amount of urine, and urinary output during CPB did not differ between groups (p>0.05).

Postoperatively, spontaneous respiratory rate was higher at 4, 6 and 12th hour (p <0.05) (Table 4), CHIPPS scores were significantly higher at 4th and 6th hours in group G and at 1st hour in group C (p <0.05) (Table 4, Figure 3)

Table 4: Postoperative Respiratory Rate and CHIPPS Scores.

	Respiratory Rate/min		CHIPPS score		P Value
	Group G	Group C	Group G	Group C	
30 min	24,0±3,7	23,1±4,7	6±0	6±0	NS

1 hour	23,3±4	23,4±4	7,4±1,4	9,3±1,4*	P<0.05
2 hour	25,1±3,3	25,8±4,5	9,7±1,7	9,1±1,5	NS
4. hour	25,9±4,7*	23,6±4	9,8±1,9*	8,6±1,8	<0.05
6 hour	25,3±3,7*	22,3±2,8	9,8±2,5*	5,7±1	<0.05
12 hour	24,2±5,5*	22,1±2,3	5,8±1	5,5±0,7	<0.05
24 hour	22,0±3,2	21,2±2,1	5±2	5±0,2	NS

P<0,05 between caudal and noncaudal groups NS: P>0.05
CHIPPS: Children's and Infant's Postoperative Pain Scale.

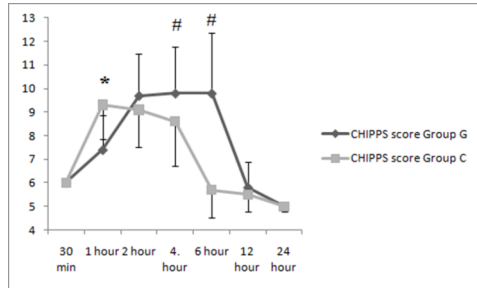


Figure 3: CHIPPS scores.

*p<0,05: Significantly higher in group C
#P<0,05: Significantly higher in group G

Duration of the operation, anesthesia, ACC and CPB time showed no significant difference between the groups. Extubation times, ICU and hospital stay were significantly shorter in group C (p <0.05) (Table 5). None of the patients needed re-intubation.

Table 5: Clinical Data.

	Group G	Group GC	P value
Operation duration (min)	156,2±20,8	159,7±19,1	NS
Anesthesia Duration(min)	185,2±74	174±22	NS
CPB Duration (min)	61,9±20	57±18	NS
ACC Duration(min)	44,7±17,3	42,9±12,8	NS
Extubation Time(min)	503,9±211*	136±79	<0.05
Stay in ICU (h)	20±8,9*	11,4±2,9	<0.05
Hospital discharge (day)	4,9±1,1*	4,3±0,7	<0.05

P<0,05 between caudal and noncaudal groups
NS, p>0.05 nonsignificant

CPB (Cardiopulmonary bypass), ACC (Aortic cross clamp), ICU (Intensive Care Unit)

Preoperatively TAS, TOS, OSI and glucose values were similar (p>0.05) (Table 6,7).

Although after CPB, TAS values were significantly higher, TOS and glucose values were significantly lower in group C (p<0.05), but OSI values showed nonsignificant difference (p>0.05) (table 6,7).

Postoperatively in group C, TAS values were higher but not statistically significant (p=0,051), TOS, OSI and glucose values were significantly lower (p<0.05),

Intra-group comparisons showed statistically significant decreases according to the preoperative values of TAS in group G after CPB, but there was no difference in group C. TOS values according to the preoperative values in both groups showed a significant decrease after CPB and postoperative period. OSI (Oksidative status index) values showed a significant reduction in group G only in the postoperative period, but in group C showed reduction after CPB and at postoperative period (p <0.05) (Table 6, 7, Figure 4). Blood glucose values in both groups showed a significant increase after CPB and postoperative period (p<0.05) (Table 7).\

Table 6: PreoperativeTAS: Total antioxidant status (mmol TroloxEQVEQV. /L), TOS: Total Oxidant Status(micromol H2O2EQV. /L), OSI: oxidative stress index(AU) values.

