Does Midazolam Improve Caudal Ropivacaine Analgesia in Adults?

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Citation

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Abstract

Purpose

:
This prospective, randomized double blind, controlled study was designed to evaluate the potentiating effect of midazolam on caudal ropivacaine analgesia in adults.Methods: Thirty adult patients scheduled for elective hemorrhoidectomy under general anesthesia were randomly allocated to one of two equal groups. All patients received 0.5 $ml.kg^{-1}$ of ropivacaine 0.2% (R group) plus midazolam 50 $\mu g.kg^{-1}$ (RM group). Intra and post-operative vital signs, post-operative visual analogue pain score, Bromage score, sedation score, the time to first analgesia request, analgesic consumption and adverse effects were assessed.Results: The time to first analgesia was significantly longer (26.8%) in RM group (5.2 hours ± 18.9) compared to R group (4.1 hours ± 17.4). The 24 hours analgesia (meperidine) consumption was significantly reduced (by 44.7%) from 63.3 mg ± 15.3 in R group to 35 mg ± 4.1 in RM group. Overall, the RM mixture seems to produce more reduction in heart rate and mean arterial pressure compared to the R group. None of the patients exhibited post-operative undue sedation, motor weakness or other adverse events. Conclusion: This study reveals that the addition of midazolam to caudal ropivacaine in adults undergoing hemorrhoidectomy significantly prolonged the time to first analgesia and reduced the 24 hours analgesic consumption without causing undue sedation, motor block, delayed recovery from anesthesia or any significant side effect. This profile suggests that ropivacaine- midazolam mixture is an attractive solution for caudal anesthesia in ambulatory surgery in adults.

INTRODUCTION

Caudal anesthesia can reduce the amount of inhaled and intravenous anesthetic required, attenuate the stress response to surgery, facilitate a rapid and smooth recovery and provide good immediate postoperative analgesia [1]. Single-shot caudal anesthesia using local anesthetics (LA) alone provides a relatively short duration of post-operative analgesia [2]. Placement of a catheter into the caudal epidural space to administer repeated doses or running of a LA solution infusion may increase the risk of infection and delay early mobilization and hence explains its unpopularity. Therefore, adjuvants are needed in order to prolong the analgesic effects of LA [3]. The addition of opioids significantly prolongs the duration of caudal analgesia but is associated with a number of unpleasant side effects such as nausea, vomiting, pruritus and urinary retention, as well as, the risk of respiratory depression [4]. In an attempt to avoid these problems, other non-opioid adjuvants such as tramadol [2], clonidine [5], ketamine [6], and neostigmine [7] were investigated with a variable degree of success. Significant side-effects, e.g. hallucination with ketamine, excessive nausea and vomiting with neostigmine, as well as sedation and bradycardia with clonidine, limit their clinical usefulness [8].

Midazolam is a widely available water soluble benzodiazepine that has been shown to have an analgesic effect by its action on the benzodiazepine GABA receptor complex when administered via the subarachnoid , epidural or caudal route [9- 14]. Several studies have demonstrated the analgesic effects of caudally administered midazolam either alone or in combination with bupivacaine in children [12-14]. To our knowledge, there are no reports on the use of caudal ropivacaine- midazolam mixture in children or in adults. Therefore, this prospective, randomized double blind, controlled study was designed to evaluate the effect of midazolam on the analgesic properties of caudal ropivacaine in adults.

MATERIALS AND METHODS

After obtaining the Institutional Ethics Committee approval and informed patients' consent, thirty adult patients ASA I-II of either sex, scheduled for elective hemorrhoidectomy (Morgan-Milligan procedure) under general anesthesia were enrolled in this study. Patients with contraindications to caudal blockade (e.g., skin infection), obesity (defined as > 20% of ideal body weight), history of allergy to drugs used in the study, chronic benzodiazepine use, and alcohol or drug abuse were excluded.

