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Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy

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In the present double-blind study we aimed to evaluate the postoperative analgesic effects of intrathecal midazolam with bupivacaine following haemorrhoidectomy. Forty-five patients were randomly allocated to one of three groups: the control group received 1 ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline intrathecally, group BM1 received 1 ml of 0.5% bupivacaine plus 0.2 ml of 0.5% preservative-free midazolam and group BM2 received 1 ml of 0.5% bupivacaine plus 0.4 ml of 0.5% midazolam. Time to first analgesia was significantly greater in the midazolam groups than in the placebo and significantly less in the BM1 group than in the BM2 group.

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Since the early 1980s, intrathecal administration of midazolam has been reported to have antinociceptive action[1] and to be an effective analgesic agent in animals[2 3] and humans.[4–7]

After haemorrhoidectomy, many patients require parenteral oral opioids and/or nonsteroidal antiinflammatory drugs (NSAIDs) for analgesia. The use of opioids in intrathecal or epidural anaesthesia has become popular to optimize postoperative analgesia. However, opioid-induced side effects, such as respiratory depression, nausea, vomiting, urinary retention and pruritus, limit their use.[8 9] The purpose of our study was to assess the effects of intrathecal midazolam as an adjunct to intrathecal bupivacaine after haemorrhoidectomy.

Methods

After local ethics committee and written informed consent had been obtained, 45 patients (ASA I–II) scheduled to undergo elective haemorrhoidectomy were enrolled in this double-blind, randomized trial. Those who had a contraindication to regional anaesthesia or were opioid-tolerant were excluded. No premedication was given. The control group received intrathecally 1 ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline; group BM1 received intrathecally 1 ml of 0.5% bupivacaine plus 1 mg of midazolam in 0.2 ml (5 mg ml^{-1}); and group BM2 received intrathecally 1 ml of 0.5% bupivacaine plus 2 mg of midazolam in 0.4 ml (5 mg ml^{-1}). Midazolam (Domicum; Hoffman-La Roche, Basle, Switzerland) available in our hospital contains midazolam hydrochloride buffered to pH 3.5 with sodium hydroxide and hydrochloric acid with no preservative.

Saddle block anesthesia was performed in the sitting position under aseptic conditions using a 25 G spinal needle and the subarachnoid space was entered at the L3–4 level. Patients were kept in the sitting position for 5 min, tested for sensory loss and then placed in the prone position before surgery.

During surgery, patients were monitored with electrocardiography, pulse oximetry and non-invasive measurement of arterial pressure and heart rate. After surgery, all patients were admitted for 1 day and instructed to take two Codety tablets (each tablet containing 300 mg paracetamol and 30 mg codeine phosphate) every 4 h as needed. No other analgesic was allowed during the 24 h after surgery.

Three parameters were assessed in this study: duration of effective analgesic time from the spinal anaesthesia; visual analogue scales (VAS) at first analgesia; and total consumption of analgesics in the 24 h after spinal anaesthesia. Any adverse events were also recorded. Neurological changes, such as motor and sensory deficits, bowel and

Table 1 Patient characteristics and duration of surgery (mean (SD) or number). The control group received 1 ml of 0.5% bupivacaine and 0.2 ml of 0.9% saline; the BM1 group received 1 ml of 0.5% bupivacaine and 1 mg of midazolam in 0.2 ml; and the BM2 groups received 1 ml of 0.5% bupivacaine and 2 mg of midazolam in 0. 4 ml; none of the differences were significant

	Control group	BM1 group	BM2 group
Gender (male/female)	6/9	6/9	5/10
Age (yr)	44.2 (10.9)	41.5 (9.7)	43.7 (13.5)
Height (cm)	164.2 (9.1)	161.8 (8.5)	163.7 (9.3)
Weight (kg)	65.7 (11.6)	60.4 (10.4)	64.0 (10.5)
Duration of surgery (min)	26.3 (6.7)	28.0 (6.2)	26.4 (6.0)

Table 2 Postoperative analgesia. Values are mean (SD). *P<0.01 compared with the control group, †P<0.05 compared with the BM1 group

	Control group	BM1 group	BM2 group
Time to first pain medication (h)	3.99 (0.78)	6.03 (1.49)*	8.37 (2.51)*†
VAS at first pain medication (mm)	35 (9.2)	36 (9.1)	34 (9.9)
Number of oral administrations of Codety requested in 24 h	3.73 (0.79)	2.53 (0.74)*	1.80 (0.94)*

bladder dysfunction, were checked before discharge. The anaesthetist who performed subarachnoid block was not involved in assessment of patients and the observers were blinded.

