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Effects of Preemptive Epidural Infusion on Cytokine Response and Postoperative Pain in Pediatric Patients

Pediatrik Hastalarda Preemptif Epidural İnfüzyonun Postoperatif Ağrı ve Sitokin Cevaba Etkisi

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Abstract

Aim: Changes in the metabolic, endocrine, and immune systems caused by surgical trauma and pain are associated with increased concentrations of the biological mediators such as cytokines. Preemptive epidural analgesia may affect pain caused by surgical trauma and the corresponding neurohumoral response induced by the neuromediators. This study investigated the effects of preemptive epidural analgesia on postoperative pain and cytokine levels.

Methods: A total of 60 children undergoing urological surgery were randomly assigned to either the preemptive epidural analgesia (Preempt EA, n=31) group or the postoperative epidural analgesia (Postop EA, n=29) group. Epidural infusion was started before the surgical incision in Preempt EA group and after the peritoneal closure in the Postop EA group. Blood samples were collected preoperatively (before anesthesia induction), 1 h and 24 h after surgery. Plasma TNF-α and IL-2 levels were measured by ELISA. Postoperative pain was assessed using the FACES pain scale, and postoperative analgesia was evaluated 1 h and 24 h after surgery.

Results: Although TNF-α levels were increased 1 h and 24 h after surgery compared to preoperative levels in both groups, the levels were significantly higher in the Postop EA group. IL-2 levels were significantly higher at both postoperative time points in the Preempt EA group than in the Postop EA group. There were no significant differences in pain scores between the groups.

Conclusion: Our results suggest that preemptive epidural analgesia may attenuate the proinflammatory response but has no effect on pain intensity. *(The Medical Bulletin of Haseki 2013; 51: 162-7)*

Key words: Epidural, analgesia, cytokine, preemptive, pediatrics

Özet

Amaç: Cerrahi travma ve ağrı nedeniyle metabolik, endokrin, immün sistemde oluşan değişiklikler sitokin gibi biyolojik mediatörlerin artışı ile beraberdir. Preemptif epidural analjezi, cerrahi travmanın neden olduğu ağrı ve nöromediatörlerin oluşturduğu nörohümoral cevabı etkileyebilir. Bu çalışmada preemptif epidural analjezinin postoperatif ağrı ve sitokin düzeyine etkisinin araştırılması amaçlandı.

Yöntem: Ürolojik cerrahi planlanan 60 çocuk; preemptif epidural analjezi (Preempt EA, n=31) grup ve postoperatif epidural analjezi grubu olarak (Postop EA, n=29) randomize iki gruba ayrıldı. Epidural infüzyon; Preempt EA grubunda cerrahi insizyon öncesi, Postop EA grubunda periton kapanışından sonra başlandı. Kan örnekleri preoperatif dönem, cerrahiden 1 saat ve 24 saat sonrasında ELISA yöntemi ile plazma TNF-α ve IL-2 düzeylerini tespit için alındı. Postoperatif ağrı FACES ağrı skalası ile cerrahiden 1 ve 24 saat sonrasında değerlendirildi.

Bulgular: Her iki grupta TNF-α değerleri 1. ve 24. saatte preoperatif değerlere oranla arttı. Postop EA grubunda değerler Preempt EA grubuna göre daha yüksek bulundu. Preempt EA grubunda, IL-2 değerleri postoperatif dönemde Postop EA grubuna göre daha yüksekti. Ağrı skorları açısından gruplar arasında istatiksel olarak fark yoktu

Sonuç: Sonuçlarımız preemptif epidural analjezinin proinflamatuvar cevabı azalttığı ama ağrı şiddetine etkisi olmadığını düşündürdü. *(Haseki Tıp Bülteni 2013; 51: 162-7)*

Anahtar Sözcükler: Epidural, analjezi, sitokin, preemptif, pediatrik

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Introduction

Surgical trauma leads to changes in the metabolic, endocrine, and immune systems. Tissue damage, surgical stress, and pain cause afferent neuronal stimulation and the activation of cellular and humoral immune pathways that are associated with local inflammatory reactions and the accompanying elevations in the biological mediators such as cytokines (1,2). Proinflammatory cytokines, especially IL-6 and TNF-α, play an important role in the development of hyperalgesia and mechanical allodynia (3). The management of analgesia may affect neuroendocrine responses and attenuate proinflammatory cytokine production. Preemptive analgesia is a method in which treatment begins before the surgical stimulus and reduces the central and peripheral sensitization (4).

