THE INFLUENCE OF POSTOPERATIVE EPIDURAL ANALGESIA ON POSTOPERATIVE PAIN AND STRESS RESPONSE AFTER MAJOR SPINE SURGERY – A RANDOMIZED CONTROLLED DOUBLE BLIND STUDY

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SUMMARY – Major spinal surgery is associated with severe postoperative pain and stress response, bowel dysfunction, and a potential for chronic pain development. Epidural analgesia has been shown to be advantageous compared to intravenous analgesia alone. The aim of the study was to investigate whether postoperative addition of epidural levobupivacaine to intravenous opioid analgesia offers advantage over intravenous opioid analgesia alone. Eighty-one patients scheduled for spinal fusion were enrolled in the study and randomized into two groups. Postoperatively, group A received 0.125% epidural levobupivacaine and group B received saline. Both groups also received intravenous piritramide as a rescue analgesic. Pain intensity, rescue analgesic consumption, blood glucose, cholesterol and cortisol levels, postoperative blood loss, paresthesia, time to first postoperative defecation, and length of hospital stay were recorded. Sixty-eight patients completed the study. The visual analog scale score (mean 2 *vs*. 4, p=0.01), consumption of piritramide (25 mg *vs*. 51.5 mg, p=0.01) and metamizole (1400 *vs*. 1875 mg, p<0.01), incidence of nausea (6% *vs*. 28% p=0.02) and blood loss (450 mL *vs*. 650 mL, p<0.05) were significantly lower in group A. Bowel recovery and first postoperative defecation also occurred earlier in group A (6% *vs*. 45%, p<0.01). Blood cortisol, glucose and cholesterol levels and the incidence of paresthesia did not differ between the groups. In conclusion, after spinal fusion, postoperative epidural administration of levobupivacaine provides better analgesia and fewer side effects with no impact on stress response.

Key words: *Spine – surgery; Analgesia, epidural; Analgesia – patient-controlled; Pain, postoperative; Stress, physiological*

Introduction

Major spinal surgery is associated with severe postoperative pain and stress response, bowel dysfunction and a potential for chronic pain development[1-4]. Postoperative epidural analgesia has already been shown to be superior to intravenous opioid analgesia with respect to pain, pulmonary and gastrointestinal dysfunction after major abdominal, thoracic and orthopedic surgery[5-10]. Its lower Visual analog scale (VAS) scores have also been demonstrated after spinal surgery[4,11-14].

Major surgery can also induce stress response as evident from the changed level of serum glucose, cor-

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Received September 30, 2013, accepted March 18, 2014

tisol[14] and cholesterol[15], which have been reported to be reduced or even abolished with extensive epidural blockade (Th_4-L_5)[14]. To our knowledge, the impact of postoperative epidural levobupivacaine on stress response after major spinal surgery has not yet been evaluated. Therefore, the aim of this prospective, randomized, double blind study was to test the hypothesis that the combination of epidural and intravenous opioid analgesia offers advantage over intravenous opioid analgesia alone in pain reduction and consequent stress response, bowel function recovery, postoperative blood loss, and opioid side effects in patients after major spine surgery[16,17].

Patients and Methods

After Ethics Committee approval (No. 135/06/07) and informed consent obtained, 81 patients with American Society of Anesthesiologists (ASA) Physical Status Classification 1-3, age 30 to 80), scheduled for spondylolisthesis with spinal fusion at one or two levels with instrumentation were prospectively included in this study conducted from June 2007 to November 2010 at Clinical Department of Orthopedic Surgery, Ljubljana University Medical Centre, Ljubljana, Slovenia.

Exclusion criteria were mental illness, drug addiction, renal and hepatic insufficiency, spondylodiscitis, neurological deficits, known allergy to local anesthetics, perforation of the dura during surgery, epidural catheter dislocation and corticosteroid administration for surgical reasons.

