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CLINICAL STUDY

The epidural postoperative analgesia after a major urological procedures – a comparison of trimecaine and morphine to bupivacaine and fentanyl

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Abstract: *Objectives:* To compare the analgesic potency and side effects of epidural combination trimecaine with morphine and bupivacaine with fentanyl in postoperative analgesia after a major urological surgery.
Methods: We randomised 150 consecutive patients. In the trimecain/morphine group (n=75) trimecaine 50 mg with 4 mg morphine was given epidurally in 8 hour intervals. In the bupivacain/fentanyl group (n=75) the infusion of 0.25 % bupivacaine and fentanyl 2 µg/ml was administered at an infusion rate of 8 ml/h.
Results: The postoperative pain scores were lower in the trimecain/morphine group, the difference was significant during the first 6 hours after surgery, there was also a trend toward higher postoperative SpO_2 values in this group, the difference was significant 36 hours after surgery. The total sum of postoperative complications and side effects was significantly higher in the bupivacian/fentanyl group (p=0.002).
Conclusion: The combination of epidural trimecaine with morphine after a major urological surgery provides a superior analgesia with fewer side effects when compared to epidurally delivered bupivacaine with fentanyl *(Tab. 2, Fig. 5, Ref. 17).* Full Text (Free, PDF) www.bmj.sk.
Key words: trimecaine, bupivacaine, fentanyl, morphine postoperative analgesia.

An acute pain is a complex multidimensional experience that usually occurs in response to tissue trauma. Although responses to acute pain may be adaptive, they can have adverse physiologic and psychological consequences (e.g., reduced tidal volume, excessive stress, progression to chronic pain, inability to comply with rehabilitation, patient suffering and dissatisfaction). An acute pain is more difficult to manage if it becomes severe, so prompt and adequate treatment of acute pain is an imperative. Failure to provide an appropriate analgesia can lead to severe physiologic responses that are associated with increased morbidity, mortality, and costs (1). An epidural administration of local anesthetics and opioids delivered singly or in combination is an effective therapy of postoperative pain (2). Opioids act by binding receptors at the spinal level and later at the systemic level after absorption into the circulation and subsequent brain distribution. Epidural morphine binds at opioid receptors in spinal and supraspinal pain pathways and has a long-lasting, potent anti-nociceptive effect (3). In contrast, local anesthetics act through inhibition of nerve influx transmission at the spinal level only, but their systemic absorption after epidural administration is significant and leads to systemic adverse effects such as cardiac and neurological toxicity. Recent research on postoperative pain management supports the treatment approach known as "multimodal analgesia" or "balanced analgesia". This approach involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes or drug plus non-drug treatment) to obtain additive beneficial effects, reduce side effects, or both (4). These modalities may function through different mechanisms or at different sites. One example of multimodal analgesia is the use of combinations of opioids and local anesthetics to manage postoperative pain. Epidurally co-administered opioid and local anesthetic produce synergistic analgesia and prolong the duration of analgesia (5, 6). Different mixtures and infusion rates are used (1, 2, 4, 10), but an optimal regimen for epidural analgesia is still absent.

The aim of this prospective randomised study was to compare the effect of epidurally administered combination trimecaine/morphine to bupivacaine/fentanyl on postoperative pain relief, hemodynamic stability and presence of side effects.

Methods

The prospective randomised study was performed at the Department of Urology, Charles University Prague, Faculty of Medicine Hradec Králové, University Hospital Hradec Králové,

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Czech Republic, from January 2002 to December 2004. All adult patients, ASA I-III, undergoing an elective urological surgery (nephrectomy, radical prostatectomy, radical cystectomy, and pelvic lymphadenectomy) were included in the study. Exclusion criteria were contraindication to epidural analgesia and expected postoperative mechanical ventilation. An informed consent on participation in the study was obtained from all patients. All patients indicated for an elective surgery with expected length of procedure more than 3 hours had an epidural catheter inserted preoperatively if contraindications were absent. Patients were randomly assigned in an open-label manner to either epidural trimecaine with morphine – Group A or epidural bupivacaine with fentanyl – Group B (a traditional method of postoperative analgesia at study site). Trimecain (Mesocain 1 %, Spofa, Czech Republic) is a locally produced local anesthetic with properties very similar to lidocain. Bupivacain (Marcain 0.5 %, AstraZeneca, United Kingdom) is a long acting local anesthetic. Sufentanil (Sufenta, Janssen, Denmark) and fentanyl (Fentanyl, Janssen, Denmark) are potent opioids used for anesthesia and postoperative analgesia.

