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Review Article

Midazolam in Subarachnoid Block: Current Evidence

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Midazolam, despite of being the commonest benzodiazepine used in anaesthesia and perioperative care, is a relatively newer addition to the list of adjuvant used in subarachnoid block. Midazolam causes spinally mediated analgesia and the segmental analgesia produced by intrathecal midazolam is mediated by the benzodiazepine-GABA receptor complex. Initial animal studies questioned the safety of intrathecal midazolam in terms of possible neurotoxicity. However subsequent clinical studies also failed to show any neurotoxicity of high dose midazolam even on long-term use. Addition of intrathecal midazolam to bupivacaine significantly improves the duration and quality of spinal anaesthesia and provides prolonged perioperative analgesia without any significant side effects. Clinical studies also reported its safety and efficacy in pregnant women, but some studies also reported mild sedation with intrathecal midazolam. It is also reported to decrease the incidence of PONV. Intrathecal midazolam does not have any clinically significant effect on perioperative hemodynamics.

1. Introduction

Midazolam, synthesized by Walsar and colleagues in 1976, is the first clinically used water soluble benzodiazepine [1]. It is also the first benzodiazepine that was produced primarily for use in anaesthesia [2].

2. Commercial Preparation

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 is characterized by a pH-dependent ring-opening phenomenon in which the ring remains open at pH value of <4, thus maintaining water solubility of the drug. 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 [3] and this lipophilicity is responsible for its rapid CNS effect and large volume of distribution [4].

The hydrochloride salt of midazolam, which is formed, is soluble in aqueous solutions. The imidazole ring of midazolam is responsible for its stability in solution and rapid metabolism.

3. Mechanism of Action

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 -$GABA_A$-chloride channel receptor complex. Benzodiazepine binding site is located on the $\gamma 2$ subunit of the GABA receptor complex [5, 6]. With the activation of the $GABA_A$ 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 [5]. Hypnotic, sedative, amnesic, and anticonvulsant effects are mediated by $\alpha 1$ GABA receptors and anxiolysis and centrally acting muscle relaxant properties are mediated by $\alpha 2$ GABA receptors [7].

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 motor circuit of brain. It exhibits a muscle relaxant effect via its action as the glycine receptors in the spinal cord. Midazolam given by intrathecal or epidural routes can produce analgesia, probably due to its GABA-mediated action [2]. Other mechanisms of action including its interaction with opiate receptors have also been proposed [8].

4. Pharmacokinetics [9]

Midazolam undergoes rapid absorption in gastrointestinal tract and prompt passage to blood-brain barrier. Oral midazolam undergoes substantial first pass metabolism (50%). It is extensively protein bound (96–98%) and has a volume of distribution of 1.0 to 1.5 L/Kg. The short duration of action of a single dose of midazolam is due to its high lipid solubility, leading to redistribution from the brain to an inactive tissue sites as well as rapid hepatic clearance. Elimination half time of midazolam is 1 to 4 hours. Elimination half time may be doubled in elderly patients reflecting age-related decrease in hepatic blood flow and possibly enzymatic activity.

Midazolam is rapidly metabolized by hepatic and intestinal cytochrome P-450 (CYP3A4) enzymes to both active and inactive metabolite.

5. Midazolam in Subarachnoid Block: Early Evidence

First spinal anaesthesia was administered by August Bier in 1898 [10, 11] using 0.5% cocaine for resection of the left ankle joint. Nowadays, the most commonly used drug for spinal anaesthesia is hyperbaric bupivacaine (0.5%). However, a major disadvantage of single injection spinal anaesthesia is its limited duration of action.

Opioids are the commonest adjuvant drugs added to the local anaesthetics for improved intraoperative and postoperative analgesia provided by 0.5% bupivacaine, when administered through intrathecal route. However, sedation, itching, urinary retention, nausea-vomiting, and the risk of respiratory depression are the most important concern of intrathecal opioid [12].

Reported since 1978 as a relatively water-soluble benzodiazepine [1], midazolam is being extensively used both in critical care medicine and operating room. It is used for its sedative, anxiolytic, and amnesic effects [2], but possible use of intrathecal midazolam as an adjuvant is a relatively newer concept in anaesthesia practice. However, intrathecal administration of midazolam like any other drug also has some safety concern that should be kept in mind.

Intrathecal midazolam was originally shown to have antinociceptive properties in animals in the early 1980s. One of the early works was done in 1983 by Niv et al. [13] on mongrel dogs, in whom intrathecal administration of 0.5–1 mg midazolam was shown to depress the nociceptive synaptic reflexes for as long as 2 hours. The effect was reversed by intravenous administration of benzodiazepine antagonists RO15-1788 (flumazenil) and RO15-3505 but not by naloxone 2 mg. They concluded that the antinociceptive effect of locally applied midazolam could be the result of a nonopioid GABA-mediated system which may have implications in the management of pain.