Premedication was omitted. Routine patient monitoring including 5-lead ECG, non- invasive blood pressure, Oxygen saturation (SpO_2) using (Dragger Infinity Kappa Monitor version VF-5W, Germany) were instituted prior to anesthesia induction. Lactated Ringer's solution was infused at a rate 6 $ml.kg^{-1}.h^{-1}$ intravenously (IV) throughout the operation and for two hours afterwards.

Patients were randomly allocated by closed envelop method to one of two groups of fifteen patients each. Patients in the ropivacaine group (R) received 1 $mg.kg^{-1}$ ropivacaine 1% (Narop, Astra , Sweden) diluted with normal saline up to a volume of 0.5 $ml.kg^{-1}$. While patients in the ropivacaine-midazolam group (RM) received 1 $mg.kg^{-1}$ ropivacaine 1% plus midazolam 50 $\mu g.kg^{-1}$, then the mixture was diluted with normal saline up to a volume of 0.5 $ml.kg^{-1}$. Thus, the final ropivacaine concentration was 0.2%. The injected solutions were all prepared by a colleague anesthetist not participating to the study and the administering anesthetist was unaware of the composition of LA solution or group allocation of patients.

Anesthesia was induced with propofol 2- 2.5 $mg.kg^{-1}$ followed by placement of a laryngeal mask airway of an appropriate size (size 3 for females and size 4 for males). Anesthesia was maintained by 0.6- 2% isoflurane together with a mixture 2:1 ratio of nitrous oxide in oxygen adjusted to maintain $P_{ET}CO_2$ between 42- 48 mmHg with the patients breathing spontaneously. No further intra-operative sedatives or opioids were administered. Patients were then placed in the lateral position and the assigned caudal solution was injected using a 23G needle under aseptic conditions. Patients were then returned to the supine position for 15 minutes before they were positioned in the lithotomy position and surgery was allowed to start.

Oxygen saturation, blood pressure and heart rate (HR) were recorded before induction of anesthesia (baseline), prior to caudal blockade, just before the start of surgery and then every five minutes till the end of operation and in the recovery room then every one hour in the surgical ward up to six hours.

Intra-operative hypotension was defined as a reduction in the mean arterial blood pressure (MAP) by > 30% of baseline value. It was then treated with ephedrine 6 mg increments every 3 minutes. Bradycardia was defined as a reduction in the HR ≤ 50 beats $minute^{-1}$. It was then treated with atropine 0.3 mg increments every 5 minutes. An increase in HR or MAP by >15% of pre-incision value within 15 min of the onset of surgery indicated inadequate analgesia, and failure of the caudal block. These patients then received IV fentanyl 0.5 $\mu g.kg^{-1}$ as required and were excluded from the study. The failure rate in each group was recorded.

In the recovery room, the patients were asked to estimate their pain on a vertical visual analogue score (VAS) on a 0 to 10 cm scale, where a score of 0 represent no pain and 10 = the worst pain imaginable [15]. A score of 1-3 represent mild pain, 4-7 = moderate pain and > 7 represent severe pain. The VAS was recorded regularly every hour until VAS exceeded 3 or the patient requested analgesia. The time to first analgesia request was defined as the time from caudal injection until VAS >3. Whenever the VAS score exceeded 3, analgesia was provided by meperidine 0.5 $mg.kg^{-1}$ IV and the total consumption during the first postoperative day was recorded.

Motor block was assessed on awakening and thereafter at 15, 30, 60 and 120 minutes by using a modified Bromage scale [16] that consisted of 4 points: 0 = full motor strength (flexion of knees and feet), 1 = flexion of knees, 2 = little movement of feet only, 3 = no movement of knees or feet. Also sensory level was determined postoperatively in both groups.

Sedation score was assessed on awakening and thereafter at 15, 30, 60 and 120 minutes on a four categorical scale as 0 = alert and aware; 1 = drowsy, not sleeping; 2 = asleep, arousable by verbal contact and 3 = asleep not arousable by verbal contact [17].