	TAS		TOS		OSI	
	Group G	Group GC	Group G	Group GC	Group G	Group GC
Preoperative	1,62±0,4	1,65±0,4	24,9±10,1	21±9	1,63±0,9	1,36±0,5

After CPB	1,03±0,2*#	1,65±0,4	16,1±6,4*#	10,7±3,4#	1,15±0,5	0,98±0,4#
Postoperative	1,45±0,5	1,73±0,4	14,7±5,1* <i>f</i>	7,6±4,7* <i>f</i>	0,9±0,3* <i>f</i>	0,69±0,2* <i>f</i>

*P<0,05: Difference between caudal and noncaudal groups

P<0,05: Difference between intra-group preoperative vs after CPB value

f P< 0,05: Difference between intra-group preoperative vs postoperative value

Table 7. Perioperative Blood Glucose Levels.

Glucose (mg/dl)	Group G	Group C	P value
Preoperative	131,5±47	112,4±20	NS
After CPB	228,4±64,4*	167,8±30,1	<0.05
Postoperative	219,5±68*	173,4±35,1	<0.05

*P<0,05: Difference between caudal and noncaudal group NS, p>0.05 nonsignificant.

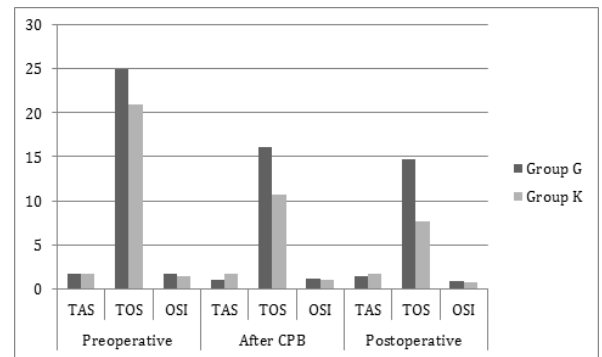


Figure 4:. Peroperative TAS, TOS, OSI values

None of the patients have showed morphine related possible complications such as nausea, vomiting, itching or urinary retention after the removal of urinary catheter. All patients were accepted as uncomplicated cases by surgeons.

DISCUSSION:

In pediatric patients undergoing open-heart surgery, aim of the anesthesia strategies are evolving to reduce the side effects that induced by surgical stress. In this study caudal epidural analgesia was performed in addition to general anesthesia to reduce the surgical stress which may occur in patients undergoing ASD and VSD closure operation. According to the results of this study, caudal analgesia group showed higher total antioxidant levels, lower total oxidant and glucose levels, furthermore had less need for intraoperative anesthetics and provided shorter extubation duration, ICU stay and hospital stay.

There are few studies reporting that oxidative stress is the most important factor for post-operative complications associated with CPB in adults (11,12). In pediatric patients undergoing elective cardiac surgery with CPB, although postoperative complications are more serious than in adults, there is very limited information about the kinetics and development of oxidative stress (13). The release of proinflammatory cytokines and complement activation are believed to play an important role at the development of postoperative complications (14,15). The possible mechanism of the inflammation associated with CPB is related to activation of blood components on the artificial surfaces of extracorporeal circulation, the intestinal endotoxin translocation and myocardial ischemia-reperfusion injury. Surgical procedures, trauma, bloodloss, transfusion, and hypothermia increases the systemic inflammatory response too (16).

The respiratory oxidase activation as a result of the activation of polymorphonuclear (PMN) cells may be the cause of this oxidative stress induced by CPB. Another potential cause of oxidative stress may be the presence of redox-active iron in plasma such as hemoglobins released from ruptured RBCs (16). Cristena et al (8), evaluated the relationship between CPB and iron status, inflammation and oxidative stress profile in children undergoing elective cardiac surgery with CPB, they concluded that cardiopulmonary bypass is associated with severe systemic oxidative stress.