Before surgery, the patients were instructed how to use the patient controlled analgesia (PCA) pump (CADD Legacy PCA, model 6300, Smiths Medical MD Inc., St. Paul, Minnesota, USA) and evaluate pain using a 10-cm VAS; (0 = no pain, 10 = worst pain imaginable). According to a random computerized list (prepared by a statistician with random algorithm available online at http://www.random.org), they were randomized into two groups to receive either 0.125% levobupivacaine (0.125% Chirocaine, Abbott, Abbott Park, Illinois, USA) (group A) or saline (group B). The patients and professionals involved were blinded for group assignment, except for the nurse who prepared the solution and placed the sealed envelope with drug name in the patient chart.

The patients were premedicated with 7.5 mg oral midazolam (Dormicum, Roche, Basel, Switzerland) 1-2 hours before surgery. On arrival in the operating room, an i.v. catheter was inserted and standard monitoring initiated. Anesthesia was induced and maintained with a combination of propofol (Propoven, Fresenius Kabi, Bad Homburg, Germany), fentanyl (Fentanyl, Torrex Chiesi, Vienna, Austria) and vecuronium (Norcuron, Organon, Oss, The Netherlands). Immediately after induction, urinary catheter, arterial and venous lines were inserted and arterial blood was withdrawn for blood glucose (glucose hexokinase test, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), cholesterol (cholesterol esterase test, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) and cortisol (Immunoassay Siemens, Immulite 2000, Tarrytown, NY, USA) measurements.

Surgery was performed in prone position. After posterior fusion and instrumentation, the epidural space was open and the catheter (Portex Epidural Minipack, Smiths Medical ASD Inc., Weston, USA) inserted through an 18-gauge Touchy needle cranially, 3 cm cephalad from the surgical wound edge under direct vision by the surgeon. After wound closure, patients were given either a bolus of 0.125% levobupivacaine or saline calculated according to the Bromage scheme[18] in both groups.

Epidural and intravenous analgesia was initiated in the recovery room using the PCA pumps. The epidural catheter was connected to the pump for 72 hours with continuous infusion of 0.125% levobupivacaine or saline in a dosage of 0.1 mL/kg/h, while intravenous anesthesia with piritramide (continuous infusion 1 mg *per* hour, bolus 2.5 mg and lock out interval 30 min) lasted for 24 hours, after which metamizole (2.5 g *per* 12 h) and piritramide (3 mg i.v.) were injected when VAS was >4.

The pain was recorded every 6 hours for 5 days by the nurses unaware of the group assignment, while motor blockade and paresthesia were assessed daily. Blood samples were taken at 24, 48, 72 and 96 hours after the operation for glucose, cholesterol and cortisol measurement. Other variables recorded were piritramide, metamizole and levobupivacaine consumption and their side effects, quality of wound healing and infection, postoperative blood loss, length of

hospital stay and recovery of bowel movements using ultrasound 24 hours after the surgery.

Statistics

The primary outcome was VAS score. Secondary outcomes were analgesic consumption, side effects, postoperative blood loss, bowel recovery, hospital stay and postoperative stress response. We estimated the interindividual pain variability in this surgical setting to be 30% and considering 20% pain reduction as significant, 36 patients *per* group were necessary to achieve statistical power at α=0.05 and β>0.80. To compensate for 10% dropout, 82 patients were included. Demographic data, bowel recovery and ASA score were compared by using the two-tailed Wilcoxon Mann-Whitney test for unpaired samples. Postoperative hematoma/infection/nausea/paresthesias were analyzed with Fisher exact test. The VAS score, blood glucose, cholesterol and cortisol were analyzed with repeated measures ANOVA.

VAS scores were measured between 6 hours postoperatively and 120 hours postoperatively at 6-hour-intervals (i.e. 20 repeated measures) in both groups and the two groups were compared with repeated measures ANOVA. Data were expressed as mean ± standard deviation unless otherwise specified.