All catheters were inserted before induction of general anesthesia after an oral premedication with midazolam, 7.5 mg. The epidural puncture was performed at the level of surgical incision to obtain sufficient postoperative analgesia. The epidural space was identified by loss of resistance using 0.9 % saline. After a negative test dose, all patients received an epidural loading bolus of bupivacaine with sufentanil. Bupivacaine 5 mg in 1 ml per segment minus one third of the calculated dose in patients older than 60 years with sufentanil 5–10 μg was used. One half of the initial dose was repeated in 2-hour intervals. After an endotracheal intubation, a standardized general anesthesia with isoflurane (end-tidal concentration was left at the discretion of the anesthesiologist) was used, a mixture of oxygen and nitrous oxide (FiO_2 0.5) and atracurium. Intravenous boluses of fentanyl could be administered if considered necessary with a dose 1 μg/kg. Extubation was done in the operating room.

Immediately after arrival to the intensive care unit, the analgesic treatment started. Group A patients received 50 mg trimecaine with 4 mg morphine into the epidural catheter in 8-hours intervals, this interval could be prolonged, if pain was absent. In case of an inadequate analgesia a nurse was empowered to deliver 50 mg trimecaine in 5 ml of normal saline into the epidural catheter.

Group B patients received an epidural infusion of 0.25 % bupivacaine and 2 μg/ml fentanyl at a initial infusion rate of 8 ml/h. If the VAS value was above 3 points, the nurse was empowered to increase the infusion rate up to 10 ml/h. In the case of a motor block, the concentration of bupivacain was changed to 0.125 %. The rate of infusion was lowered to 5 ml/h if the VAS value was below 3 points. If failure of analgesia was observed, a more concentrated solution was administered and/or the infusion rate was increased depending on anesthesiologist's decision. An adequate control of pain was defined as a VAS value ≤3 at rest, during cough and mobilization. In case of over-sedation (difficulty in patient awakening and inability to obey commands), respiratory depression (respiratory rate less than 10 breaths/min), motor block or bradycardia (heart rate less than 45/min), the anesthesiologist was consulted.

The following parameters were recorded every hour during the first six hours, and then after 12, 24 and 36 hours using a standardized protocol: heart rate (HR), pain at rest and during mobilization using the 10-point visual analog scale (VAS), sedation score (0 – alert, 1 – sleepy but cooperative, 2 – drowsy but cooperative after being stimulated, 3 – difficult to awake and unable to obey commands), oxygen saturation measured by pulse oximetry (SpO_2), respiratory rate (RR), noninvasive blood pressure expressed as mean arterial pressure (MAP), presence of motor block, nausea, vomiting and pruritus. Total dose of analgesics, rescue boluses and complications were recorded.

Results are presented as mean and standard deviation. Demographic data, operation times, drug requirements and perioperative hemodynamic characteristics were assessed using an unpaired Student t test or Mann-Whitney Rank Sum Test as required. Postoperative evolution of SpO_2, HR, MAP, sedation score and VAS score were analysed using a one-way analysis of variance or Kruskal–Wallis one-way analysis of variance on ranks; for the comparisons of these values between groups in selected time points, an unpaired Student t test or Mann-Whitney Rank Sum Test were used. Comparisons between groups for gender and frequency of side effects were performed using z-test, differences with a p value less than 0.05 were considered significant.

Results

A total of 150 consecutive patients were enrolled, 75 patients in the epidural trimecaine with morphine group – Group A, 75 patients in the epidural bupivacaine with fentanyl group – Group B. Baseline characteristics of patients are shown in Table 1. There were no significant differences in baseline characteristics of study groups, baseline hemodynamical data and type of surgery except for higher age in Group B.