Any side effects, like nausea, vomiting, bradycardia, hypotension, excessive sedation, inadequate analgesia, retention of urine or respiratory depression defined as respiratory rate <10 min^{-1} or SpO_2 < 90 % were recorded. During the post-operative period, whenever patients complained of nausea and/or vomiting or received meperidine, an anti-emetic ondansetron 4 mg IV was given.

Patients were discharged from post anesthesia care unit (PACU) when they reached an Aldrete score of 10 i.e., when they were able to move all extremities in response to a request, able to breath deeply and cough freely, stable systemic blood pressure (± 20% of pre-anesthetic level), fully awake and had oxygen saturation >92% while breathing room air [18].

STATISTICAL ANALYSIS

We assumed that adding midazolam to caudal ropivacaine will prolong the time to first analgesia request. To determine the sample size, a pilot study involving 8 patients was performed. Power analysis using the pilot study results indicated that a sample size of 26 (13 patients in each group) would detect a 15% increase in the time to first analgesia request, which was assumed to be clinically significant, with an - type error of 0.05 and a -type error of 0.01. Therefore, a sample size of 30 patients in two equal groups was chosen to allow for drop-outs. Statistical analysis was performed using Student's t-test for comparing means of independent groups. The times at which analgesia were treated as being analogous to survival data. “Survival curves” were plotted to indicate the proportion of patients in each group who had received no analgesia by a given time after operation. Kaplan- Meier method was performed to estimate analgesic duration using long rank test to compare the two curves.

Haemodynamic data at various timings were compared using two ways ANOVA for repeated measures to evaluate the effect of time in each group with Bonferroni correction as post hoc test. Percent change in HR and MBP from baseline was compared among both study groups using Mann-Whitney test to evaluate significant group interaction. A p-value of ≤ 0.05 was considered significant [19].

RESULTS

Only one patient in the RM group was excluded from the study for technical difficulty due to excessive condensation of body fat obscuring the landmarks and the block could not be performed after three attempts. Patients of both groups were matching for age, weight, gender distribution and operative time (Table 1). All patients were ASA I.

The time course of post-operative analgesia is presented as survival curves for the proportions of patients requiring analgesia during the post-operative period (Figure 1). The time to first analgesia was significantly longer (26.8%) in the RM group compared to the R group (Table 1).

The 24 hours postoperative meperidine consumption in the RM group showed a statistically significant reduction (44.7%) compared to the R group with a p value < 0.001 (Table 1).

There was no statistically significant difference in the percent reduction in HR in the two groups before the caudal block and at 15 minutes after giving the block. Throughout surgery and for up to two hours post-operatively, there was a statistically significant more reduction in the RM group compared the R group except at 20 and 30 minutes post surgery and upon admission to the recovery room when the difference did not reach statistical significance. Throughout the remaining study period, there was no statistically significant difference in the percent reduction in HR between both groups (Figure 2).

There was no significant difference in the percent reduction of MAP between the two groups before the caudal block. However, following the caudal block, throughout surgery and for up to two hours post-operatively there was statistically significant more reduction in the MAP in the RM group compared to the R group except at 20 minutes post surgery and 15 minutes after the admission to the recovery room when the reduction did not reach statistical significance. After the first two hours from recovery and throughout the remaining study period, there was no significant difference in the percent reduction of MAP between the two groups except at 6 hours post-operatively (Figure 3).

Upon admission to recovery room, there was no statistically significant difference in sedation score between patients in R group (median 1 and range 0-1) and RM group (median 1 and range 0-2) (p value= 0.2). The sedation score of all patients returned to normal after 15 minutes and throughout the study period without a statistically significant difference between both groups.

There was no significant difference in the time required to achieve PACU discharge criteria in both groups (9.7 ± 2.8, 10.4 ± 3.5 min in R and RM groups respectively) (p value = 0.7).

