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Midazolam in Spinal Anesthesia — Intrathecal or Intravenous?

Beyazit Zencirci

Additional information is available at the end of the chapter

1. Introduction

The first spinal anesthesia was carried out by Dr August Bier in 1899 and his anesthetic technique has become the standard practice for lower extremity and abdominal surgery worldwide [1]. Nowadays, the most commonly used drugs for spinal anesthesia are local anesthetics. However, a major disadvantage of single injection spinal anesthesia is its limited duration of action. In clinical practice, a number of adjuvants have been added to intrathecal local anesthetics for supplementation of intraoperative anesthesia and postoperative analgesia. They have advantages as they reduce the dose of local anesthetic; provide long lasting postoperative analgesia with reduced incidence of central nervous system depression, motor effects or hypotension [2].

Midazolam, synthesized by Walsar and colleagues in 1976, was the first clinically used water soluble benzodiazepine [3]. It is also the first benzodiazepine that was produced primarily for use in anesthesia [4]. In 1986, Faull and Villiger demonstrated 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 [5]. One year later, Goodchild and Serrao reported that benzodiazepines might have analgesic effects at the spinal cord level in animals [6]. In 1990s, analgesic efficacy of intrathecal midazolam in humans has been demonstrated [7-9]. Naltrindole, a δ-selective opioid antagonistic agent, suppresses the antinociceptive effect of intrathecal midazolam, suggesting that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal δ receptors [10].

This chapter is going to focus on the relationship between midazolam and spinal anesthesia.

2. Midazolam

Benzodiazepines commonly used in the perioperative period include diazepam, midazolam, and lorazepam, as well as the selective benzodiazepine antagonist flumazenil (Figure 1). The chemical structure of the benzodiazepines contains a benzene ring fused to a seven-member diazepine ring, hence their name. They are all composed of a benzene ring (*A*) fused to a seven-membered 1, 4-diazepine ring (*B*). Anesthesiologically relevant benzodiazepine agonists also contain a 5-aryl substituent (*ring C*), which enhances the pharmacological potency. However, the benzodiazepine antagonist flumazenil has two important structural differences as compared to the above agonists. Flumazenil has a keto function at position 5 instead of ring C, and a methyl substituent at position 4. Hence benzodiazepines are unique among the group of intravenous anesthetics in that their action can readily be terminated by administration of their selective antagonist flumazenil [11, 12].
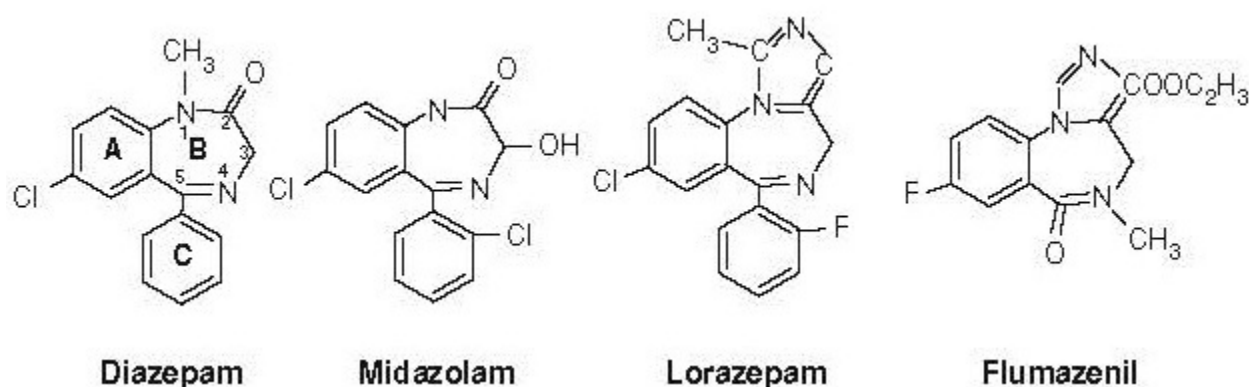

Figure 1. Chemical structure of the three commonly used benzodiazepines and their antogonist flumazenil.