The postoperative VAS scores were lower in the epidural trimecaine/morphine Group A, the differences were significant

Tab. 1. Baseline characteristics of patients, baseline hemodynamical data, duration and type of surgery.

	Group A	Group B	p
Age (yr)	56.2±14.6	61.9±10.8	0.022
Male sex (n/%)	60/80 %	63/84 %	0.671
Duration of surgery (hr)	3.7±1.7	3.3±1.2	0.593
MAP before surgery (mmHg)	98.4 10.4	103.3 11.2	0.079
HR before surgery (min-1)	74.4±9.2	73.6±10.0	0.551
Type of surgery			
Radical prostatectomy (n/%)	20/26.6 %	19/25.3 %	0.996
Surgery with lumbotomy	22/29.3 %	29/38.6 %	0.303
Other	33/44 %	27/36 %	0.405

Group A – epidural trimecaine and morphine analgesia, Group B – epidural bupivacaine and fentanyl analgesia, MAP – mean arterial pressure, HR – heart rate

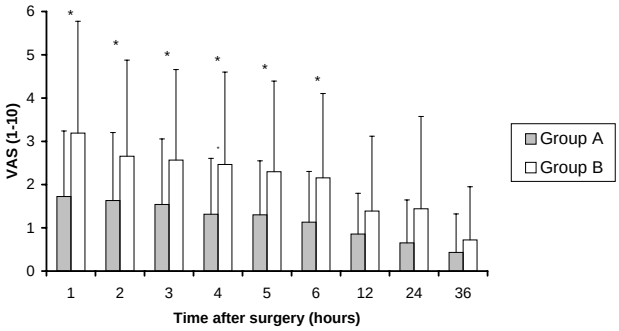

Fig. 1. A comparison of postoperative analgesia (using 10-point visual analog scale – VAS) between the groups. Group A – epidural trimecaine with morphine analgesia, Group B – epidural bupivacaine with fentanyl analgesia, * p<0.05.

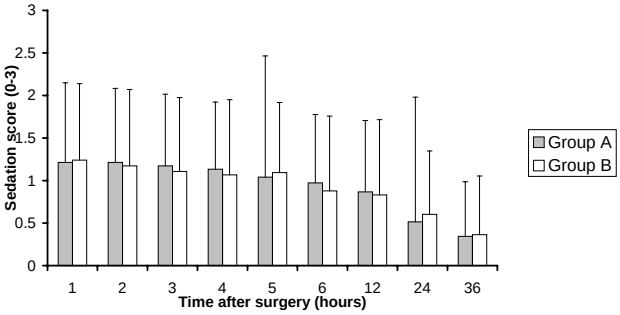

Fig. 2. Postoperative sedation scores. Group A – epidural trimecaine with morphine analgesia, Group B – epidural bupivacaine with fentanyl analgesia. Sedation score: 0 – alert, 1 – sleepy but cooperative, 2 – drowsy but cooperative after being stimulated, 3 – difficult to awake and unable to obey commands.

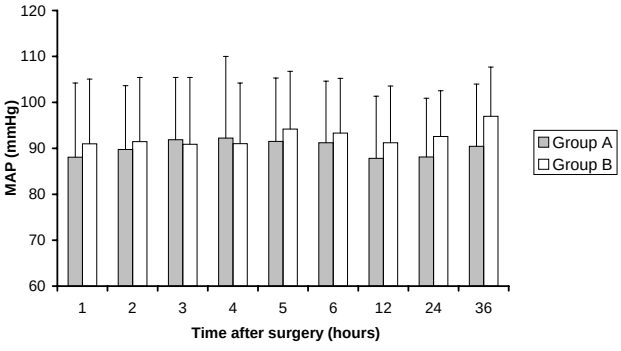

Fig. 3. Postoperative mean arterial pressure (MAP). Group A — epidural trimecaine with morphine analgesia, Group B — epidural bupivacaine with fentanyl analgesia.

during the first 6 hours after surgery (Fig. 1). There were no significant differences in postoperative sedation score values (Fig. 2). Postoperative mean arterial pressure was stable in both groups and was similar to preoperative values (Fig. 3). No fluid