Our objective was to evaluate whether a preemptive analgesia method that used a continuous epidural infusion could attenuate cytokine production postoperatively in pediatric patients undergoing urological surgery. We chose an antiinflamatory cytokine - IL-2 and a proinflamatory cytokine - TNF-α as a marker of the efficacy of preemptive analgesia on neuroendocrine response induced by pain.

Methods

Patients

After obtaining ethical approval of the University Hospital (no:18447) and written consent of parents, 60 children aged 3-12 years (American Society of Anesthesiologists [ASA] physical status I-III) were included the study. Exclusion criteria were a recurrent operation, congenital cardiac defects, malignancy, and an endocrine or immune disease. All patients were scheduled for elective ureteropelvic junction obstruction or vesicoureteral reflux surgery. The participants were randomly assigned to receive one of the two methods of analgesia and postoperative pain. Thirty-one patients received general anesthesia and a continuous epidural infusion (preemptive epidural analgesia [Preempt EA] group), whereas twenty-nine patients received general anesthesia and a perioperative ultra short-acting intravenous opioid infusion (postoperative epidural analgesia [Postop EA] group). Postoperative analgesia control was provided by continuous epidural infusion in both groups.

Anesthesia and Analgesia

Electrocardiogram, arterial blood pressure (noninvasively prior to the induction of anesthesia, invasively thereafter), oxygen saturation, ETCO2, and temperature were monitored in all patients during the surgery. Anesthesia was induced with intravenous 1 μg/kg fentanyl, 3-5 mg kg-1 thiopental, and 0.5 mg kg-1 atracurium. The patients were intubated and ventilated with 40% oxygen at 12-18 breaths per minute, and the tidal volume was adjusted to maintain an end tidal CO_2 of 30-35 mmHg and a peak airway pressure of 15-20 cm H2O. Anesthesia maintained with 2-3%sevoflurane in air-oxygen mixture. After the anesthesia induction, the patients were turned onto left lateral position for insertion of epidural catheter. The epidural catheter was placed at the T12-L1 or L1-L2 interspace and advanced 4-5 cm. A test dose of 2 ml of 1% lidocaine was used to ensure a spinal placement did not occur.

Thirty minutes before the surgical incision, a continuous infusion of 0.1% bupivacaine plus 0.02 mg ml^{-1} morphine at a rate of 0.4 ml kg^{-1} h^{-1} (maximal dose=6 ml) was initiated in the Preempt EA group. The epidural infusion was continued without cessation through the postoperative period. The analgesia provided to the Postop EA group was an infusion of remifentanyl at a rate of 0.1-0.25 μg kg^{-1} min^{-1} that was initiated after the induction of anesthesia. After the peritoneal closure, an infusion of 0.1% bupivacaine plus 0.02 mg ml^{-1} morphine at a rate of 0.4 ml kg^{-1} h^{-1} was administered epidurally for postoperative analgesia. The time of the analgesic request during three time periods, in the recovery room (t1), the first 6 h postoperatively (t2), and between 6 to 24 h after surgery (t3), was recorded. A continuous infusion of Ringer's lactate solution was given (the 4:2:1 rule was followed), and 6% hydoxyethyl starch was added when the mean arterial pressure dropped 30% below the baseline level. The mean arterial blood pressure and heart rate were maintained within 20% of their baseline values.