Table 1. Demographic and surgical characteristics (results are expressed as mean ± standard deviation unless otherwise specified)

	Group A	Group B
N	33	35
Gender F/M	26	27
Age (yrs)	60.2±12.9	63.4±14.9
Body mass index (kg/m^2)	28.7±3.7	28.2±3.8
American Society of Anesthesiologists (ASA) Physical Status Classification median	2 (range 1-3)	3 (range 1-3)
Surgical procedure duration (min)	144±40	139±42
Peri- and postoperative blood loss (mL)	450±300	650±350*

* p<0.05; group A = epidural levobupivacaine; group B, epidural saline

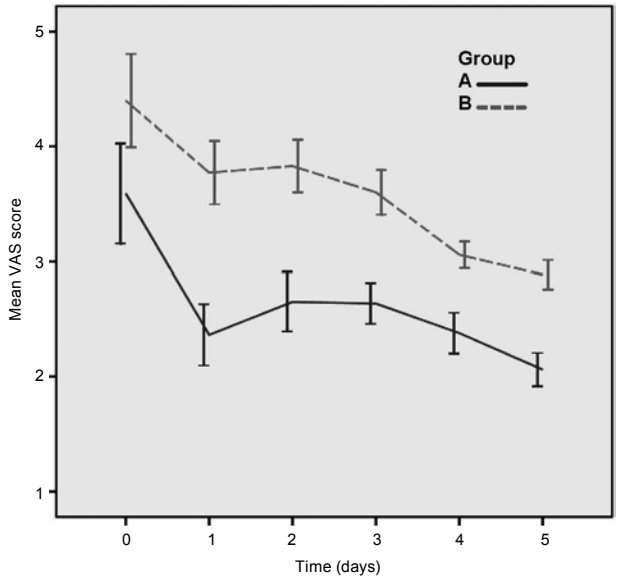


Fig. 1. Mean visual analog scale (VAS) score: between-group difference in VAS score was statistically significant (p<0.05); group A, levobupivacaine epidural; group B, saline epidural: I: mean ± SD.

Results

Demographic and surgical data were similar between the two groups (Table 1).

Out of 81 randomized patients, 13 were excluded during the course of the study, 6 in group A (4 because of catheter displacement, 1 because of confusion and 1 because of consent withdrawal) and 7 in group B (3 because of catheter displacement, 3 patients received corticosteroid treatment and 1 because of consent withdrawal).

VAS score was significantly lower in group A at any time point. Group B had significantly higher VAS scores than group A, as confirmed with the ANOVA tests of between-subject-effects (F=24.3; p<0.001; observed power = 0.998) (Fig. 1).

There was a statistically significantly lower piritramide (p<0.01) and metamizole (p=0.01) consumption in group A. The incidence of nausea was higher in group B. The incidence of paresthesias did not differ between the groups. Group A also had significantly less blood loss after the surgery (p=0.01). Bowel recovery occurred early in group A (p<0.01). First postoperative defecation occurred earlier in group A than in group B (p=0.01). Hospital stay was similar between the two groups (Table 2).

Table 2. Perioperative and postoperative course of treatment (results are expressed as mean ± standard deviation unless otherwise specified)

	Group A	Group B	p value
Postoperative hematoma and/or infection (n)	5 15%	1 3%	0.10
Nausea (n)	2 6%	10 28%	0.02
Postoperative paresthesia (%)	12	3	0.19
Postoperative piritramide consumption (mg)	69±47	149±65	<0.01
Postoperative metamizole consumption (mg)	13900±700	18700±7900	0.01
Time to first postoperative defecation (days)	4 (range 3-6)	5 (range 2-7)	0.01
Hospital stay (days)	7 (range 4-32)	8 (range 5-14)	0.21

