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Preemptive Epidural Analgesia with Bupivacaine and Sufentanyl and the Effects of Epiduraly Added Epinephrine for Thoracic Surgery

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Abstract

Aim. The aim of the study was to determine if preemptive epidural analgesia in thoracic surgery reduces postoperative pain, and to compare these effects in relation to the usage of epinephrine.

Material and Methods. Sixty patients admitted for thoracic surgery were randomly allocated into three groups (n = 20 each). Group A received bupivacaine and sufentanyl epiduraly prior to skin incision, followed by infusion of bupivacaine and sufentanyl. Group B (control) received saline in the epidural. In both groups patients received bupivacaine and sufentanyl epiduraly at the time of the chest closure. In Group C the same doses of bupivacaine and sufentanyl as in Group A were given to the patients including epinephrine in the epidural mixture. The level of statistical significance was pointed at $p < 0.05$.

Results. The patients in Group A had lower intraoperative isofluran requirements, lower postoperative epidural infusion rates and lower pain scores in first eight postoperative hours, compared with the control. In the epinephrine group patients had lower pain intensity and smaller needs for postoperative epidural infusion rate than those in Group A.

Conclusion. The usage of epinephrine has caused less nausea and easier mobilization. While there was a beneficial effect of the reduced intraoperative anesthetic requirements, any lasting effect of preemptive analgesia did not extend beyond eight hours after the operation.

Introduction

Acute postoperative pain is a complex physiological reaction upon the damage of the tissue, the distension of the viscera and the underlying surgical disease. The surgeons and the anesthesiologists in the past used to assign less importance to this pain, thus the patients accepted it as an unseparated part of the postoperative experience. With the development of comprehension about the epidemiology and the pathophysiology of pain, greater consideration is being directed to the different types of its therapy, in the effort of improving the treatment quality and outcome [decrease patient morbidity [1, 2], improve patient satisfaction [3], and help prevent the development of chronic pain syndromes [4, 5].

The postoperative pain that emerges after thoracotomy is noteworthy and detrimental since it can increase the patient's discomfort and lessen the capability for deep breaths and coughing, thus leading to pulmonal dysfunction. Intravenous narcotics may depress respiration

and also produce side effects such as nausea and vomiting. Epidural analgesia regardless of analgesic agent (i.e. local anesthetic only, combination of local anesthetic and lypophilic/hydrophilic opioid, and lypophilic opioid only), epidural delivery technique [continuous epidural infusion (CEI) or patient-controlled epidural analgesia (PCEA)], type of surgery determining ultimately the location of catheter (thoracic or lumbar) and type of pain (at rest or during movement) provides better analgesia than any type of parenteral opioid including that delivered via intravenous patient-controlled devices (PCA) for up to four days postoperatively. Thoracic epidural anesthesia (TEA) with local anesthetics is increasingly being combined with general anesthesia (GA) for thoracic surgery. A combination of TEA with GA might maximize the benefits of each form of anesthesia. Furthermore, epidural anesthesia and postoperative epidural analgesia with their effects that exceed pain release, may improve outcome in high-risk patients [6,7].

The surgical injury of the tissue leads to changes in the central nervous system (CNS) identified as central nervous sensitization that produces postoperative hypersensitivity to pain. The reason of this phenomenon is considered to be the lower threshold to pain in the peripheral nociceptors as well as the increased excitability of the spinal cord neurons. The recent laboratory studies (8-11) of nociception indicate that the timing of an analgesic regimen with respect to the onset of painful stimuli may play a significant role in the perception of following stimuli. By preventing sensitization of CNS by painful stimuli, appropriate interventions limit the response to future nociceptive input [12] and prevent a degree of CNS sensitization which is sufficient to enable normally painless stimuli to be experienced as pain [13].

Preemptive analgesia [14,15] describes the concept of decreasing pain perception and overall analgesic needs by use of a drug regimen capable of inhibiting CNS sensitization before the application of painful stimuli. Animal studies demonstrate that clinically adequate levels of general anesthesia produced by volatile anesthetics such as isoflurane do not prevent central sensitization by nociceptive impulses [16]. This is of critical importance for appreciating the potential of preemptive analgesia in a surgical setting.