Midazolam is an imidazobenzodiazepine. This results in the ability of a water molecule to open the diazepine ring, thus encouraging aqueous solubility. The equilibrium between the two forms of midazolam is determined by pH. The change from one form to the other is relatively slow, having a half-life of 10 minutes. The pH in the ampoule containing midazolam hydrochloride is 3.0 and so the ring is open and it is soluble. Once subjected to body pH 7.4, the diazepine ring closes and the midazolam becomes lipid-soluble, allowing it readily to cross the blood–brain barrier. In the plasma most of the midazolam (*95%*) is protein-bound. Small changes in its plasma protein binding will produce large changes in the amount of free drug available, which may have consequences in clinical practice [13]. The high lipophilicity of midazolam accounts for the relatively large volume of distribution at steady-state [14]. Older age does not increase the volume of distribution significantly [15, 16]. However, in obese patients, the volume of distribution is increased and the elimination half-time is prolonged while the clearance remains unchanged [15].

Elimination half-time is independent of the route of administration. Major operations seem to increase the volume of distribution and prolong the elimination half-time [16]. Following intravenous administration, midazolam is rapidly distributed and the distribution half-time

is 6-15 min [17]. The fused imidazole ring of midazolam is oxidized much more rapidly than the methylene group of the diazepine ring of other benzodiazepines [18-20]. In elderly men, the clearance of midazolam is reduced and the elimination half-time is prolonged as compared to young males. Between elderly and young women, however, no significant differences were detected in the clearance or the elimination halftime of midazolam [15]. In addition to the liver, midazolam is also metabolized at extrahepatic sites. This has been demonstrated by the discovery of metabolites following intravenous injection of midazolam during the anhepatic period of liver transplantation [21]. In patients with advanced cirrhosis of the liver, the plasma clearance is reduced and the elimination half-time is prolonged as compared to healthy volunteers, while the volume of distribution remains unchanged [22].

The first step in the metabolism of midazolam is hydroxylation [23]. The two metabolites formed are α-hydroxymidazolam and 4-hydroxymidazolam, both are pharmacologically active [14, 24]. The α-hydroxymidazolam is as potent as the parent compound and may contribute significantly to the effects of the parent drug when present in sufficiently high concentrations. 4-Hydroxymidazolam is quantitatively unimportant [25]. Both metabolites are rapidly conjugated by glucuronic acid to form products which have been considered to be pharmacologically inactive [14]. On the other hand; glucuronidated α-hydroxymidazolam, the main metabolite of midazolam, has a substantial pharmacological effect and can penetrate the intact blood–brain barrier. The elimination half-time of α-hydroxymidazolam is about 70 min [25]. However, it can accumulate in patients with renal failure. Furthermore, in vitro binding studies show that the affinity of glucuronidated α-hydroxymidazolam to the cerebral benzodiazepine receptor is only about ten times weaker than that of midazolam or unconjugated α-hydroxymidazolam [26].

Midazolam is supplied as hydrochloride salt with a pH less than 4.0 (*buffered to an acidic pH of 3.5*). This is important because midazolam displays pH-dependent solubility. The diazepine ring of midazolam accounts for its stability in solution and rapid metabolism. It remains open at pH value of <4, thus maintaining drug′s water solubility. The ring closes at pH value of > 4, as when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid soluble drug [27] and this lipophilicity is responsible for its rapid CNS effect and large volume of distribution [28]. Therefore the pH of the commercial midazolam hydrochloride preparation is adjusted to 3 with hydrochloride acid and sodium hydroxide. As midazolam is injected into patients, pH is increased and the ring is closed thus increasing the lipid solubility.

Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ-amino butyric acid (*GABA*), the major inhibitory neurotransmitter in the brain. Benzodiazepine receptors are found in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, inferior colliculus, brain stem, and spinal cord. There are two types of GABA receptors; benzodiazepine receptors are part of the benzodiazepine-GABAA-chloride channel receptor complex. Benzodiazepine binding site is located on the $\gamma2$ subunit of the GABA receptor complex [29, 30]. With the activation of the GABAA receptor, gating of the channel for chloride ions is started after which the cell becomes hyperpolarised and resistant to neuronal excitation. The hypnotic effects of benzodiazepine are mediated by alterations in the potential dependent calcium ion flux [31]. Hypnotic, sedative, amnesic, and anticonvulsant effects are mediated by

α1 GABA receptors and anxiolysis and centrally acting muscle relexant properties are mediated by α2 GABA receptors [31].