group A = epidural levobupivacaine; group B = epidural saline

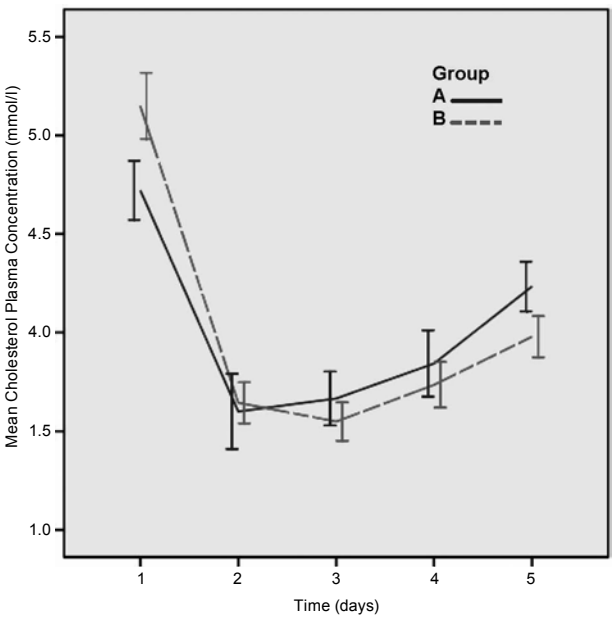


Fig. 2. Mean plasma cholesterol concentration: there was no statistically significant between-group difference; group A, levobupivacaine epidural; group B, saline epidural; I: mean ± SD.

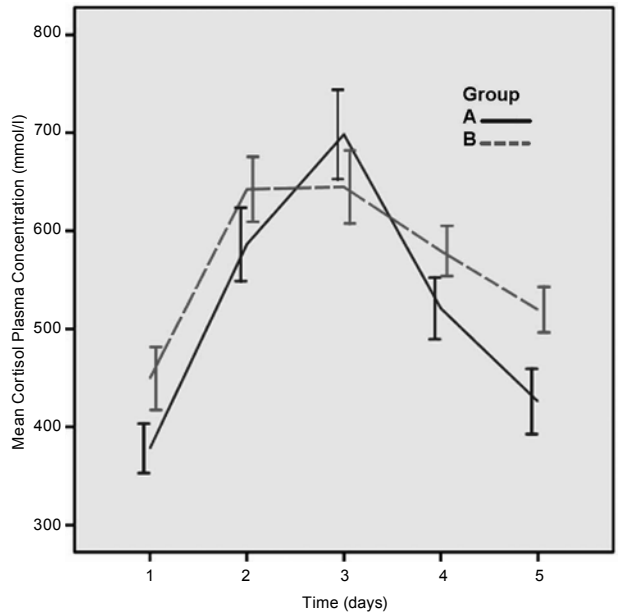


Fig. 3. Mean plasma cortisol concentration: there was no statistically significant between-group difference; group A, levobupivacaine epidural; group B, saline epidural; I: mean ± SD.

Group A and group B were also compared with repeated measures ANOVA test for consecutive mea-

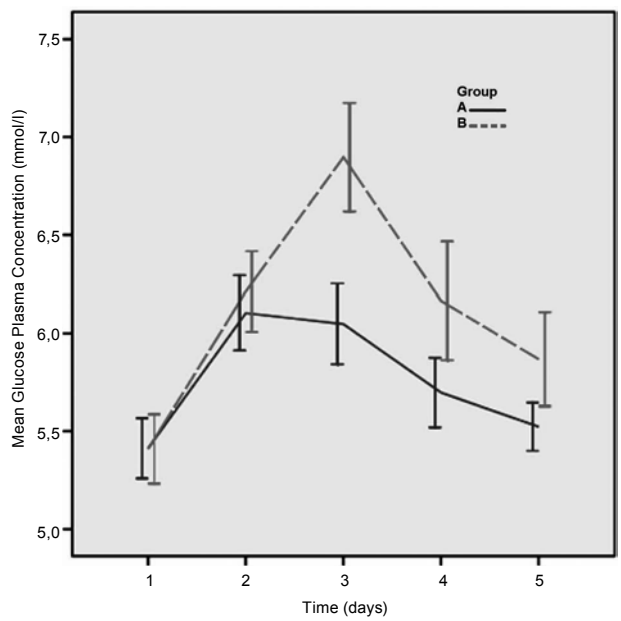


Fig. 4. Mean plasma glucose concentration: there was no statistically significant between-group difference; group A, levobupivacaine epidural; group B, saline epidural; I: mean ± SD.