The aim of this study was to determine if preemptive epidural analgesia that was provided before thoracotomy incision and intra-operatively reduces postoperative pain and postoperative analgesic usage. We hypothesized that preemptive epidural analgesia, initiated prior to a major thoracic surgical procedure with adequate doses of local anesthetic and opioid, would favorably impact short-term postoperative pain and would influence other postoperative outcome variables, such as the postoperative pulmonal function. Therefore, we examined the role of 2 preemptive epidural analgesic regimens in a uniform group of generally healthy patients undergoing thoracotomy, after which all patients, including those in the control group, received the same aggressive postoperative epidural analgesia initiated at the beginning of thoracic closure.

Material and Methods

This prospective randomized interventional clinical double-blind study was performed at the University Clinic of Anesthesiology, Reanimation and Intensive care and the Clinic of Thoracic-vascular surgery in Skopje, from June to December 2004, after obtaining an approval by our ethics committee, and signed, informed consent from all 60 patients who were studied.

The patients were scheduled to undergo elective thoracic surgery (thoracotomy). All patients included in the study had a thoracic epidural catheter placed while in the preoperative holding area. A test dose of 3 ml of bupivacaine 0.25% was administered via all of the epidural catheters immediately following placement.

These 60 patients were randomly allocated into three groups (n=20 each), according to a list of random numbers. Group A received 9 ml 0.25% of bupivacaine and 1 ml of sufentanyl forte (50 μg/ml) via the epidural route after induction of general anesthesia and prior to skin incision, followed by an infusion of bupivacaine 0.125% and sufentanyl forte 2 μg/ml at 6 ml/hr that was continued throughout the procedure until chest closure was performed. Group B (control) received 10 ml of normal saline in the epidural catheter after induction of general anesthesia and before skin incision. This was followed by an epidural infusion of normal saline at 6 ml/hr that was continued throughout the procedure until the chest closure. In both groups patients received 9 ml of bupivacaine 0.25% and 1 ml of sufentanyl forte (50 μg/ml) via the epidural route at the time of the chest closure. In the third group (group C), the same doses of bupivacaine and sufentanyl forte, identically as in group A, were given to the patients including epinephrine in the epidural mixture (1:200000).

Intraoperatively, all patients received oxygen, isoflurane, neuromuscular blockers, and a maximum total fentanyl dose of 3 μg/kg intravenously. The main variables that were recorded intraoperatively were heart rate (HR), main arterial pressure (MAP), respiratory rate (RR) and

end-tidal isofluran (%), each of them on a ten – minute interval. Patients were continued in the study protocol only if a thoracotomy incision was performed. At the conclusion of surgery, patients were extubated if clinical criteria were satisfied. Otherwise, patients were transferred to the Post Anesthesia Care Unit (PACU) still intubated, and were extubated later when extubation criteria were met.

Upon each patient's arrival at the PACU, an epidural infusion of bupivacaine 0.125% with sufentanyl forte 2 μg/ml was begun at 2 ml/hr. This epidural infusion was carried out for the first 48 postoperative hours and was titrated according to the clinical needs of each patient. The patients graded their pain on a linear analog scale (Visual Analogue Scale — VAS) of 1 – 10 for 48 hours postoperatively, on an hourly basis while awake. The rate of the postoperative epidural infusion was recorded at the same intervals as VAS. The postoperative pulmonal function was assessed by measuring patients' spirometry (FVC, FEV1) for the first 48 postoperative hours, using the portable Ganshorn Spirojet Spirometer (Schiller).

The side-effects from the usage of the epidural analgesics (nausea, vomitus, urinary retention and pruritus) were also recorded during the first 48 postoperative hours.

The data were analyzed using unpaired Student's t-tests. A $p<0.05$ was considered statistically significant.

Results

All 60 patients initially enrolled in the study underwent a thoracotomy incision, and all of these patients completed the study. The demographic data of the patients were similar in all three groups, with respect to age, weight, height and duration of surgery. The results are summarized in Table 1.

Table 1: Demographic data of the patients.