Four milliliters of blood were collected for plasma TNF-α and IL-2 analysis before the induction of anesthesia (T1), 1 h after surgical peritoneal closure (T2), and 24 h after surgery (T3). The patients were extubated following reversal of the neuromuscular block. All patients were transferred to a patient room after 2 h in the recovery unit. Crystalloid and colloid solutions were infused during the postoperative period. FACES pain scale scores were assessed by an anesthetist based on drawings of five faces that corresponded to five levels of pain (scores ranged from 0-6 with 0 = no pain and 5 = worst pain) and were recorded 1 h and 24 h after surgery. Intravenous paracetamol (15 mg kg^{-1}) was infused to all patients with a FACES pain score of at least 3 during the postoperative period. Sedation scores were evaluated at the same time as pain scores with the University of Michigan Sedation Scale (0 = awake and alert and 4 = unarousable to stimuli). The pain and sedation scoring were done by another anesthetist group who were blinded to the technique.

Laboratory Tests

Blood samples obtained at the T1, T2, and T3 time points were centrifuged at 2000g for 10 min within 30 min of being collected, and the plasma was stored at -80°C until further analysis. TNF-α and IL-2 levels were measured with quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (TNF, Assaypro, catalog number: ET2010-1; IL-2, eBioscience, catalog numbers: BMS221CE and BMS221TENCE). These kits showed no significant cross-reactivity or interference with other cytokines.

Statistical Analysis

SPSS version 17.0 for Windows was used for statistical analysis. Statistical analysis was estimated using the data from previous studies performed in our institution (5). One standard deviation was aimed for detecting a difference in pain scores. The study required at least 16 patients per group to have a power of 80% and type I error of 0.05. Demographic data were analyzed by Student's t-test, and cytokine data were compared with the Mann-Whitney U test (between groups) and the Wilcoxon test (within groups). Data are expressed as mean±standard deviation (SD). Pain and sedation scores were analyzed with the Pearson's chi-squared test (between groups) and the McNemar's test (within groups). A p value of less than 0.05 was considered significant.

Results

There were no significant differences between the two groups in terms of age, weight, sex, and duration of anesthesia (Table 1), and the preinduction values of the two cytokines measured did not differ significantly between the two groups. The plasma levels of TNF-α in the Preempt EA group at T1, T2, and T3 were 29.2±15.0, 33.2±17.7, and 39.9±23.6 pg ml^{-1}, respectively, whereas the plasma levels of TNF-α in the Postop EA group at T1, T2, and T3 were 29.8±8.2, 38.9±11.6, and 49.5±15.76 pg ml^{-1}, respectively. TNF-α levels were significantly increased at T2 and T3 compared to T1 in both groups (Table 2a). The Postop EA group had significantly higher levels of TNF-α than the Preempt EA group at T2 and T3 (p=0.039 and p=0.023, respectively). In the Preempt EA group, TNF-α levels were significantly increased at T3 compared to T1 and T2, whereas in the Postop EA group, the TNF-α levels were significantly increased at T2 and T3 compared to T1 (Table 2b).

The plasma levels of IL-2 in the Preempt EA group at T1, T2, and T3 were 20.5±3.4, 19.9±3, and 20.6±3.4 pg ml^{-1}, respectively, whereas the Postop EA group IL-2 levels at T1, T2, and T3 were 19.8±2.8, 17.8±2.1, and 16.5±1.8 pg ml^{-1}, respectively (Table 3a). IL-2 values were significantly higher at T2 (p=0.005) and T3 (p=0.001) in the Preempt EA group than in the Postop EA group. There was a statistically significant decrease in IL-2 levels at T2 compared to T1 in the Preempt EA group. On the other hand, in the Postop EA group, the significant changes were also observed in IL-2 levels at T1, T2, and T3 (Table 3b).

Pain scores were divided into two groups (no pain: score between 0 and 2 and painful: score between 3 and 5), and there were no statistically significant differences found between the Preempt EA and Postop EA groups (Table 4a). The distribution of pain scores between the groups and within the groups are described in Table 4a, patients categorized by the time of the request for analgesia are described in Table 4b. There were no differences in postoperative sedation scores between the groups (Table 5).