surements of cortisol, cholesterol and blood glucose on 5 postoperative days. Neither cortisol (F=1.84; p=0.180; observed power = 0.266), cholesterol (F=0.02; p=0.891; observed power = 0.052) nor blood glucose (F=2.67; p=0.108; observed power = 0.362) showed any consistent statistical difference between the two groups on 5 postoperative daily repeated measures (Figs. 2-4).

Discussion

After spinal fusion with instrumentation, the addition of continuous postoperative infusion of 0.125% levobupivacaine through an epidural catheter placed intraoperatively by an orthopedic surgeon resulted in significant reduction of pain, opioid and non-opioid analgesic consumption, nausea and vomiting, postoperative blood loss, earlier bowel recovery and first postoperative defecation.

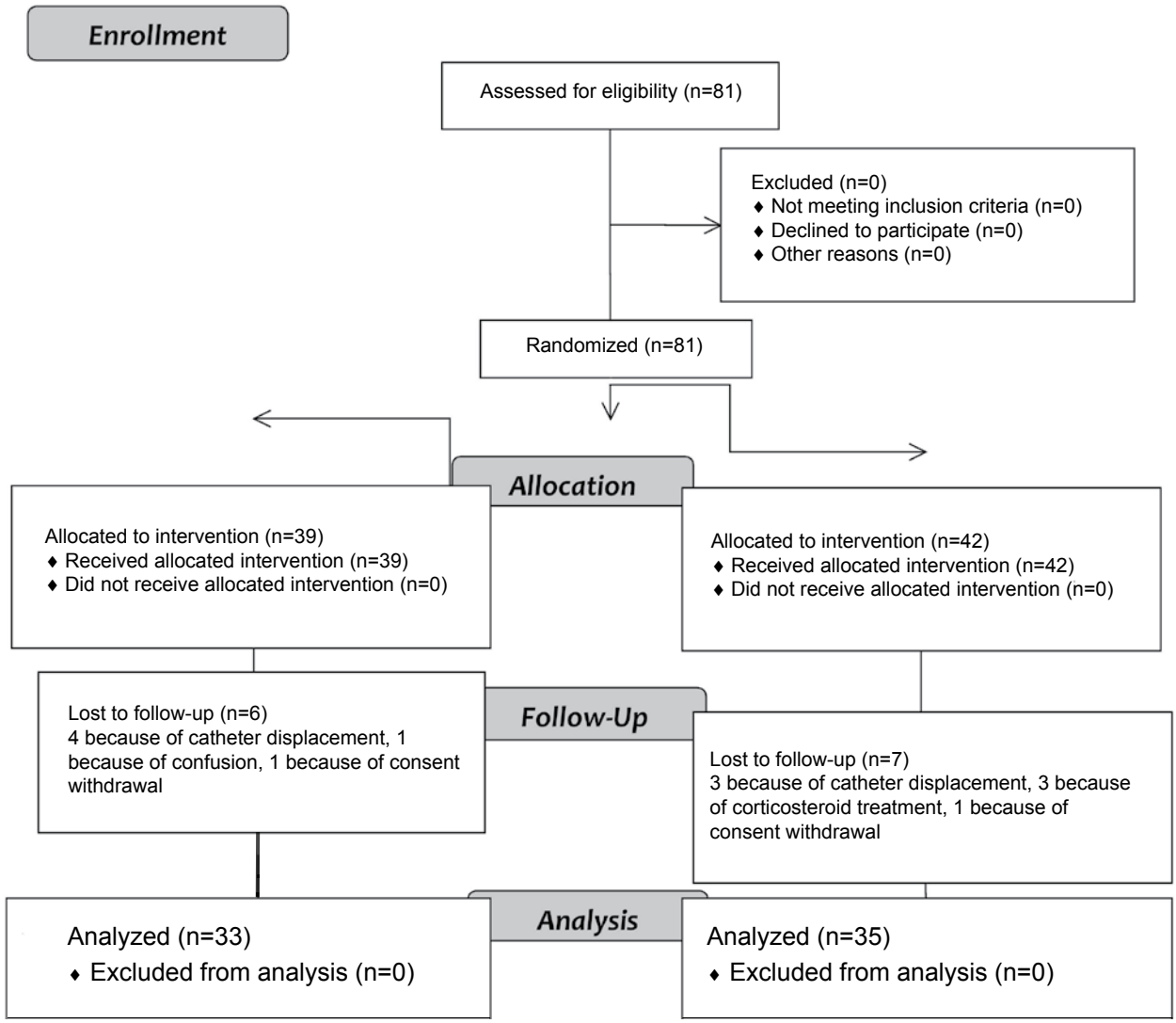
To our knowledge, this is the first prospective, randomized, double blind study using an intraoperatively placed epidural catheter for postoperative analgesia assessing the postoperative stress in this surgical setting. Kumar *et al.*[12] showed that epidural analgesia significantly lowered postoperative pain after major spine surgery independently of the drug administered *via* epidural catheter. However, this study was neither randomized nor blinded. Tobias *et al.*[13] successfully managed postoperative pain after scoliosis surgery with two epidural catheters. Cohen *et al.*[19] compared epidural 0.0625% bupivacaine with morphine 0.004% to PCA i.v. morphine. This study did not demonstrate any advantage of epidural analgesia. This investigation can be criticized since the epidural catheter was placed 2-3 levels cephalad to surgical wound and not in the middle of the wound. Two other studies demonstrated the advantages of epidural analgesia for this type of surgery. Gottschalk *et al.