	Group A	Group B	Group C	" t "	" p "
Age (y)	58.6 ± 4.6	60.6 ± 5.8	57.9 ± 3.9	1.7	0.09
Weight (kg)	71.8 ± 6.2	74.3 ± 4.1	72.2 ± 5.0	1.83	0.07
Height (cm)	171.2 ± 5.3	169.7 ± 2.2	170.1 ± 4.3	1.24	0.22
Duration of surgery	119.0 ± 7.8	115.0 ± 5.9	111.9 ± 6.7	1.82	0.07

The patients in Group A and Group C had lower intraoperative requirements for isoflurane than those in Group B (A: 0.45 ± 0.1 vs. B: 0.70 ± 0.05; C: 0.40 ± 0.2 vs. B: 0.70 ± 0.05 respectively, $p<0.0001$). The intraoperative hemodynamics and respiratory rate were similar in all three groups (Table 2).

Postoperatively, the patients in Group A and Group C had lower maximum pain scores in the first 8 hours compared with Group B (VAS A: 3.25 ± 0.75 vs. B: 5.4 ± 1.6; and VAS C: 2.15 ± 0.9 vs. B: 5.4 ± 1.6 respectively, $p<0.0001$). Also, the postoperative pain scores in the epinephrine group (Group C) were lower than those in Group A (VAS C: 2.15 ± 0.9 vs. A: 3.25 ± 0.75; $p<0.0005$). The pain scores didn't differ significantly between the groups after the first 8 postoperative hours (Table 3).

Table 2: Intraoperative data.

n	Group A 20	Group B 20	Group C 20	p- value
Mean end-tidal isofluran (intraoperative) %	0.45 ± 0.1	0.70 ± 0.05	0.40 ± 0.2	p A,B<0.0001 p B,C<0.0001 p A,C = NS
Median HR (intraoperative) bpm	77.22 ± 8.76	76.48 ± 8.63	76.12 ± 8.13	p A,B = NS p B,C = NS p A,C = NS
Median MAP (intraoperative) mmHg	93.40 ± 1.49	92.64 ± 1.50	92.90 ± 1.60	p A,B = NS p B,C = NS p A,C = NS
Median RR (intraoperative) bpm	17.13 ± 1.48	16.85 ± 2.35	16.27 ± 2.04	p A,B = NS p B,C = NS p A,C = NS

n = number of patients; HR = heart rate; bpm = beats per minute; MAP = mean arterial pressure.

Table 3: Postoperative data.

n	Group A 20	Group B 20	Group C 20	p - value
Median epidural infusion rate (postoperative) ml/h	3.13 ± 0.88	4.33 ± 1.03	2.47 ± 0.38	p A,B < 0.0005 p B,C < 0.0001 p A,C < 0.005
Max postoperative pain score – VAS (0-8h)	3.25 ± 0.75	5.4 ± 1.60	2.15 ± 0.90	p A,B < 0.0001 p B,C < 0.0001 p A,C < 0.0005
Max postoperative pain score – VAS (9-16h)	3.1 ± 1.05	4.0 ± 1.85	3.0 ± 2.10	p A,B = NS p B,C = NS p A,C = NS
Max postoperative pain score – VAS (17-24h)	4.13 ± 0.50	4.3 ± 2.00	3.95 ± 0.72	p A,B = NS p B,C = NS p A,C = NS
Max postoperative pain score – VAS (25-48h)	2.8 ± 1.60	3.2 ± 0.5	2.88 ± 0.83	p A,B = NS p B,C = NS p A,C = NS

n = number of patients; p = significance between the groups; NS = non significant.

The clinical needs of the patients for the rate of the epidural infusion postoperatively were significantly smaller in Group A and Group C compared with those in Group B (A: 3.13 ± 0.88 vs. B: 4.33 ± 1.03; and C: 2.47 ± 0.38 vs. B: 4.33 ± 1.03, respectively; $p<0.05$); there was statistically significant difference between Group A and Group C, also ($p<0.05$) (Table 3).