There was no evidence of motor weakness in the two groups in the postoperative period (median promage score= 0, range 0-0 in both groups). There was no statistically significant difference in the sensory level between both groups in the postoperative period. None of the patients in both groups exhibited post-operative complications or delayed recovery from general anesthesia.

Figure 1

Table 1: Patients' demographic data, operative time, analgesic duration and consumption

	Group (R) (n=15)	Group (RM) (n= 14)	p-Value
Age (yr)	30.8 (4.5)	32.7 (5.4)	0.31
Weight (Kg)	70 (9.3)	71 (7.8)	0.76
Male: Female (number)	9:6	8:6	0.69
Operative duration (min)	32 (4.8)	31 (4.1)	0.47
Analgesic duration (hr)	4.1 (17.4)	5.2 (18.9) $	< 0.001
24 hr PO meperidine consumption (mg)	63.3 (15.3)	35 (4.1) $	< 0.001

Data are presented as mean (standard deviation) unless otherwise indicated.

R: Ropivacaine group. RM: Ropivacaine-Midazolam group. PO: postoperative.

$ p< 0.001 relative to ropivacaine group.

Figure 2

Figure 1: Median duration of analgesia (hours) in Ropivacaine (R) group and Ropivacaine- midazolam (RM) groups. Proportion of patients in each group with analgesia.

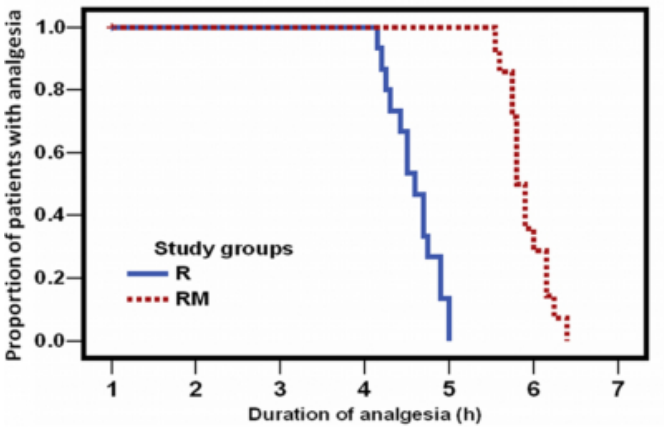
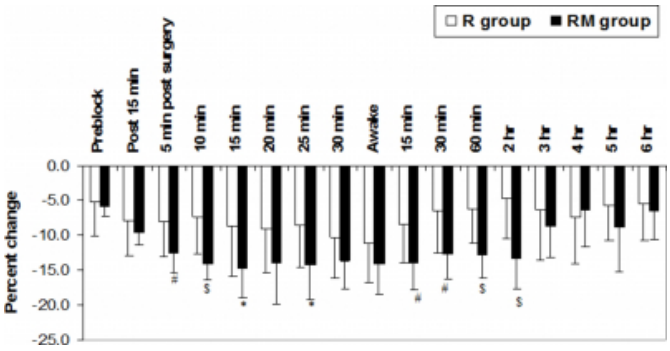


Figure 3

Figure 2: Percent reduction in heart rate

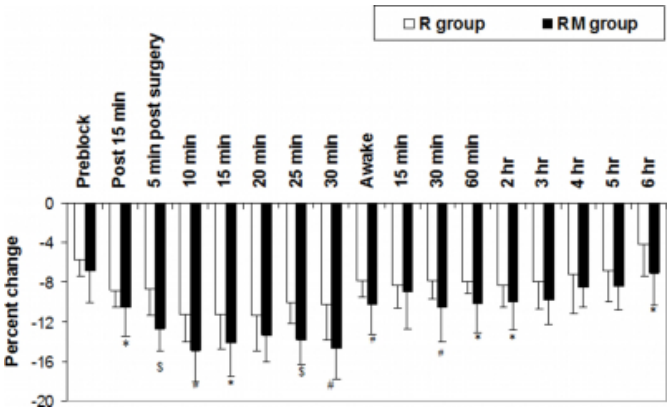


R group: Ropivacaine group, RM group: Ropivacaine-Midazolam group.