Discussion

There have been many studies with different results on the effects of preemptive analgesia on pain scores and neurohumoral changes (4-6). However, these studies used different methods and drugs. The definition of preemptive

Table 1. Patient characteristics

	Preempt EA n=31	Postop EA n=29
Age (years)	6.51±3.84	7.76±4.06
Weight (kg)	20.68±6.55	23.25±4.97
Surgery duration (min)	248.00±127.58	231.45±97.55
Sex (F/M)	14/17	16/13

Table 2a. Inter-group comparisons of the changes in TNF-a levels

TNF-α (pg/ml)	Prempt EA (n=31) Mean±SD	Postop EA (n=29) Mean±SD	p
T1 (preop)	29.2±15.0	29.8±80.2	0.179
T2 (1 hpostop)	33.2±17.7	38.9±11.6	0.039*
T3 (24 hpostop)	39.9±23.6	49.5±15.7	0.023*

Mann Whitney U test, p<0.05

Table 2b. Intra-group comparisons of the changes in TNF-a levels

	Preempt EA z	Postop EA z
T1-T2	(p>0.05) -1.79	(p<0.01) -4.39
T2-T3	(p<0.01) -3.1	(p<0.01) -4.54
T3-T1	(p<0.01) -3.28	(p<0.01)) -3.67

Wilcoxon test, p<0.05

Table 3a. Inter-group comparisons of the changes in IL-2 levels

IL-2 (pg/ml)	Preempt EA (n=31) Mean±SD	Postop EA (n=29) Mean ±SD	P
T1 (preop)	20.5±3.4	19.8±2.8	0.676
T2 (1 h postop)	19.9±3.0	17.8±2.1	**0.005****
T3 (24 h postop)	20.6±3.4	16.5±1.8	**0.001****

Mann Whitney U test, p<0.05

Table 3b. Intra-group comparisons of the changes in IL-2 levels

	Preempt EA z	Postop EA z
T1-T2	(p<0.01) -2.19	(p<0.01) -3.98
T2-T3	(p>0.01) -0.77	(p<0.01) -4.55
T3-T1	(p>0.01) -1.021	(p<0.01) -3.46

Wilcoxon test, p<0.05

Table 4a. Distribution of the pain scores (FACES rating scale) between and within groups

	Preop EA n (%)	Postop EA n (%)		
1 (1 h postop)	**0**	3 (9.7%)	1 (3.4%)	2=5.563 p=0.351
	1	2 (6.5%)	1 (3.4%)	
	2	17 (54.8%)	12 (41.4%)	
	3	9 (29.0%)	12 (41.4%)	
	4	0 (0.0%)	2 (6.9%)	
	5	0 (0.0%)	1 (3.4%)	
2 (24 h postop)	**0**	2 (6.5%)	2 (6.9%)	2=1.308 p=0.860
	1	11 (35.5%)	8 (27.6%)	
	2	13 (%41.9)	11 (%37.9)	
	3	4 (%12.9)	6 (%20.7)	
	4	1 (%3.2)	2 (%6.9)	

Pearson's chi-squared
McNemar test

Table 4b. Patients categorized by the time of the request for analgesia

	Preempt EA (n=31)	Postop EA (n=29)
T1	9	15
T2	3	6
T3	2	2

Table 5. Distribution of the sedation scores between and within groups

	Preop EA n (%)	Postop EA n (%)		
1 (1 h postop)	**0**	12 (38.7%)	10 (34.5%)	2=3.369 p=0.498
	1	10 (32.3%)	6 (20.7%)	
	2	7 (22.6%)	9 (31.0%)	
	3	0 (0.0%)	2 (6.9%)	
	4	2 (6.5%)	2 (6.9%)	
2 (24 h postop)	**0**	26 (83.9%)	18 (62.1%)	2=5.171 p=0.270
	1	2 (6.5%)	2 (6.9%)	
	2	2 (6.5%)	7 (24.1%)	
	3	1 (3.2%)	1 (3.4%)	
	4	0 (0.0%)	1 (3.4%)	