Table 4: Postoperative pulmonal function.

n	Group A 20	Group B 20	Group C 20	p - value
Postoperative FVC (0-7h)	3.18 ± 0.16	2.21 ± 0.20	3.14 ± 0.29	p A,B < 0.0001 p B,C <0.0001 p A,C = NS
Postoperative FVC (8-48h)	3.15 ± 0.39	3.21 ± 0.27	3.25 ± 0.24	p A,B = NS p B,C = NS p A,C = NS
Postoperative FEV1 (0-7h)	2.79 ± 0.42	2.14 ± 0.27	2.77 ± 0.27	p A,B < 0.0001 p B,C < 0.0001 p A,C = NS
Postoperative FEV1 (8-48h)	3.00 ± 0.12	2.89 ± 0.26	2.95 ± 0.14	p A,B = NS p B,C = NS p A,C = NS

n = number of patients; p = significance between the groups; NS = non significant.

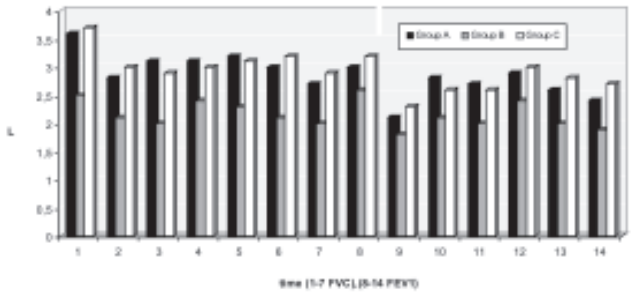

Figure 1: Changes in postoperative pulmonal functions (FVC, FEV1 – litres/L) expressed as mean ± SD, p<0.05 compared to baseline.

The postoperative pulmonal function (FVC, FEV1) was better in Group A and Group C than in Group B in first seven postoperative hours.

The registration of side-effects showed that the highest incidence was seen in patients from Group A. The patients in epinephrine group (Group C) had the lowest incidence of side-effects.

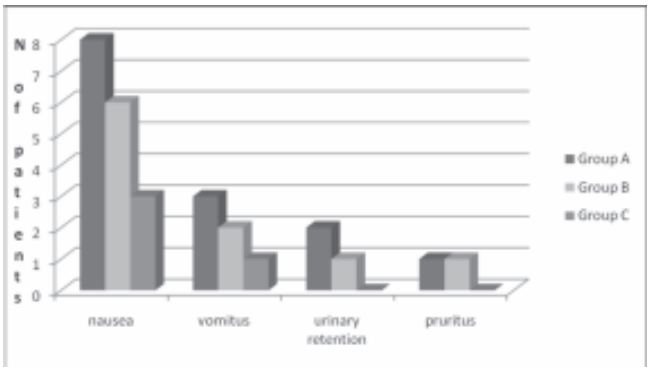

Figure 2: Incidence of side effects in the Groups A, B, C.

The tables and figures summarizing the main results of this paper are included as SI.

Discussion

The present study shows that the patients who received local anesthetic plus opioid through the thoracic epidural catheter before skin incision had lower maximum pain scores postoperatively, with less isofluran requirements intraoperatively and better postoperative pulmonal functions, compared with the control (patients who received preemptive saline through the epidural). In the epinephrine group patients had lower pain intensity (for 2-3 scores at VAS) and smaller clinical needs for the rate of the epidural infusion postoperatively than those who received preemptive anesthesia/analgesia with only local anesthetic and opioid. The usage of epinephrine has caused less nausea and easier mobilization.

Studies of preemptive analgesia in humans have shown conflicting results. The study design, patient population and the duration of assessment of postoperative pain are important in the evaluation of preemptive analgesia.

Gottschalk A. et al. showed that administration of specific analgesic regimens through an epidural catheter prior to skin incision is associated with long-term benefits in generally healthy patients undergoing major lower abdominal surgery. Although there was a trend toward increased efficacy of preemptive bupivacaine treatment compared with preemptive fentanyl treatment, this difference did not reach statistical significance. These differences were observed even though all subjects received an aggressive postoperative epidural analgesic regimen initiated well before the end of surgery and maintained for several postoperative days [17].