The anxiolytic effect of midazolam is via its action at mammillary body. Presumably midazolam exerts its anxiolytic property like other benzodiazepines by increasing glycine inhibitory neurotransmitter. Midazolam also possesses anticonvulsant action which is attributed to enhanced activity of GABA on the brain's motor circuit. It exhibits a muscle relaxant effect via its action at the glycine receptors in the spinal cord. Midazolam administered via intrathecal or epidural routes can produce analgesia, probably due to its GABA mediated action [4]. Other mechanisms of action including its interaction with opiate receptors have also been proposed [10].

3. Intrathecal midazolam: Useful or toxic?

Spinal anesthesia is the most commonly used regional anesthetic technique. Local anesthetic agents used for this purpose provide good intraoperative analgesia. However, they provide a very limited postoperative duration of action. In order to overcome this problem and to maximise the duration of anesthesia-analgesia, many adjuvants, such as intrathecal opioids and non-opioids, have increasingly been tried in the last two decades to relieve postoperative pain [32-34]. Among the various methods availabe for providing post-operative analgesia, the benefits of intrathecal opioids and non-opioids as adjuncts in spinal anaesthesia are well documented. Unfortunately the addition of intrathecal opioids is associated with dose-related adverse effects such as respiratory depression, nausea, vomiting, urinary retention, pruritus, and sedation [35]. Therefore, the use of non-opioids such as ketamine, clonidine, neostigmine, magnesium sulfate, and midazolam have become popular adjuncts for post-operative analgesia. However, side-effects in the postoperative period render most adjuvants less than ideal.

Midazolam, a water soluble benzodiazepine, has been used via intrathecal route in the management of acute (*perioperative*) [36, 37], chronic [38] and cancer [39] pain. Goodchild and Noble were the first to demonstrate the role of intrathecal midazolam in relieving pain of somatic origin in humans [36]. The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentameric gammaaminobutyric acid (*GABA-A*) receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA-A receptor. The GABA receptor is a chloride ionophore that, when activated, typically stabilises the transmembrane potential at, or near, the resting potential. In neurons, this typically serves to decrease excitability [40]. Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation [36]. The present cumulative experience with intrathecal midazolam across species broadly confirms the safety thereof, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effects [8].

Intrathecal midazolam was originally shown to have antinociceptive properties in animals in the early 1980s [41, 42]. And later in 1991, Malinovsky et al. demonstrated potential of neurotoxic effect of intrathecal administration of ketamine and midazolam in rabbits [43]. Midazolam-treated rabbits showed significant changes in both blood-brain barrier and light microscopy studies. They postulated that, the neurotoxicity might be due to the 10% HCL used as a vehicle in the preparation of midazolam. In 1999 Erdine et al. conducted a study of intrathecal midazolam in rabbits and reported neurotoxicity [44]. They concluded that the neurotoxicity was due to the use of intrathecal catheter. They also reported that this toxic change did not produce any change in the vital parameters of those animals. However, in 1991 Schoeffler et al. conducted a detailed histological study in rats following administration of midazolam via subarachnoid catheter while investigating control of cancer pain [45]. They found that the amount of fibrosis, infiltration, and deformation in midazolam group is not different from saline control group. Aguilar et al. in 1994, conducted study and reported that intrathecal midazolam can relieve pain in different clinical situations (*as long as 13 months*) and they did not show any toxic neurological effects following prolonged administration of intrathecal midazolam [46]. Nevertheless, in 1995 Svensson et al. conducted a morphological study on rat spinal cords following chronic subarachnoid administration of midazolam, documenting its neurotoxic effect [47].