Data are expressed as mean (SD). Statistical analysis was performed using the computer program SPSS (version 9.0; SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used for normally distributed parametric data. Time to first analgesia, pain scores at first pain medication and the number of analgesics requested in 24 h were analysed by the Kruskal–Wallis test followed by the *post hoc* multiple comparison test using the Dunnett method. P<0.05 was considered statistically significant.

Results

There were no significant differences between the groups in patient characteristics or duration of surgery (Table 1).

Time to first analgesia in groups BM1 and BM2 was significantly longer than that in the control group (P<0.01 in both cases). Time to first analgesia in group BM1 was also significantly less than that in group BM2 (P<0.05) (Table 2). There were no significant differences in VAS on analgesia administration among the three groups (Table 2).

All patients required analgesia during the 24 h after surgery. The number of oral administrations requested in this period was significantly less in the BM1 and BM2 groups than in the control group (P<0.01 in each case). There was no significant difference in frequency of analgesic rescue between the BM1 and BM2 groups (P=0.073) (Table 2).

There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients. Three of the 15 patients from each group developed urinary retention. Time to the first episode of self-voiding was similar in all groups. No neurological deficits were detected at discharge (Table 3).

Table 3 Postoperative side effects; values are mean (SD) or number of patients

	Control group	BM1 group	BM2 group
Nausea/vomiting	1	0	0
Sedation	0	0	0
Urinary retention	3	3	3
Time to first self-voiding (h)	4.99 (2.99)	4.95 (2.56)	5.31 (2.12)

Discussion

In this study, we found that the analgesic effect of intrathecal bupivacaine was potentiated by intrathecal midazolam. The addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by approximately 2 h and 4.5 h, respectively, compared with controls after haemorrhoidectomy. In addition, midazolam-treated groups used less analgesic in the first 24 h after surgery. Our results suggest a dose-dependent effect of intrathecal midazolam.

This study may be criticized on account of the different volumes of subarachnoid injection (1.2 ml was injected in the control and BM1 groups; and 1.4 ml in the BM2 group) and the consequent differences in bupivacaine concentration. However, Van Zundert and colleagues[10] have shown that the concentration and volume do not affect sensory block, motor block or duration of spinal anesthesia as long as the dose of local anaesthetic is constant.

In vitro autoradiography has shown that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation.[11] In 1987, Goodchild and Serrao reported that benzodiazepines might have analgesic effects at the spinal cord level in animals.[2] Analgesic efficacy of intrathecal midazolam in humans has been demonstrated recently.[5–7] The δ-selective opioid antagonist,

naltrindole, suppresses the antinociceptive effect of intrathecal midazolam,[12] suggesting that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal δ receptors.

The most serious risk of intrathecal midazolam is its possible neurotoxicity. So far, animal studies have revealed no damage to the spinal cord, nerve roots or meninges.[13] There have been some reports on the spinal application of midazolam in humans. A single intrathecal injection of 2 mg midazolam did not cause any clinical neurological deficits and produced significant analgesia for 2 months in patients with chronic low back pain.[5] Intrathecal midazolam was also effective after leg surgery, without any side effects.[4] In addition to the effectiveness of intrathecal midazolam against somatic pain, an antinociceptive effect against visceral pain has been demonstrated in rabbits subjected to intestinal distension[3] and in humans after caesarean section.[6] Intrathecal midazolam has been used in a continuous infusion with doses of $\leqslant$6 mg day^{-1} for a long-term period in four patients with refractory neurogenic and musculoskeletal pain.[7] *In vitro* studies have suggested that clinically useful doses of intrathecal midazolam are unlikely to be neurotoxic.[14] In our study, we paid special attention to any potential side effects or complications during the perioperative period. There were no neurological complications. The analgesic effect of intrathecal midazolam was segmental, with no alteration in sympathetic tone or reflexes.

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