The peak production of the proinflammatory cytokin of IL-6 and IL-8, do not occur until a few hours after the cross-clamp removal, this is the time of when the oxidative stressmarkers (such as MDA, protein-carbonyls, dehydroascorbates) return to preoperative levels. If the primary cause of oxidative stress is inflammation, even after the end of the CPB it should have continued to increase. However there should be other reasons for oxidative stress. Increased plasma carbonyls levels were determined 30 min after the start of CPB (12) or immediately after cross-clamp is removed (approximately 40-60 min after CPB) (17). In our study,oxidative and antioxidative stress markers were measured by a new, recent, calorimetric TAS and TOS measuring method instead of one by one measuring (10). Similarly to previous studies, in caudal group we observed the suppression of oxidative stress.

We determined increased oxidative stress immediately after CPB in group G. The same raise determined at the time of pain and awake time postoperatively in children. In group C, TAS values were significantly higher after CPB (1.03 ± 0.2 , 1.65 ± 0.4), TOS (16.1 ± 6.4 , 10.7 ± 3.4) and glucose (228.4 ± 64.4 , 167.8 ± 30.1) values were significantly lower ($P < 0.05$). Postoperatively, TAS values were higher in Group C but was not statistically significant (1.45 ± 0.5 , 1.73 ± 0.4) ($p = 0.051$), TOS, OSI and glucose values were significantly lower ($p < 0.05$). For intra-groups comparisons according to the preoperative values, TAS values were significantly lower after CPB in Group G.

Due to surgical stress, the increased levels of stress hormones, hemodynamic instability and nitrogen imbalance are determined (18). Avoid of severe hypothermia, less traumatizing and effective analgesia might reduce the occurrence of oxidative stress. In our study, body temperatures and surgical conditions were similar, but in caudal epidural analgesia group we observed significantly lower oxidative stress that attributed to more effective analgesia.

Surgery-related stress response, may cause many hormonal alterations proportional to the surgical damage. Nasr et al. (19) suggested the efficacy of caudal epidural anesthesia on attenuation of perioperative stress response and postoperative pain in pediatric patients undergoing cardiac surgery. In a review of 18650 pediatric patients who underwent caudal anesthesia for pain control, the complication rate including failed block, blood aspiration and IV injection was 1.9%.

Caudal anesthesia was found to be safe as long as Bupivacain was used $< 2\text{mg} / \text{kg}$. (20). However there are very few reports about the effects of caudal epidural anesthesia on pain and stress response. In study of Bichel et al (21) suppression of surgical stress in pediatric cardiac surgery with epidural sufentanil is reported. Rojas-Perez et al (22) used caudal bupivacaine and morphine in pediatric heart surgery and reported less hemodynamic alterations in caudal group and determined less opioid need. Sendasgupta et al (23) evaluated the level of blood glucose, cortisol and the hemodynamic response on elective congenital heart surgery in children, they reported that caudal epidural sufentanil and bupivacaine in addition to general anesthesia suppresses the stress response.

The advantages of early extubation on late extubation are still controversial (24). Pediatric pulmonary complications after cardiac surgery can be minimized with early extubation, consequently this shortens the ICU and hospital stay (25,26). In a large group of pediatric patients who underwent cardiac surgery in the presence of caudal anesthesia, 87.1% of the patients could be extubated at the operating room. The increase in postoperative analgesia quality, decrease in intensive care unit and hospital stay was recorded when there was no increase in mortality and morbidity (27). Combination of general anesthesia with regional anesthesia accelerates early extubation due to less intraoperative opioid requirements (28). Moure et al (29) reported that early extubation did not reduce the morbidity, mortality and postoperatively length of hospital stay. As a result of our study, early extubation in the caudal anesthesia group, decrease in intraoperative opioid requirement and shortening in intensive care and hospital stay were recorded. However more extensive studies are needed for the effects on morbidity and mortality.

Regional anesthesia administered by experienced anesthesiologists in pediatric surgery is safe and effective (2). However, use of this tool in cardiac surgery, especially in infants is still limited (30). Regional anesthesia also decreases the amount of the anesthetic drugs used for general anesthesia. When ASD, VSD and TOF cases in which caudal

anesthesia is applied with general anesthesia are examined, less intraoperative opioid needs are shown (31). In our study in caudal analgesia group, atracurium ($113.7 \pm 40.2 \text{ mg}$ vs $94.5 \pm 20.4 \text{ mg}$), fentanyl ($185 \pm 71 \text{ mcg}$ vs $135 \pm 12.2 \text{ mcg}$) and sevoflurane consumption were significantly lower ($P < 0.05$) (Figure 2).