*[4] in a prospective double blind study compared epidural 0.1% ropivacaine 12 mL/h with 0.9% saline. The authors demonstrated that pain scores were statistically significantly lower in the epidural group. Piritramide requirements were lower and patient satisfaction was higher. Schenk *et al.*[11] in a prospective, double blind, double dummy study, compared patient controlled epidural analgesia (PCEA) with 0.2% ropivacaine and sufentanil to i.v. PCA morphine. Patients receiving ropivacaine had significantly less pain at rest and during motion. The incidence of nausea was lower, but sensory deficits were observed more frequently in the epidural group. Gottschalk *et al.*[4] report an incidence of 53% of paresthesias in the epidural ropivacaine group. In our study using 8.2 mL/h of 0.125% levobupivacaine, the incidence of paresthesias was lower and similar between the two groups. This difference can be explained by different drugs and doses administered.

It has been shown that local anesthetics administered *via* epidural catheter shorten postoperative ileus by suppressing primary afferent neurons that are responsible for reflex inhibition of intestinal motility[20]. Cassidy *et al.*[1] demonstrated that patients receiving 0.125% ropivacaine through epidural catheter after posterior spinal fusion had better and earlier bowel recovery than patients with intravenous morphine PCA pump. However, no better analgesia in the epidural group could be demonstrated. In our study, early bowel recovery could be explained by both the effects of epidural local anesthetics and lower consumption of opioids. Despite early bowel recovery, group A patients were not able to take fluids or food earlier than group B patients. The same observation has been reported by Cassidy *et al.*[1]. We have no clear explanation for this finding.