* p< 0.05; # p< 0.01; $ p< 0.001 relative to R group.

Figure 4

Figure 3: Percent reduction in mean arterial pressure



R group: Ropivacaine group, RM group: Ropivacaine-Midazolam group.

* p< 0.05; # p< 0.01; $ p< 0.001 relative to R group.

DISCUSSION

This study reveals that the addition of midazolam to caudal ropivacaine in adults undergoing hemorrhoidectomy significantly prolonged the time to first analgesia and reduced the 24 hours analgesic consumption without causing undue sedation, motor block, delayed recovery from anesthesia or any significant side effect.

The finding that the local anesthetic- midazolam mixture prolonged the time to first analgesia is consistent with the findings of other reports performed on children [12-13]. In spite of this agreement, the extent of such prolongation varies widely. The prolongation reported in this study (26.8%) is shorter compared to the other two pediatric

studies of Güleç et al., (by 300%) [12] and in Kumar et al., (by 57%) [13].

In this study, the finding that the addition of midazolam to ropivacaine reduced the 24 hours analgesic requirements (by 44.7 %) confirms the findings of Naguib et al., who reported comparable reductions (42.9%) using midazolam - bupivacaine mixture [14].

Contrary to the results of the present study, Baris et al., [20] found that caudal block with bupivacaine and midazolam or fentanyl provided no further analgesic advantages to bupivacaine alone in children undergoing unilateral inguinal herniorrhaphy. They explained their results by suggesting that bupivacaine alone provided sufficient analgesia for this minor surgery and obviated the need for adjuvants.

Several reasons co-exist in explaining the discrepancies between our results and other investigations mentioned above. These reasons include a different local anesthetic solution used (ropivacaine versus bupivacaine), a more painful type of surgery performed (anal surgery versus inguinal herniorrhaphy or urogenital surgery), a different patient population (adult versus paediatric) with the inherent difficulty in reliably assessing pain in the paediatric age group and finally the larger volume injected in their studies (0.75-1 $ml.kg^{-1}$) compared to the volume used in our study (0.5 $ml.kg^{-1}$) [12-14,20,21].

The increased percent reduction of the HR and MAP suggests that the RM mixture provides a more intense block during the surgical procedure. These changes were not limited to the operative period but extended for two hours into the post-operative period. This could be due several factors such as difference in the autonomic block level, systemic absorption of midazolam or difference of the depth of general anesthesia. The former could be ruled out by the lack of difference in autonomic block elicited in the post-operative period. Further pharmacokinetic studies with measured and adjusted anesthetic depth were required to confirm these hemodynamic changes and detect its mechanism.

Local anesthetics have been shown to suppress post-incisional pain, either when the drugs are focally delivered at the neural axis (spinal or epidural administration) or when they are present systemically, as the result of vascular redistribution of locally delivered drug or by intentional systemic delivery [22]. It is becoming increasingly apparent that local anesthetics in the systemic circulation can profoundly alter postoperative pain by supra-spinal mechanisms in addition to the well known spinal effects [23]. Therefore, it is likely that caudal midazolam may alter the redistribution of caudal ropivacaine and vice versa.

Patients were slightly sedated only upon admission to the recovery room in both groups that resolved 15 minutes later which suggests residual effects of general anesthesia rather than the effect of caudal midazolam administration. No motor weakness, retention of urine, desaturation, respiratory depression, nausea and vomiting or delay in reaching the PACU discharge criteria suggesting the lack of significant side-effects.