Rojas-Pe 'Rez et al (22) used bupivacaine to provide analgesia at T1-level in children undergoing cardiovascular surgery. Although when compared, our drug doses ($2.5\text{mg}/\text{kg}$ levobupivacaine, and $100\text{mcg}/\text{kg}$ morphine) are much lower than this study ($4\text{mg}/\text{kg}$ bupivacaine and $150\text{mcg}/\text{kg}$ morphine), postoperatively our patients with caudal block did not required analgesics and also in our study extubation time was significantly shorter and we did not observed any complications associated with caudal block. In our study, we used levobupivacaine. Duration of analgesic and anesthetic effects of bupivacaine and levobupivacaine are similar to each other. Considering that the mean duration of operation was 3 hours, we thought that levobupivacaine alone would not be enough and we added morphine, which is an opioid with long-acting and rostral spread.

Moyao-Garcia et al. (32), added high doses of morphine to bupivacaine. They reported a shorter duration of intubation but the duration of hospital stay was not changed. In our study extubation time, ICU and hospital stay were shorter in Group C. Our results may be different because the morphine dose used in our study is lower. In our study, CHIPPS score were higher only at 1th hour in group C, but in the other periods it was higher in Group G. We attributed this to the less use of anesthetic drugs and early extubation.

In our study, the other reason to choose morphine for caudal epidural was positive reports about its rostral spread. Angst et al (33) showed the increase of heat-pain tolerance at trigeminal dermatome after epidural morphine and related to the presence of morphine in the brain stem it was continuing even at 10th hour. In proportional to the dose of morphine, the thermal analgesia lasts for 24 hours in the spinal field and also supraspinal analgesia after lumbar epidural morphine with rostral spread has showed. This situation proves the effects of epidural morphine ensuring at both spinal and supraspinal analgesia.

In addition, Angst et al showed thermal analgesia at all dermatoms and decrease in electrical response at lumbar and thoracic dermatoms in their study after caudal epidural morphine. Between 5-10 hours after epidural morphine, analgesia was reported at the level of T10. There are studies reporting decrease in blood levels of epinephrine and norepinephrine due to the afferent neural blockade after the use of local anesthetic alone (34,35).

Galante et al (36) reported, no alterations in terms of hemodynamic parameters after caudal block performed with levobupivacaine and remifentanyl when they evaluated with Transesophageal Doppler. In our study, MAP and HR did not differ between groups.

The main risk for performing of regional techniques in cardiac surgery is peridural hematoma due to the use of heparin. Peterson et al (2) reported excellent analgesia results with regional anesthesia in 220 children underwent cardiac surgery without any symptomatic peridural hematoma. In our study we did not observed any symptomatic peridural hematoma. Levobupivacaine used in our study which is less toxic than bupivacaine and reported lower incidence of arrhythmia and QRS enlargement in animal studies.

Peterson and his colleagues (2) evaluated in 220 pediatric patients in pediatric cardiac surgery, and reported regional anesthesia can be used safely and effectively. Epidural morphine provides effective and long-term analgesia in children. However, it also can cause prolonged respiratory depression and urinary incontinence. However, they did not observed apnea. Although we observed the similar clinical positive effects in our patients, we attributed the absent of side effects such as itching or nausea and vomiting and respiratory suppression to dose of morphine they used ($50 \text{ mcg}/\text{kg}$) was about 5 times of the dose we used ($10\text{mcg}/\text{kg}$).

Our work had some limitations. Because many ASD and VSD patients were now treated with angiography, the number of patients was limited. The patient group was relatively hemodynamic stable patients. Our study was not performed at hemodynamically unstable patients. For this reason, further studies are necessary.

CONCLUSION:

In conclusion, in children undergoing cardiac surgery with cardiopulmonary bypass, caudal analgesia reduces the stress response, hence suppresses oxidative stress, decreases CHIPPS score, and shortens the time of extubation significantly. In addition, shortens the duration of intensive care and hospital stay. We considered that, caudal analgesia in addition to general anesthesia in pediatric patients undergoing open heart surgery, may be effective in reducing the surgical stress, as well as may provide early extubation, and low CHIPPS score.