In 1996, Valentine et al. studied the effect of intrathecal midazolam along with hyperbaric bupivacaine for caesarean section delivery under spinal anaesthesia and found no side effects attributable to midazolam [8]. In the same year, Borg and Krijnen reported long-term intrathecal administration of midazolam and clonidine in patients with refractory musculoskeletal pain persisting more than 2.5 years [9]. They administered intrathecal midazolam up to 6mg/day which showed promising results, they also reported that this high dose did not cause any neurological deficits in those patients suffering with chronic refractory musculoskeletal pain [9]. One year later, Bozkurt et al. studied the histological change following epidural administration of midazolam in neonatal rabbits and showed a variable degree of neurotoxic effects such as degeneration of vacuoles, cytoplasm and neurofilaments, disruption of myelin sheaths, lysis of cell membranes, perivascular oedema, and pyknosis of nuclei [48]. The toxic effects of acidic saline and midazolam (*commercially available preparations*) were similar. In the same year, Bahar et al. examined in an animal model whether intrathecal midazolam, alone or with fentanyl, can achieve anaesthesia sufficient for laparotomy, comparable to lidocaine; they concluded that midazolam, when injected intrathecally, produces reversible, segmental, spinally mediated antinociception, sufficient to provide balanced anaesthesia without any adverse effect [49]. In 1999, Nishiyama et al. conducted histopathological study in cats with intrathecal midazolam. Neither acute histological damage nor inflammatory reaction of the spinal cord were seen in the cats [50].

In 1998, Nishiyama et al. studied the effect of continuous infusion of midazolam with local anesthetic for treatment of postoperative pain and showed that adding midazolam to a continuous epidural infusion of bupivacaine provides better analgesia, amnesia, and sedation than bupivacaine alone without any side effects [51]. Also Nishiyama et al. in the same year studied the effect of adding midazolam and bupivacaine to human cerebrospinal fluid in glass

test tubes and the solution was examined for any change of pH and a reduction in the transparency of the solution [52]. Cerebrospinal pH was decreased to below 7.0 adding more than 3 mg of midazolam, more than 1.9 mL of 0.25% bupivacaine or 1.3 mL of the mixture. Cerebrospinal transparency by adding more than 0.7 mg of midazolam, 1.1 mL of 0.25% bupivacaine or 0.6 mL of the mixture. Midazolam in saline neither decreased the pH below nor reduced transparency. These results are very important so this study showed that clinically useful doses of intrathecal or epidural midazolam were not neurotoxic. In the same year, Gulec et al. showed that caudal administration of a bupivacaine-midazolam mixture produces a longer duration of postoperative analgesia than a bupivacaine-morphine mixture and bupivacaine alone [53]. Batra et al. in 1999, conducted a study on postoperative analgesia in patients undergoing knee arthroscopy following intrathecal administration of midazolam in combination with hyperbaric bupivacaine [54]. They demonstrated that this combination produces better postoperative analgesia. In 2001, Kim and Lee showed a dose-dependent effect of intrathecal midazolam [55]. Sen et al. reported that intrathecal midazolam produced significant postoperative pain relief together with antiemetic effect and tranquillity in patients undergoing caesarean section delivery [56]. Maharjan et al showed that caudal administration of midazolam-bupivacaine mixture significantly prolongs postoperative analgesia compared to bupivacaine alone in children undergoing genitourinary surgery [57]. Moreover, other studies have shown that addition of intrathecal midazolam significantly improves the duration and quality of spinal anesthesia and provides prolonged perioperative analgesia without any significant side effects and neurological damage [58-61]. Prochazka shared their decade long experience of using intrathecal midazolam in 2006 [62]. According to them, intrathecal midazolam is able to provide good analgesia in most patients and is a very suitable supplement for postoperative and long-term analgesia without demand of expensive systems (*Patient Controlled Analgesia and other drug infusion systems, etc.*). On the other hand, recent studies showed that intrathecal midazolam appears to improve perioperative analgesia and it can be useful and safe adjunct to bupivacaine for intrathecal analgesia during different surgical operations [35, 63-66].