A recent meta-analysis indicated that epidural analgesia initiated before the thoracotomy incision was associated with a statistically significant reduction in the severity of acute dynamic pain in the first 48 hr postoperatively compared to thoracic epidural analgesia initiated after surgery completion. Therefore, it is sensible to always use epidural analgesia intraoperatively, and decrease in the same time the need for opioids and their unwanted systemic side effects [18].

Yegin A.et al. showed that preoperative epidural analgesia with 0.25% bupivacain and fentanyl was an appropriate method for treating post-thoracotomy pain and was more effective in preventing acute postoperative pain, evaluated at 2, 4, 8, 12, 24 and 48 h at rest and coughing [19].

On the other hand, Aguilar JL et al., found no significant differences in pain scores at rest, during mobilization of the ipsilateral arm or after cough between patients with pre-incisional (30 min) and postincisional (15 min) administration of a thoracic extradural with 0.5% bupivacain in thoracic surgery. There may be several explanations for this. Namely, surgical trauma differs from the conditioning stimuli applied in experimental studies because it is extensive, with mixed cutaneous, muscular and visceral components, contrary to a well localized thermal or chemical injury made in the laboratory studies. This uncontrolled, prolonged stimulus is maintained while the inflammatory surgical response lasts [20].

Aida S. et al. in a randomized, double blind study found that the effectiveness of preemptive analgesia with

morphine varies according to the type of surgery. Epidural preemptive analgesia was reliably effective in limb and breast surgeries but ineffective in abdominal surgery, suggesting involvement of the brainstem and cervical spinal cord via the vagus and phrenic nerves (21).

Ong CKS et al. made a meta-analysis about the efficacy of preemptive analgesia for acute postoperative pain management. They systematically searched for randomized controlled trials that specifically compared preoperative analgesic interventions with similar postoperative analgesic interventions via the same route. The retrieved reports were stratified according to five types of analgesic interventions: epidural analgesia, local anesthetic wound infiltration, systemic *N*-methyl-d-aspartic acid (NMDA) receptor antagonists, systemic nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic opioids. Sixty-six studies with data from 3261 patients were analyzed. Whereas preemptive epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. The least proof of efficacy was found in the case of systemic NMDA antagonist and opioid administration, and the results remain equivocal [22].

Burmeister MA et al. found that intraoperative TEA with ropivacaine 0.375% did not significantly reduce the amount of analgesics required after major abdominal gynecological tumor surgery [23].

Baris S. et al. demonstrated that the management of patients undergoing orthopedic surgery of the lower extremities with 2 µg/kg fentanyl intravenously or epiduraly before painful stimuli lowers the VAS and postoperative morphine use, although there was no statistical significance. Differences in the plasma concentration of glucose and cortisol were neither consistently nor significantly different between the study groups. Higher doses of fentanyl may be necessary for optimal and significant results [24].

Garcia JBS et al. showed no preemptive effect of epidural fentanyl plus bupivacaine on postoperative pain and stress response as measured by IL-6 concentrations in patients scheduled for hysterectomy [25].

The study of de Castro FE et al. failed to demonstrate a preemptive effect of epidural administration of bupivacaine and S(+)ketamine in the doses tested (17 ml bupivacaine 0.25% plus 3 ml S(+)ketamine-30 mg) for abdominal hysterectomy, since there were no significant differences between groups in time to first analgesic request, total analgesic consumption and numeric or verbal scale pain scores [26].

Esmaoglu A. et al. in their study showed that the dose of fentanyl (100 µg fentanyl in 10 ml 0.9% NaCl) administered epiduraly prior to surgical incision did not produce any clinically useful pre-emptive analgesic effect in patients who underwent elective abdominal surgery [27]. Subramaniam B. et al. carried out a prospective, randomized, double-blind controlled study in patients undergoing upper abdominal and thoracic surgery, and showed that epidural morphine plus bupivacaine (morphine, 50 µg/kg; 0.1% bupivacaine in 10 ml of normal saline) was effective as a preemptive analgesic (significantly increased interval between the analgesic top-ups and decreased total postoperative morphine requirements and number of top-ups). Morphine plus bupivacaine had better efficacy than morphine given alone before the induction of anesthesia [28].