REFERENCES

- Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJ, Bax L. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology*. 2011;114(2):271-82.
- Peterson K L, DeCampi W D, Pike N A, Robbins R C, Reitz B A. A Report of Two Hundred Twenty Cases of Regional Anesthesia in Pediatric Cardiac Surgery. *Anesth Analg* 2000;90:1014-9.
- Kimo K, Friberg P, Grzegorzczak A, et al: Thoracic epidural anesthesia during coronary artery bypass surgery: Effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. *Anesth Analg* 1994;79:1075-1081.
- Stenseth R, Bjella L, Berg EM, et al: Thoracic epidural analgesia in aortocoronary bypass surgery. II. Effects on the endocrine metabolic response. *Acta Anaesthesiol Scand* 1994;38:834-839.
- Moore CM, Cross MH, Desborough JP, et al: Hormonal effects of thoracic extradural analgesia for cardiac surgery. *Br J Anaesth* 1995;75:387-393.
- Fawcett WJ, Edwards RE, Quinn AC, et al: Thoracic epidural analgesia started after cardiopulmonary bypass. Adrenergic, cardiovascular and respiratory sequelae. *Anaesthesia* 1997;52:294-299.
- Wolf AR, Eyres RL, Laussen PC, et al: Effect of extradural analgesia on stress responses to abdominal surgery in infants. *Br J Anaesth* 1993;70:654-660.
- Christena S T, Finckhb B, Lykkesfeldt J et al. Oxidative stress precedes peak systemic inflammatory response in pediatric patients undergoing cardiopulmonary bypass operation. *Free Radical Biology & Medicine* 2005;38:1323-1332.
- McGrath P.J, Unruh A.M, Finley G.A. Pain measurement in children. *Pain: Clinical updates*. 1995;(3):2.
- Ozcan Erel. A novel automated method to measure total antioxidant response against potent free radical reactions. *Clinical Biochemistry*. 2004; 37:112-119.
- Clermont G, Vergely C, Jazayeri e al: Systemic free radical activation is a major event involved in myocardial oxidative stress related to cardiopulmonary bypass. *Anesthesiology* 2002;96:80-87.
- Matata B M, Sosnowski A W, Galinanes M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. *Ann. Thorac. Surg.* 2000;69:785-791.
- Pyles, L. A.; Fortney, J. E.; Kudlak, J. J.; Gustafson, R. A.; Einzig, S. Plasma antioxidant depletion after cardiopulmonary bypass in operations for congenital heart disease. *J. Thorac. Cardiovasc. Surg.* 1995;110:165-171.
- Paparella, D.; Yau, T. M.; Young, E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur. J. Cardiothorac. Surg.* 2002;21:232-244.
- Laffey, J. G.; Boylan, J. F.; Cheng, D. C. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology* 2002;97:215-252.
- Mummy S, Chaturvedi R R, Brierley J et al. Iron overload in paediatrics undergoing cardiopulmonary bypass. *Biochim. Biophys. Acta* 2000;1500:342-348.
- Pantke U, Volk T, Schmutzler M, Kox W J, Sitte N, Grune T. Oxidized proteins as a marker of oxidative stress during coronary heart surgery. *Free Radic. Biol. Med.* 1999;27:1080-1086.
- Wolf AR, Doyle E, Thomas E. Modifying infant stress responses to major surgery: spinal vs extradural vs opioid analgesia. *Paediatr Anaesth* 1998;8:305-11.
- Nasr DA, Abdelhamid HM. The efficacy of caudal dexmedetomidine on stress response and postoperative pain in pediatric cardiac surgery. *Ann Card Anaesth*. 2013 Apr-Jun;16(2):109-14.
- Suresh S, Long J, Birmingham PK, De Oliveira GS Jr. Are caudal blocks for pain control safe in children? an analysis of 18,650 caudal blocks from the Pediatric Regional Anesthesia Network (PRAN) database. *Anesth Analg*. 2015 Jan;120(1):151-6.