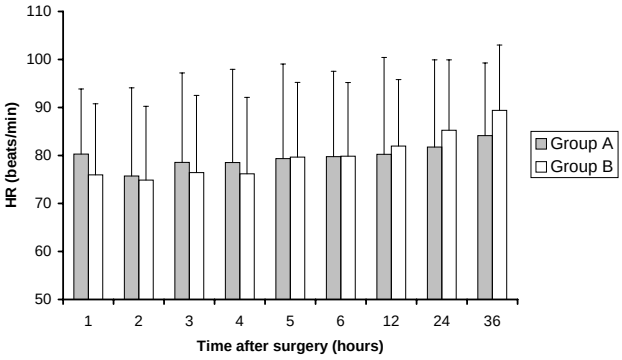

Fig. 4. Postoperative heart rate (HR). Group A – epidural trimecaine with morphine analgesia, Group B – epidural bupivacaine with fentanyl analgesia.

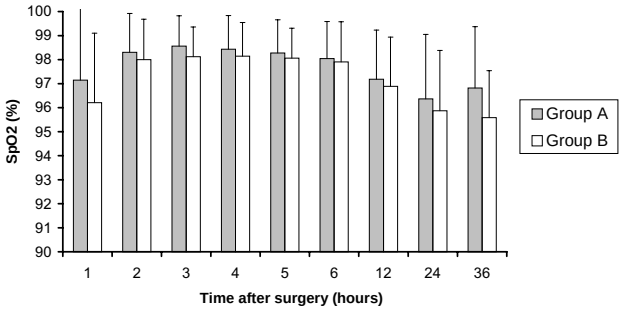

Fig. 5. Postoperative pulse oximetry – hemoglobin saturation values. Group A – epidural trimecaine with morphine analgesia, Group B – epidural bupivacaine with fentanyl analgesia, * p< 0.05.

boluses or infusions of catecholamines were required. Postoperative values of heart rate did not differ between the groups (Fig. 4).

There was a trend toward higher postoperative SpO_2 values in the epidural trimecaine with morphine Group A, but the difference was significant only 36 hours after surgery (Fig. 5).

The mean number of trimecaine and morphine boluses was 4.0±1.9 throughout the study period in Group A. Time to 2nd, 3rd and 4th doses were 7.9±3.4, 10.2±5.1, 10.5±4.8 hours. The mean total doses of morphine and trimecaine were 16.9±8.6 mg and 206±100.9 mg, respectively.

The mean epidural infusion rate of bupivacaine and fentanyl was 15.9±11.8 mg per hour and 18.1±8.5 g per hour respectively in Group B.

The incidence of postoperative complications and side effects for both regimens is reported in Table 2. Serious bradycardia developed after an accidental intravenous administration of bupivacaine in 2 patients in Group B. One patient (Group B) was resuscitated after pulmonary embolism with a good recovery. There was a trend toward a higher incidence of inadequate analgesia requiring the use of alternative method of analgesia in

Tab. 2. Postoperative complications and side effects of analgesia.

	Group A	Group B	p
Respiratory depression (n/%)	4/5.3 %	3/4 %	0.992
Lower limb paresthesia (n/%)	1/1.3 %	4/5.3 %	0.361
Lower limb motor blockade (n/%)	1/1.3 %	5/6.6 %	0.212
Inadequate analgesia requiring alternative method of analgesia (n/%)	1/1.3 %	7/9.3 %	0.068
Sedation score 3 any time after surgery (n/%)	5/6.6 %	7/9.3 %	0.757
Sedation score 3 later than 2hours after surgery (n/%)	4/5.3 %	4/5.3 %	1.000
Hypotension (n/%)	1/1.3 %	4/5.3 %	0.361
Death (n/%)	0/0 %	0/0 %	1.000
Pulmonary embolism (n/%)	0/0 %	1/1.3 %	0.980
Arrhythmia (n/%)	0/0 %	3/4 %	0.243
Cardiac arrest (n/%)	0/0 %	1/1.3 %	0.980
Malfunction of catheter (n/%)	0/0 %	1/1.3 %	0.980
Intestinal paralysis (n/%)	0/0 %	1/1.3 %	0.980
Nausea, vomiting (n/%)	0/0 %	1/1.3 %	0.980
Accidental i.v. administration (n/%)	0/0 %	2/2.6 %	0.93
Total number of patients with any postoperative complication (n/%)	8/10.5 %	27/36.0 %	<0,001