It is noteworthy that the dose of midazolam used in this study is the same dose used in the children [12-14]. It is also the dose recommended for epidural use (without LA) in adults since the higher doses (75 and 100 $\mu g.kg^{-1}$) were associated with an unacceptable degree of sedation while the lower dose (25 $\mu g.kg^{-1}$) was less effective [24].

Epidural midazolam exerts its analgesic effect through the GABA—benzodiazepine system in the spinal cord. Benzodiazepine binding sites have been demonstrated in the spinal cord, particularly within lamina II of the dorsal horn, and appear to be linked to the $GABA_A$ receptor complex. Furthermore, endogenous benzodiazepine-like substances have been isolated from human cerebrospinal fluid [25]. The anti-nociceptive effects of midazolam are antagonized by flumazenil and possibly also by naloxone, thereby implying that the mechanism of analgesia may involve activation of opioid receptors [26].

Dose-dependent analgesia without respiratory depression or any adverse neurological effects following the intra-thecal or epidural administration of midazolam has been demonstrated in both animal and adult human studies [10,11,27,28]. Even after a constant subarachnoid infusion of midazolam 50 $\mu g.day^{-1}$ for 15 days, no signs of spinal cord or meningeal toxicity were found in the rat [28]. Changes in the blood-brain barrier were observed only after administration of very large doses of midazolam 0.1% (0.3 ml) intra-cisternally in rabbits (equivalent to 111 $\mu g.kg^{-1}$) [29]. Furthermore, several other human studies using higher doses than that used in this study have confirmed the safety of peri-dural midazolam administration by illustrating the lack of neurological or urologic symptoms, as suggested by some preclinical animal experimentation [9-14,30].

CONCLUSION

The present study reveals that the addition of 50 $\mu g.kg^{-1}$ midazolam to (0.5 $ml.kg^{-1}$) caudal ropivacaine 0.2% significantly prolonged the time to first analgesia in adults undergoing hemorrhoidectomy and may cause more pronounced reduction of heart rate and blood pressure. This mixture also reduced analgesic consumption in the first post-operative day without significant side effects or delaying recovery room discharge. This profile suggests that ropivacaine- midazolam mixture is an attractive solution for caudal anesthesia in ambulatory surgery in adults.

The optimum volume and concentration of midazolam-ropivacaine mixture for caudal analgesia needs to be investigated further. Future studies aiming at the evaluation the mutual effects of both components of this admixture on their respective pharmacokinetics are warranted.