- Bichel T, Rouge JC, Schlegel S, Spahr-Schopfer I, Kalangos A. Epidural sufentanil during paediatric cardiac surgery: effects on metabolic response and postoperative outcome. *Paediatr Anaesth* 2000;10:609-17.
- Rojas-Pe' Rez E, Castillozamora C, Nava-Ocampo A A. A randomized trial of caudal block with bupivacaine 4 mg/kg (1.8 ml/kg) plus morphine (150 mg/kg) vs general anaesthesia with fentanyl for cardiac surgery. *Paediatric Anaesthesia* 2003; 13: 311-317.
- Sendasgupta C, Makhija N, Kiran U, Choudhary S K, Lakshmy R, NDas S. Caudal epidural sufentanil and bupivacaine decreases stress response in paediatric cardiac surgery. *Annals of Cardiac Anaesthesia*. 2009; 12(1):27-33.
- Alghamdi AA, Singh SK, Hamilton BC, Yadava M, Holtby H, Van Arsdell GS, Al-Radi OO. Early Extubation after Pediatric Cardiac Surgery: Systematic Review, Meta-analysis, and Evidence-Based Recommendations. *J Card Surg*. 2010;25(5):586-95.
- Harris KC, Holowachuk S, Pitfield S, Sanatani S, Froese N, Potts JE, Gandhi SK. Should early extubation be the goal for children after congenital cardiac surgery? *J Thorac Cardiovasc Surg*. 2014 Dec;148(6):2642-7.
- Stuth EA, Berens RJ, Staudt SR, Robertson FA, Scott JP, Stucke AG, et al. The effect of caudal vs intravenous morphine on early extubation and postoperative analgesic requirements for stage 2 and 3 single-ventricle palliation: a double blind randomized trial. *Paediatr Anaesth*. 2011 Apr;21(4):441-53.
- Garg R, Rao S, John C, Reddy C, Hegde R, Murthy K, Prakash PV. Extubation in the operating room after cardiac surgery in children: a prospective observational study with multidisciplinary coordinated approach. *J Cardiothorac Vasc Anesth*. 2014 Jun;28(3):479-87.
- Hammer GB, Ngo K, Macario A: A retrospective examination of regional plus general anesthesia in children undergoing open-heart surgery. *Anesth Analg* 2000; 90:1020-24.
- Figueira Moure A, Pensado Castañeras A, Vázquez Fidalgo A et al: Early extubation with caudal morphine after pediatric heart surgery. *Rev Esp Anestesiol Reanim*. 2003; 50(2):64-9.
- Silvani P, Camporesi A, Agostino MR, Salvo I. Caudal anesthesia in pediatrics: an update. *Minerva Anesthesiol*. 2006;72(6):453-9.
- Nguyen KN, Byrd HS, Tan JM. Caudal analgesia and cardiothoracic surgery: a look at postoperative pain scores in a pediatric population. *Paediatr Anaesth*. 2016 Nov;26(11):1060-1063.
- Moyao-Garcia D, Garza-Leyva M, Velazquez-Armenta EY et al. Caudal block with 4 mg/kg (1.6 ml/kg) of bupivacaine 0.25% in children undergoing surgical correction of congenital pyloric stenosis. *Paediatr Anaesth*. 2002; 12: 404-410.
- Angst MS, Ramaswamy, Riley ET, Stanski DR: Lumbar epidural morphine in humans and supraspinal analgesia to experimental heat pain. *Anesthesiology*. 2000; 92:312-24.
- Ivani G, DeNegri P, Conio A et al. Comparison of racemic bupivacaine, ropivacaine and levo bupivacaine for paediatric caudal anaesthesia: effects on post-operative analgesia and motor block. *Reg Anaesth Pain Med*. 2002; 27: 157-161.
- Gaitini L, Somri M, Vaida S, et al. Effect of caudal block on the epinephrine and norepinephrine in paediatric patients undergoing ilioinguinal herniorrhaphy. *Eur J Anaesthesiol*. 1999;16:92-7.
- Galante D, Pellico G, Meola S, et al. Hemodynamic effects of levobupivacaine after pediatric caudal anesthesia evaluated by transesophageal doppler. *Pediatric Anesthesia* 2008; 18: 1066-1074.