The results of the study of Aida S. et al. suggest that for definitive preemptive analgesia, blockade of opioid and N-methyl-D-aspartate receptors is necessary for upper abdominal surgery such as gastrectomy; singly, either treatment (epidural morphine or intravenous low-dose ketamine) provided significant, but not definitive, postsurgical pain relief. Epidural morphine may affect the spinal cord segmentally, whereas intravenous ketamine may block brain stem sensitization via the vagus nerve during upper abdominal surgery. The possible mode of interaction between these two groups of drugs is that opioids are able to block the initial response of dorsal horn nociceptive neurons to C-fiber stimulation, while NMDA antagonists affect mainly the potentiation of responses to repeated stimulation. Another possible explanation for reduction of wind up like pain is that ketamine prevents acute tolerance to opioids and opioid induced hyperalgesia [29].

The same authors at the 9th World Congress on Pain, 1999 in Vienna, Austria, demonstrated the results of a study with an aim to clarify the speculation that pain existing before surgery may induce central sensitization, thus making preemptive analgesia (PA) ineffective. The study included patients undergoing limb surgery (some had presurgical pain - fracture surgery and arthritis surgery; while others had no presurgical pain - removal of a limb tumor, nail or plate). For preemptive treatment, morphine (bolus 0.06 mg- kg^{-1}-h^{-1} before surgery, and continuous 0.02 mg-kg^{-1}-h^{-1} during surgery) was administered epidurally at the C6-7 (upper limb) or LI-2 (lower limb) level. After complete recovery from anesthesia, a patient controlled analgesia pump was set to inject epidural morphine. The

authors concluded that central sensitization may be pre-established by presurgical pain, and the presurgically imprinted central sensitization is preserved until the termination of surgery. Presence of presurgical pain might be responsible for the controversy over the clinical validity of preemptive analgesia [30].

At the same Congress Kobeliatski Y. presented the results of the study about the preemptive mutual administration of lamotrigine and $MgSO_4$ in patients undergoing spinal surgery. Namely, the total morphine consumption in the group where both agents were given was the lowest between all other groups. This study shows that glutamate mechanisms play an important role in development and maintenance of hyperalgesia and demand on modulation of excitatory mechanisms for its removal. The mutual administration of lamotrigine (prevention presinaptic glutamate uptake) and $MgS0_4$ (block of NMDA receptor canal and prevent Ca^ influx) for management of postincisional pain has better results comparatively with traditional analgesia and the use of each of these drugs alone [31].

Klasen J. et al. conducted a clinical study investigating the effect of long-lasting pre-emptive epidural analgesia on consumption of analgesics and acute pain in patients scheduled for elective hip replacement for osteo-arthritis. For preemptive analgesia they used 5 $ml.h^{-1}$ epidural ropivacaine 0.2%, on the day before operation. Epidural blocks provided sufficient operative analgesia in all patients. Pre-emptive analgesia was continued for 11–20 h and led to significantly decreased pain scores before surgery. The consumption of local anesthetics was decreased postoperatively in the preemptive group. Furthermore, bolus requests occurred more frequently in the control group. VAS scores did not differ significantly between groups. The authors concluded that long-lasting 'pre-emptive' epidural analgesia decreases postoperative pain with improved pain control [32].

The results of the study of Akural EI et al. suggest that preemptive epidural sufentanyl (50 µg in 20 ml normal saline before surgical incision) in abdominal hysterectomy is associated with a short-term opioid-sparing effect, which is most pronounced between 12-18 and 36-42 hours [33].

One possible reason for failure to demonstrate a preemptive analgesic effect in a big number of clinical studies, t.e. the similarity in postoperative pain relief between the groups with preemptive and non-preemptive analgesia, is the administration of opioids as premedication, at the induction of general anesthesia, or during the operation. The administration of opioids as a part of general anesthetic regimen in studies of preoperative (preemptive) analgesia may lower postoperative pain even in modest doses. So, in order to establish the real effect of preemptive analgesia in a trial, maybe one should avoid opioids as a part of general anesthetic technique.