References

1. Yao YS, Qian B, Chen BZ, Wang R, Tan L. The optimum concentration of levobupivacaine for intra-operative caudal analgesia in children undergoing inguinal hernia repair at equal volumes of injectate. Anaesth. 2009; 64:23-6.
2. Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadius surgery. Br J Anaesth. 1997; 79:293-6.
3. Turan A, Memis D, Basaran ÜN, Karamanlioğlu B, Süt N. Caudal ropivacaine and neostigmine in pediatric surgery. Anesthesiol. 2003; 98:719-22.
4. De Beer DAH, Thomas ML. Caudal additives in children: solution or problems? Br J Anaesth. 2003; 90:487-98.
5. Lee JJ, Rubin AP. Comparison of a bupivacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J Anaesth. 1994; 72:258-62.
6. Naguib M, Sharif A, Seraj M, El Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine. Br J Anaesth. 1991; 67:559-64.
7. Abdulatif M, El Sanabary M. Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadius surgery in children. Anesth Analg. 2002; 95:1215-8.
8. Silvani P, Camporesi A, Agostino MR, Salvo I. Caudal anesthesia in pediatrics: an update. Minerva Anestesiol. 2006; 72:453-9.
9. Edwards M, Serrao JM, Gent JP, Goodchild CS. One the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiol. 1990; 73:273-7.
10. Nishiyama T, Matsukawa T, Hanaoka K. Continuous epidural administration of midazolam and bupivacaine for postoperative analgesia. Acta Anaesthesiol Scand. 1999; 43:568-72.
11. Nishiyama T, Yokoyama T, Hanaoka K. Midazolam improves postoperative epidural analgesia with continuous infusion of local anaesthesia. Can J Anaesth. 1998; 45:551-5.
12. Güleç S, Buyukkidan B, Oral N, Ozcan N, Tanriverdi B. Comparison of caudal bupivacaine, bupivacaine-morphine and bupivacaine-midazolam mixtures for post-operative analgesia in children. Eur J Anaesthesiol. 1998; 15:161-5.
13. Kumar P, Rudra A, Pan AK, Acharya A. Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine co-administered with bupivacaine. Anesth Analg. 2005; 101:69-73.
14. Naguib M, El Gammal M, El Hattab YS, Seraj M. Midazolam for caudal analgesia in children: comparison with caudal bupivacaine. Can J Anaesth. 1995; 42:758-64.
15. Reinhart DJ, Goldberg ME, Roth JV, Dua R, Nevo I, Klein KW, Torjman M, Vekeman D. Transdermal fentanyl system plus IM ketorolac for the treatment of postoperative pain. Can J Anaesth. 1997; 44:377-84.
16. Luz G, Innerhofer P, Häussler B, Oswald E, Salner E, Sparr H. Comparison of ropivacaine 0.1% and 0.2% with bupivacaine 0.2% for single shot caudal anaesthesia in children. Paediatr Anaesth. 2000; 10:499-504.
17. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JA. Comparison of extradural ropivacaine and bupivacaine. Br J Anaesth. 1991; 66:31-7.
18. Aldrete JA. The post anesthesia recovery score revisited. J Clin Anesth. 1995; 7:89-91.
19. Norman GR, Streiner DL. Biostatistics, The bar essentials. B.C. Decker Inc, Hamilton, Ontario, Canada, third ed. 2008.
20. Baris S, Karakaya D, Kelsaka E, Güldogus F, Ariturk E, Tür A. Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. Paediatr Anaesth. 2003; 13:126-31.
21. Aitkenhead AR. Post-operative pain. In: Aitkenhead AR, Smith G, Rowbotham DJ, editors. Textbook of Anaesthesia, 5th ed. Edinburgh, UK: Churchill Livingstone, 2007. p.510-25.
22. Duarte AM, Pospisilova E, Reilly E, Mujenda F, Hamaya Y, Strichartz GR. Reduction of post-incisional allodynia by subcutaneous bupivacaine: findings with a new model in the hairy skin of the rat. Anesthesiol. 2005; 103:113-25.
23. Strichartz G R. Novel ideas of local anaesthetic actions on various ion channels to ameliorate postoperative pain. Br J Anaesth. 2008; 101:45-7.
24. Nishiyama T, Hirasaki A, Odaka Y, Mikane T, Kobayashi O, Seto K. Epidural midazolam with saline — optimal dose for postoperative pain. Masui 1992; 41: 49-54.
25. Möhler H, Okada T. The benzodiazepine receptor in normal and pathological brain. Br J Psychiatry. 1978; 133:261-8.
26. Serrao JM, Goodchild CS, Gent JP. Reversal by naloxone of spinal anti-nociceptive effects of fentanyl, ketocyclozocine and midazolam. Eur J Anaesthesiol. 1991; 8:401-6.
27. Serrao JM, Marks RL, Morley SJ, Goodchild CS. Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. Pain. 1992; 48:5-12.
28. Schoeffler P, Auroy P, Bazin JE, Taxi J, Woda A. Subarachnoid midazolam: histologic study in rats and report of its effect on chronic pain in humans. Reg Anesth. 1991; 16:329-32.
29. Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, Souron R. Ketamine and midazolam neurotoxicity in the rabbit. Anesthesiol 1991; 75: 91-97.
30. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal Midazolam I: A Cohort Study Investigating Safety. Anesth Analg. 2004; 98:1512-20.

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