analgesia refers in practice, the prevention of central sensitization caused by incisional and inflammatory injury through the preoperative, intraoperative, and postoperative periods. The initial analgesic dose starts before surgery and continues through the intraoperative and postoperative periods (7-10). Gottschalk et al. (11) compared a preemptive bolus of bupivacaine with a postoperative continuous epidural infusion of bupivacaine that began at the fascial closure in radical prostatectomy patients. They found that the preemptive group had better visual analog scale (VAS) scores during the first 4 postoperative days. A meta-analysis of eight studies that compared the presurgical versus postsurgical initiation of continuous epidural analgesia (including opioids, local anesthetics, and ketamine) in terms of pain relief for 24-72 h postoperatively showed that a preemptive epidural regimen offered no improvement in postoperative pain relief (8). Another meta-analysis of nine studies that compared the preincisional and postincisional continuous epidural infusion of a local anesthetic with or without opioid demonstrated significantly better VAS scores in only two of the reports. Three of the nine studies were on abdominal surgery, and one of them showed that preemptive administration led to a benefit in pain control (9). We did not find statistically significant differences between the two groups in pain scores at 1 h and 24 h after surgery, although we did observe that a higher percentage of patients in the preemptive group had better scores; 71% of patients in the preemptive group had a pain score between 0 and 2, whereas only 48.3% had these scores in the postoperative group. We thought the possible explanation is that preemptive analgesia may not yield the effects in young children as the central nervous system pathways to transmit, process, and respond to stimuli may

be immature compared to that in adults. Ho et al. (12) compared preemptive and postoperative caudal blocks for outpatient urogenital surgery in children aged 1-6 years and did not find any difference. Furthermore, Holthusen et al. (13) could not demonstrate any differences when they compared the effects of preoperative and postoperative caudal blocks on pain in 25 children. Altintas et al. (14) compared the efficacy of presurgical versus postsurgical axillary blocks on postoperative pain in 49 children aged 1-11 years and observed that although facial pain scores were higher in the presurgical group than in the postsurgical group, both groups had effective analgesia, with pain scores of less than 2.

Surgical trauma induces peripheral nerve and tissue injury that leads to a local inflammatory reaction and elevated levels of proinflammatory cytokines that can induce peripheral and central nerve sensitization. Preemptive analgesia can suppress the nociceptive stimuli from an injured tissue to prevent the central sensitization (15). Furthermore, a continuous epidural infusion during the preoperative and postoperative periods may prevent central sensitization and also pain hypersensitivity due to the inhibition of acute inflammatory mediators in the postoperative period (9). Preemptive analgesia may produce a blockade of sufficient depth and duration to prevent the afferent transmission of noxious stim uli from the periphery to the central nervous system. Pain intensity measurement is one method to evaluate the effectiveness of analgesic treatment, and another is the detection of neurohumoral and inflammatory mediators. Nociceptive mediators and cytokines play important roles in the mechanism of acute pain (15). TNF–α is a proinflammatory cytokine and one of the early mediators of neuroinflammation and central pain sensitization (4). Both preoperative and postoperative epidural analgesia are important in controlling the immunological effects of surgery-induced stress. The production of proinflammatory cytokines, such as TNF-α may decrease when the afferent transmission of noxious stimuli is blocked (1,6). Moselli et al. (1) compared the proinflammatory responses (including cytokines) of two groups. The first group received a preoperative epidural infusion of levobupivacaine that continued through the postoperative period, whereas the second group received an infusion of remifentanyl perioperatively and an epidural infusion of levobupivacaine postoperatively. While the TNF-α levels did not change in the preemptive epidural analgesia group, postoperative increases in TNF-α levels were observed in the postoperative analgesia group. Akural et al. (16) did not find a significant difference in TNF-α levels between a group that received a preemptive epidural infusion of sufentanil and one that received sufentanil postoperatively.