Yegin et al. in 2004, conducted a study on the analgesic and sedative effects of intrathecal 2mg preservative free midazolam in perianal surgery under spinal anesthesia [37]. They found that the addition of bupivacaine produces a more effective and longer analgesia with a mild sedative effect in patients in the experimental group. One year later Agrawal et al. investigated postoperative pain relief following intrathecal administration of 1mg preservative free midazolam with bupivacaine in patients scheduled for elective lower abdominal, lower limb, and endoscopic urological surgeries [67]. They showed that intrathecal midazolam and bupivacaine provide longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone, without prolonging time for dermatomal regression. Also, Prakash et al. [35] with Ho and Ismail [64] found that intrathecal midazolam appears to improve perioperative analgesia and reduce nausea and vomiting during caesarean delivery. On the other hand in 2011, Shadangi et al. concluded that the addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block [68].

Addition of preservative free midazolam to hyperbaric bupivacaine for spinal anesthesia in different surgical procedures/operations prolongs the duration of effective analgesia as compared to bupivacaine alone and delays the need for postoperative rescue analgesics without having any sedative effect, pruritus, or respiratory depression. The use of intrathecal midazolam also decreases the incidence of postoperative nausea vomiting (*PONV*). Moreover, intrathecal midazolam does not have any clinically significant effect on perioperative hemo-dynamics. A small diluted dose of preservative-free intrathecal midazolam *(<1mg/mL concentration and 1 to 2.5mg*) appears to have few systemic side effects and is free of short-term neurotoxicity.

4. Sedation in spinal anesthesia with intravenous midazolam

The use of spinal anesthesia is often limited by the unwillingness of patients to remain awake during surgery [69]. Spinal anesthesia provides anesthesia at the surgical site, yet unpleasant and uncomfortable patient experiences result from having to remain in the same position, prolonged duration of surgery or ambient noise in the operating room. To avoid spontaneous movements by an inadequately sedated patient that can interfere with the surgical procedure, intravenous sedative medications can be useful in patients who are positioned in specific postures that can be considered uncomfortable [70]. On the other hand, the goals of sedation during spinal anesthesia include rapid achievement of adequate sedation, its maintenance at a constant level during the surgical procedure and awakening the patient quickly at the end. This can be attained by continuous infusion of sedative drugs preceded by a bolus.

Conscious sedation is a minimally depressed level of consciousness that retains the patient's ability to maintain his or her airway independently and continuously, and to respond appropriately to physical stimulation and verbal command, produced by pharmacologic or non-pharmacologic methods, alone or in combination [71]. With conscious sedation only some of the centers in the medullary reticular formation and thalamus are depressed in a dose dependent manner [72]. Thus, this level of sedation provides the additional benefit of preser-vation of protective airway reflexes, especially in monitored anesthesia care. An ideal supple-mental sedative should provide effective anxiolysis, an easily controllable level of sedation, predictable depth of amnesia, a rapid and clear headed recovery, minimal intraoperative side effects, no evidence of cumulation and minimal postoperative side effects. Numerous agents have been used as sedative adjuvants to spinal anesthesia, each with their own advantages and disadvantages.

The most widely used technique for administering sedation in regional anesthesia is the intermittent intravenous bolus dose technique. This technique has been shown to be associated with peaks and troughs in plasma concentration producing significant side effects and delayed recovery [73]. Continuous infusions have been proven to produce lesser side effects, faster recovery, easy controllability over the desired depth of sedation and, should the regional block prove to be ineffective, easy conversion to general anesthesia [74, 75].

Of the currently available benzodiazepines, midazolam has a fast onset and short recovery time, because of which it is one of the most widely used sedatives in spinal anesthesia. With a low context sensitive half time (*70 minutes for a four hour long infusion and up to 100 minutes for longer infusions*), it can be easily titrated to the needs of the patient, making its use well suited for ambulatory conscious sedation techniques [4, 76]. It produces good sedation and excellent amnesia but has no specific analgesic properties [77].

Benzodiazepines cause greater depression of upper airway muscle tone in the elderly, resulting in a higher incidence of airway obstruction [78, 79]. On the other hand, the synergistic effects between benzodiazepines and other drugs, especially opioids and propofol, facilitate better sedation and analgesia. However, the combination of these drugs also enhances their respiratory depression and may lead to airway obstruction or apnea [80]. Administration of oxygen to all the patients during sedation and immediate relief of airway obstruction prevented the occurrence of oxygen desaturation. A smaller volume bolus and a slow infusion rate avoided apnea.