Group A – epidural trimecaine with morphine analgesia, Group B – epidural bupivacaine with fentanyl analgesia

Group B, but the difference didn't reach statistical significance. The total sum of postoperative complications and side effects was significantly higher in Group B, this difference was maintained even if excluding patients with accidental intravenous administration of bupivacaine (p=0.002).

Discussion

This study found that a combination of epidural trimecaine with morphine after a major urological surgery provides a superior analgesia with fewer side effects when compared to epidurally delivered bupivacaine with fentanyl.

Recent experimental investigations showed that after an epidural administration, the cerebrospinal fluid bioavailability of lidocaine, a drug with similar properties to trimecaine, was approximately three-times higher than that of bupivacaine and was supported by the fact that epidural clearance of bupivacaine was higher than lidocaine with a higher amount of bupivacaine diffusing into systemic circulation (9). This could explain some systemic side effects observed in Group B patients (moderate hypotension, arrhythmias, nausea and vomiting) and better analgesia in Group A patients.

Epidural co-administration of morphine and trimecaine produces synergistic analgesia and prolongs the duration of analgesia (7, 8). Direct inhibition of the sympathetic nervous system at the level of the brain stem and spinal cord by morphine and less systemic toxicity of trimecaine could also explain good analgetic properties and hemodynamic stability in A group patients after operation. The combination of epidural morphine and lidocaine significantly increases the peak effect and prolongs the duration of effects compared to each drug alone (10). This effect could be due to the vascular effect of trimecaine (11), reducing the systemic absorption of morphine from the epidural space, leading to an increase in the extent of it's absorption through the meninges into cerebrospinal fluid thus targeting more receptors and channels, acting more globally and preventing windup (12). A direct comparison of fentanyl and morphine in addition to a novel local anesthetic ropivacaine showed that patients receiving fentanyl were more likely to experience pain, the infusion rate was higher, required more rate adjustments, as well as a greater need for noradrenaline and antiemetic drugs (13). The importance of a local anesthetic component in epidural analgesia was shown in a study comparing fentanyl – bupivacaine to morphine alone. The combination of fentanyl with bupivacaine was clearly superior to morphine in terms of quality of analgesia (14).

The incidence of side effects in bupivacaine with fentanyl group was quite high. In a study of 1030 patients managed by epidural analgesia with a combination of 0.05 % bupivacaine and fentanyl 4 μg/ml, the incidence of side effects was 16.7 % for pruritus, 14.8 % for nausea, 13.2 % for sedation, 6.8 % for hypotension, 2 % for motor block, and 0.3 % for respiratory depression (15). A lower incidence of certain side effects such as nausea and sedation, but a higher incidence of lower limb motor block or paresthesias might be caused by a higher concentration of bupivacaine and lower infusion rate of fentanyl used in our study. The reported incidence of an inadequate analgesia requiring an alternative analgesic treatment ranges between 1 % (15) to 20 % (16). Rates observed in both groups of our study fit well in this range.

There are some limitations of this study. Our study was randomised but not blinded. Although the use of study drugs was not blinded, data analysis of the postoperative course and the incidence of side effects and complications were performed blindly by an independent person. This practice is common in similar studies. The study is also limited due to the existence of some differences between both groups, namely the age of patients. It is unclear if this difference could influence our results but recent studies in patients after gynecological procedures showed the opposite, a negative correlation between age and analgesic requirements (17). It was also suggested that different disease patterns and body mass indexes affect consumption of analgesics in patients treated with patient-controlled epidural analgesia (17). There are minor differences in the types of surgery between both groups, but these differences are not significant. Body mass index was not recorded in our study.

In summary, the combination of epidural trimecaine with morphine after a major urological surgery provides superior analgesia and fewer side effects when compared to epidurally delivered bupivacaine with fentanyl.

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