Also, multimodal pre-emptive analgesia, such as used in the study of Wong CS et al., might be necessary to produce enough noxious input block during and after surgery to prevent central nociceptor sensitization [34].

In our study, while there was a beneficial effect of the reduced intraoperative anesthetic requirements, any lasting effect of preemptive analgesia (epidural bupivacaine-sufentanyl forte combination) did not extend beyond 8 hours postoperatively. This difference may be due to the smaller loading epidural dose in our study (9 ml bupivacain 0.25% plus 1 ml sufentanyl forte – 50 µg/ml versus the same dose of sufentanyl in 20 ml of saline in the above mentioned study). Also, this paper shows that epinehrine could be used as an adjuvant to the mixture for epidural infusion, since it makes a significant difference in pain relief and postoperative analgesic requirements when added to epidural local anesthetics and opioids.

References

1. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology. 1987;66:729-36. doi:10.1097/00000542-198706000-00004 PMID:3296854.

2. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia: their role in postoperative outcome. Anesthesiology. 1995;82(6);1474-1506.doi:10.1097/00000542-199506000-00019 PMID: 7793661.

3. Ferrante FM, Ostheimer GW, Covino BG. Patient-Controlled Analgesia. Boston, Mass: Blackwell Scientific Publications; 1990.

4. Bach S, Noreng MF, Tjéllden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain. 1988;33:297-301. doi:10.1016/0304-3959(88)90288-6 PMID:3419837.

5. Jahangiri M, Jayatunga AP, Bradley JW, Dark CH. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl. 1994;76:324-326. PMID:7979074.

6. Temeck BK, Schafer PW, Park WY, Harmon JW. Epidural anesthesia in patients undergoing thoracic surgery. Arch Surg. 1989;124:415– 8. PMID:2930350.

7. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology. 1987;66(6):729 –36. doi:10.1097/00000542-198706000-00004 PMID:3296854.

8. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurons in the rat: differential response to an intrathecal opiate administered pre or post formalin. Pain. 1987;30:349-360. doi:10.1016/0304-3959(87)90023-6 PMID:3670880.

9. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. Brain Res. 1990;535:155-158. doi:10.1016/0006-8993(90)91835-5 PMID:2292020.

10. Yamamoto T, Yaksh TL. Comparison of the antinociceptive effects of pre- and post treatment with intrathecal morphine and MK801, an NMDA antagonist, on the formalin test in the rat. Anesthesiology. 1992;77:757-763. doi:10.1097/00000542-199210000-00021 PMID:1416174.

11. Gonzalez-Darder JM, Barbera J, Abellan MJ. Effects of prior anesthesia on autotomy following sciatic transection in rats. Pain. 1986;24:87-91. doi:10.1016/0304-3959(86)90029-1 PMID:3005947.

12. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature. 1983;306:686-688. doi:10.1038/306686a0 PMID:6656869.

13. Woolf CJ. Recent advances in the pathophysiology of acute pain. Br J Anaesth. 1989;63:139-146. doi:10.1093/bja/63.2.139 PMID:2669905.

14. McQuay HJ. Pre-emptive analgesia. Br J Anaesth. 1992;69:1-3. doi:10.1093/bja/69.1.1 PMID:1637592.

15. Woolf CJ, Chong MS. Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77:362-379. PMID:8346839.

16. Abram SE, Yaksh TL. Morphine, but not inhalation anesthesia, blocks post-injury facilitation: the role of preemptive suppression of afferent transmission. Anesthesiology. 1993;78:713-721. doi:10.1097/00000542-199304000-00015 PMID:8385425.

17. Gottschalk A, Smith DS, Jobes DR et al. Preemptive Epidural Analgesia and Recovery From Radical Prostatectomy. JAMA. 1998;279(14):1076-1082. doi:10.1001/jama.279.14.1076 PMID:9546566.

18. Bong CL, Samuel M, Ng JM, Ip-Yam C. Effects of preemptive epidural analgesia on post-thoracotomy pain. J Cardiothorac Vasc Anesth. 2005;19(6):786-93. doi:10.1053/j.jvca.2005.08.012 PMID:16326309.