Bolus administration of midazolam 0.05 mg/kg was reported to give enough amnesia and sedation without any adverse effects on hemodynamics and respiration [80]. With this method, patients did not respond to verbal command but recovered in 25 minutes [81] and opened their eyes spontaneously in 47 minutes [82]. As long as patients closed their eyes, amnesic effect was kept and when they opened their eyes, additional midazolam 1 mg (*approximately 18 mcg/kg*) was enough for patient's comfort [82]. However, bolus administration of sedative can not provide constant level of sedation. In contrast, continuous infusion can provide constant sedation level but usually prolongs onset time of sedation compared with the intermittent bolus technique [83]. Different studies showed that during spinal anesthesia, midazolam (*1-2 mg given and followed by 0.1-0.5 mg/kg/hr intravenously*) provides rapidly induced sedation and amnesia with stable hemodynamics and respiration. Oxygen must be administered at 3-6 L/min through a mask during the procedure. Intraoperative monitoring must include electrocardiography, pulse oxmetry, noninvasive sphygmomanometry, and capnography.

Midazolam is considered safe even at high doses and, at equipotent doses, it affects (*via GABA*) the central nervous system in a similar fashion [84]. GABA receptors are found in different parts of the brain. The sedative effects of the benzodiazepines are mediated by the brainstem GABA receptors that inhibit the ascending pathways that activate the brain cortex. The ataxia and memory impairment are mediated by GABA receptors in the cerebellar, hippocampal, and forebrain areas. While hypnosis or sedation is always achieved after appropriate individually based doses, anxiolysis is seldom transformed into anxiety, restlessness, rage or a myriad of uncontrolled behaviours (*midazolam paradox*)[84]. The relationship of the paradoxical reaction to alteration of the cholinergic homeostasis, serotonin levels, the role of genetics, and gamma-aminobutyric acid receptor configuration are suspect [85]. Such paradoxical reactions may harm the unconscious or semiconscious patient. Low dose of flumazenil (*0.2-0.3 mg, range 0.1-0.5 mg*) completely reverses midazolam-induced paradoxical reactions and they are more frequent in older patients [84, 85].

5. Conclusion

Spinal anesthesia has the advantage of being able to maintain spontaneous breathing as well as relaxing the necessary muscles for surgery. However, the time limit and patient's anxiety of spinal anesthesia are important disadvantages. On the other hand, the impediments to the effective use of spinal anesthesia are the predictable decreases in arterial blood pressure and heart rate through the accompanying sympathectomy with its attendant vasodilatation and blockade of cardio accelerator fibres. Another clinically important impediment to successful block is inadequate sedation. Adjunctive drugs are used to decrease anxiety, alleviate discomfort, improve hemodynamic stability and induce a feeling of calmness during spinal anesthesia.

When using sedative medication during spinal anesthesia, the anesthesiologist attempts to titrate the drug to optimize patient comfort while maintaining cardiorespiratory stability and intact protective reflexes. Morever, adequate sedation in spinal anesthesia relieves the anxiety of the patient, improves physiological and psychological stress, and increases the satisfaction of the surgeon, anesthetist and patient. Midazolam is most frequently used as the agent for sedation. It is often used intravenously in single doses of between 0.5 mg and 2.5 mg. Midazolam provides rapidly induced sedation and amnesia with stable hemodynamics and respiration during spinal anesthesia.

Moreover, midazolam has been shown to have antinociceptive effects when administered intrathecally, both in laboratory animals and in humans. Intrathecal injection up to 2 mg midazolam have been reported without adverse effects. The paucity of studies on intrathecal midazolam warrants caution in elderly patients, the obese, and those who are already on other sedatives. When intrathecal midazolam is used, all patients should be closely monitored intra and postoperatively. In brief, intrathecal preservative free midazolam appears safe and has clinically acceptable analgesic properties.

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