In our study, we observed significantly less blood loss after the surgery. Epidural blockade may be associated with reduced blood loss during surgery because of reduced splanchnic artery and venous pressure resulting from reduced arterial and venous tone and peripheral vasodilation. Several studies failed to demonstrate significantly lower blood loss in patients with epidural anesthesia[5,7]. However, Kakiuchi[20] and Yashimoto *et al.*[21] report on a significantly lower blood loss during lumbar spine fusion if the patients had epidural anesthesia.

Epidural analgesia with local anesthetics can greatly reduce the endocrine and metabolic response to surgery in the pelvis and lower limb if the blockade is extended from T_4 to S_5. In our study, we were not able to abolish stress response in group A. This could be explained by the epidural catheter insertion after completion of the surgery. Therefore, the most stressful part of the study was not influenced by epidural analgesia. A statistically significant reduction of cortisol and blood glucose was not observed dur-

CONSORT 2010 Flow Diagram



ing the study. This limited influence on postoperative stress is consistent with the study by Moller *et al.*[22]. A recent study by Ezhevskaya *et al.*[23] showed significantly lower cortisol, blood glucose and interleukins after major spine surgery with epidural anesthesia and postoperative epidural analgesia. This is also consistent with our study because they performed epidural anesthesia already during the surgery when the stress was the highest.

The small number of patients can be considered a limitation for assessing the effect of this technique on stress response. However, this investigation was not powered on this issue.

In conclusion, this study demonstrated significantly better postoperative analgesia and lower opioid consumption in group A where epidural analgesia was added to intravenous piritramide. Other benefits in the epidural group included a lower incidence of opioid side effects like nausea/vomiting and earlier recovery of bowel function.

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Sažetak

UTJECAJ POSLIJEOPERACIJSKE EPIDURALNE ANALGEZIJE NA POSLIJEOPERACIJSKU BOL I STRESNI ODGOVOR NAKON VEĆE OPERACIJE KRALJEŽNICE – RANDOMIZIRANO KONTROLIRANO DVOSTRUKO SLIJEPO ISPITIVANJE

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Cilj naše studije je bio usporediti poslijeoperacijsku epiduralnu analgeziju s intravenskom analgezijom piritramidom koju bolesnik kontrolira sam (*patient controlled analgesia*, PCA). Ocjenjivali smo poslijeoperacijske bolove i stresni odgovor. U ovu prospektivnu randomiziranu dvostruko slijepu studiju bio je uključen 81 bolesnik u razdoblju od srpnja 2007. do studenoga 2010. godine. Bolesnici su bili podijeljeni u skupinu A koja je dobila levobupivakain kroz epiduralni kateter i skupinu B koja je istim putem dobivala fiziološku otopinu za poslijeoperacijsku analgeziju. Obje skupine su poslijeoperacijski dobile piritramid putem PCA pumpe. Poslijeoperacijski smo ocjenjivali bolove prema vizualno analognoj ljestvici (VAS), potrošnju analgetika, koncentraciju glukoze, kolesterola i kortizola u krvi, gubitak krvi, peristaltiku, razdoblje do prve defekacije i trajanje boravka u bolnici. Na kraju studije bilo je uključeno 68 bolesnika. Ocjena bolova prema VAS, potrošnja piritramida, metamizola, incidencija mučnine i gubitak krvi su bili značajno niži u skupini A ($p<0,05$). Peristaltika i prva poslijeoperacijska defekacija su se pojavile ranije u skupini A ($p<0,01$). Među skupinama nije bilo razlike u koncentraciji kortizola, kolesterola i glukoze u krvi. Nakon operacije kralježnice epiduralni levobupivakain je omogućio bolju poslijeoperacijsku analgeziju i manje nuspojava, manji gubitak krvi i raniji povratak crijevne funkcije u usporedbi s intravenskom analgezijom piritramidom.

Ključne riječi: *Kralježnica – kirurgija; Analgezija, epiduralna; Analgezija koju regulira bolesnik; Bol, poslijeoperacijska; Stres, fiziološki*