19. Yegin A, Erdogan A, Kayacan N, Karsli B. Early postoperative pain management after thoracic surgery; pre- and postoperative versus postoperative epidural analgesia: a randomised study. Eur J Cardiothorac Surg. 2003;24(3):420-4. doi:10.1016/S1010-7940(03)00345-2 PMID:12965314.

20. Aguilar JL, Rincón R, Domingo V, Espachs P, Preciado MJ, Vidal F. Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery. Br J Anaesth. 1996;76(1):72-6. PMID:8672384.

21. Aida S, Baba H, Yamakura T, Taga K, Fukuda S, Shimoji K. The effectiveness of preemptive analgesia varies according to the type of surgery: a randomized, double-blind study. Anesth Analg. 1999;89(3):711-6. doi:10.1097/00000539-199909000-00034 PMID:10475311.

22. 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(3):757-73. doi:10.1213/01.ANE.0000144428.98767.0E PMID:15728066.

23. Burmeister MA, Gottschalk A, Freitag M, Horn EP, Böhme C, Becker C, Standl TG. Pre- and intraoperative epidural ropivacaine have no early preemptive analgesic effect in major gynecological tumour surgery. Can J Anaesth. 2003;50(6):568-73. doi:10.1007/BF03018642 PMID:12826548.

24. Baris S, Sarihasan B, Karakaya D, Guldogus F, Tur A. Small dose fentanyl in intravenous versus epidural preemptive analgesia. Turkish Journal of Medical Sciences. 2000;30(1):63-70.

25. Garcia JBS, Issy AM, Salomão R, Sakata RK. Preemptive analgesia with epidural bupivacaine plus fentanyl in gynecological surgery—effects on serum interleukin-6 concentrations. Acute Pain. 2002;4(1):23-26. doi:10.1016/S1366-0071(02)00006-2

26. Castro FE, Garcia JB. [Preemptive analgesia with epidural bupivacaine and S(+)ketamine in abdominal hysterectomy.]. Rev Bras Anestesiol. 2005;55(1):28-39. doi:10.1590/S0034-70942005000100004 PMID:19471806.

27. Esmaolu A, Cuha Y, Boyaci A. Pre-emptive efficacy of epidural fentanyl in elective abdominal surgery. Eur J Anaesthesiol. 2001;18(1):59-63. PMID:11270012.

28. Subramaniam B, Pawar DK, Kashyap L. Pre-emptive analgesia with epidural morphine or morphine and bupivacaine. Anaesth Intensive Care. 2000;28(4):392-8. PMID:10969365.

29. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology. 2000;92(6):1624-30. doi:10.1097/00000542-200006000-00020 PMID:10839912.

30. Aida S, Shimoji K. Involvement of presurgical pain in

preemptive analgesia for orthopedic limb surgery. 9th World Congress of Pain 1999, Vienna, Austria; http://www.painstudy.ru/pje/1999pain.htm. Accessed November 29, 2009.

31. Kobeliatsky Y. Preemptive mutual administration of lamotrigine and MgSO4 decreases the level of postoperative pain after spinal surgery. 9th World Congress of Pain 1999, Vienna, Austria; http://www.disser.com.ua/content/247313.html. Accessed November 29, 2009.

32. Klasen J, Haas M, Graf S, Harbach H, Quinzio L, Jürgensen I, Hempelmann G. Impact on postoperative pain of long-lasting pre-emptive epidural analgesia before total hip replacement: a prospective, randomised, double-blind study. Anaesthesia. 2005;60(2):118-23. doi:10.1111/j.1365-2044.2004.03999.x PMID:15644006.

33. Akural EI, Salomaki TE, Alahuhta S. Can pre-emptive epidural analgesia with sufentanyl reduce postoperative pain after abdominal hysterectomy? 9th World Congress of Pain 1999, Vienna, Austria; http://bja.oxfordjournals.org/cgi/content/full/88/6/803. Accessed November 29, 2009.

34. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can J Anaesth. 1997; 44 (1): 31-37. doi:10.1007/BF03014321 PMID:8988821.