IL-2 is an anti-inflammatory cytokine that is important in cell-mediated immunity. Theimmunosuppression after surgical incision results from T cell dysfunction, and impaired synthesis of IL-2 correlates with injury severity (17). In hysterectomy patients, Beilin et al. (4) observed lower IL-6 levels, reduced suppression of IL-2 levels, no significant changes in TNF-α levels, and better analgesia scores in those treated with preemptive analgesia compared to intravenous analgesia group. Yokoyama et al. (18) reported no differences in TNF-α levels and pain scores except at the end of surgery in radical esophagectomy patients given in preemptive analgesia group. Our study demonstrates significant increases in TNF-α levels in both the preemptive and postoperative epidural infusion groups, but the increase was more prominent in the postoperative group for at least 24 h after surgery. IL-2 levels were higher in the preemptive group, but there were no differences in the analgesic score. We believe that lower levels of TNF-α and the reduction in the suppression of IL-2 in the Preemp EA group compared to that in the Postop EA group demonstrate the preemptive effects of epidural infusion. It has been demonstrated that preemptive epidural infusion attenuates the suppression of the Th1 CD4+ T cells that secrete IL-2 (4).

In conclusion, the present study demonstrates that patients who received preemptive analgesia exhibited reduced proinflammatory but increased antiinflammatory cytokine levels and that sufficient analgesia was provided to both the preemptive and postoperative groups. We believe that although both the preemptive and postoperative epidural administration of a local anesthetic and an opioid seem to be fairly effective at blocking afferent nervous transmission and central sensitization and, can ensure adequate pain relief, only preemptive administration leads to a reduction in inflammatory mediators.

References

1. Moselli NM, Baricocchi E, Ribero D, et al. Intraoperative epidural analgesia prevents the early proinflammatory response to surgical trauma. Results from a prospective randomized clinical trial of intraoperative epidural versus general analgesia. Ann Surg Oncol 2011;18:2722-31.
2. Dermitzaki E, Staikou C, Petropoulos G, et al. A randomized study of maternal serum cytokine levels following cesarean section under general or neuraxial anesthesia Int J Obstet Anesth 2009;18:33-7.
3. Hogevold HE, Lyberg T, Kahler H, Haug E, Reikeras O. Changes in plasma IL-1beta, TNF-alpha and IL-6 after total hip replacement surgery in general or regional anaesthesia. Cytokine 2000;12:1156-9.
4. Beilin B, Bessler H, Papismedov L, et al. Continuous physostigmine combined with morphine-based patient-controlled analgesia in the postoperative period. Acta Anesthesiol Scand 2005;49:78-84.
5. Bozkurt P, Kaya G, Yeker Y et al. Effectiveness of morphine via thoracic epidural vs intravenous infusion on postthoracotomy pain and stress response in children. Paed Anesth 2004;14:748-54.

6. Shavit Y, Fridel K, Beilin B. Postoperative pain management and proinflammatory cytokines: animal and human studies. J Neuroimmune Pharmacol 2006;1:443-51.
7. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138-43.
8. Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2004;13:13-27.
9. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005;100:757-73.
10. Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anesthesiol 2006;19:551-5.
11. Gottschalk A, Smith DS, Jobes DR et al. Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. JAMA 1998;2791:1076-82.
12. Ho JWS, Khambatta HJ, Pang LM, et al. Preemptive analgesia in children, does it exist. Reg Anesth 1997;22;125-30.
13. Holthusen H, Eichwede F, Stevens M, et al. Pre-emptive analgesia: comparison of preoperative with postoperative caudal block on postoperative pain in children. Br J Anaesth 1994;73:440-2.
14. Altintas F, Bozkurt P, Ipek N, et al. The efficacy of pre- versus postsurgical axillary block on postoperative pain in paediatric patients. Paed Anaesth 2000;10:23-8.
15. Carvalho B, Aleshi P, Horstman DJ, et al. Effect of a preemptive femoral nerve block on cytokine release and hyperalgesia in experimentally inflamed skin of human volunteers. Reg Anesth Pain Med 2010;35:514-9.
16. Akural EI, Salomaki TE, Bloigu AH et al. The effects of pre-emptive epidural sufentanil on human immune function. Acta Anesthesiol Scand 2004;48:750-5.
17. Helmy SAK, Wahby MAM, El-Nawaway M. The effect of anesthesia and surgery on plasma cytokine production. Anesthesia 1999;54:733-8.
18. Yokoyama M, Itano Y, Katayama H et al. The effects of continuous epidural anesthesia and analgesia on stress response and immune function in patients undergoing radical esophagectomy. Anesth Analg 2005;101:1521-7.