The site and mode of action began to be appreciated, when in 1986, Faull and Villiger [14] undertook a detailed anatomical and pharmacological study of benzodiazepine receptors in human spinal cord under the electron microscope. They demonstrated that benzodiazepine receptors were distributed in a consistently similar fashion in the gray matter of the cervical, thoracic, lumbar, and sacral regions of the human spinal cord. At all levels, the highest densities of benzodiazepine receptors were found to be localized within lamina II of the dorsal horn. Within this lamina the receptors were concentrated mainly in its deeper, inner portion which lies immediately adjacent to lamina III, with some overlap dorsally into the outer segment of lamina II and ventrally into the adjacent region of lamina III. The lowest density of receptors was found in regions of laminae I, IV, VII, and X; in particular, in lamina VII the lowest concentration of receptors was found in the dorsal nucleus of Clarke and the sacral parasympathetic nucleus. The remaining laminae of the spinal gray matter (laminae V, VI, VIII, and IX) showed a moderate density of receptors. These results showed a high concentration of Type II benzodiazepine receptors in the substantia gelatinosa of the human spinal cord and suggested a possible role for these receptors in spinal sensory functions.

On the basis of the appreciation of the role of GABA in regulating motor tone, Muller et al. [15] in 1986, using unanaesthetised spinally catheterized cats, reported an antispasticity effect of intrathecal midazolam with little effect on normal motor function. Importantly, there were no adverse clinical signs.

Goodchild and Noble [16] in 1987 observed that 0.3–2 mg of intrathecal midazolam interrupts somatic nociceptive afferent pathway of pain. However it did not significantly block the abdominal visceral nociceptive afferent pathway of pain. Serrao et al. [17] in 1989 reported that intrathecal administration of midazolam in rats produced segmental analgesia which was reversed by naloxone.

In 1990, Waldvogel et al. [18] investigated the regional, cellular, and subcellular distribution of GABA, GABA receptors, and benzodiazepine receptors. The results showed a close correspondence in the regional distributions of GABA, GABA (GABA-A and GABA-B) receptors, and benzodiazepine receptors. The highest density of GABA-like immunereactivity, GABA receptors, and benzodiazepine receptors was localized as a dense band within lamina II of the dorsal horn (especially inner lamina II) with moderately high densities in laminae I and III. The remaining laminae of the spinal gray matter showed much lower levels of labeling. These results show a high concentration of GABA, GABA receptors, and benzodiazepine receptors in lamina II of the dorsal horn of the human spinal cord and suggest a possible role for GABA in spinal sensory functions.

Edwards et al. [19] in 1990 investigated the mechanism by which midazolam causes spinally mediated analgesia and the authors concluded that the segmental analgesia produced

by intrathecal midazolam is mediated by the benzodiazepine-GABA receptor complex that is involved in other benzodiazepine actions. Bonica [20] in 1990 carried out detailed investigation of intrathecal midazolam on its chronic pain relief property.

In 1996, Goodchild et al. [8] reported that intrathecal midazolam causes antinociception by endogenous neurotransmitters acting at spinal cord delta opioid receptors and nociceptive effect has been suppressed or blocked by the delta selective opioid antagonist naltrindole suggesting an additional pathway of action, namely, via the delta-opioid receptors.

6. Safety Issues of Intrathecal Midazolam

However there was concern for the possible neurotoxicity of intrathecal midazolam. In 1991, Malinovsky et al. [21] demonstrated potential of neurotoxic effect of intrathecal administration of ketamine and midazolam in rabbits. The aim of this study was to evaluate by histologic and blood-brain barrier (BBB) studies whether ketamine or midazolam could be used as an alternative to local anesthetics or opioids to produce spinal analgesia. Midazolam-treated rabbits showed significant changes in both BBB and light microscopy studies. They postulated that, the neurotoxicity might be due to 10% HCL which is used as vehicle in the preparation of midazolam. They concluded that the intrathecal use of midazolam should be avoided in humans. In the year 1999 Erdine et al. [22] conducted study of possible neurotoxicity of intrathecal midazolam in rabbits and reported neurotoxicity of midazolam. They concluded that neurotoxicity of midazolam was due to the use of intrathecal catheter. They also reported that this toxic change does not produce any change in the vital parameters of those animals.

However, in 1991 Schoeffler et al. [23] conducted detailed histological study in rats following administration of midazolam via subarachnoid catheter and was tested in the control of cancer pain. They found that the amount of fibrosis, infiltration, and deformation in midazolam group is not different from saline control group. They also concluded that intrathecal midazolam has effects on chronic pain in humans and efficacy of intrathecal midazolam on chronic pain was established.

Aguilar et al. [24] in 1994 conducted study and reported that intrathecal midazolam can relief pain in different clinical situations like sacrococcygeal chondroma as long as 13 months and they did not show any neurological toxic effects following prolonged administration of intrathecal midazolam.

But in 1995, Svensson et al. [25] conducted morphological study on spinal cord for possible neurotoxic effect in rats, following chronic subarachnoid administration of midazolam (100 micrograms per day for twelve days) and they showed the neurotoxic effect of intrathecal midazolam on spinal cord in their report. They emphasize both the necessity of morphometric and ultrastructural studies before spinal administration of novel drugs to humans and the neurotoxic potential of midazolam.

In 1996, Valentine et al. [26] studied the effect of intrathecal midazolam along with hyperbaric bupivacaine for caesarean delivery under spinal anaesthesia and found that no side effects attributable to midazolam were identified. Intrathecal midazolam appears safe and has clinically detectable analgesic properties. In the same year, Borg and Krijnen [27] reported long-term intrathecal administration of midazolam and clonidine in patients with refractory musculoskeletal pain persisting more than 2.5 years and they used intrathecal midazolam up to 6 mg/day which showed promising result, and they reported that this high dose did not cause any neurological deficits in those patients suffering with chronic refractory musculoskeletal pain. Bozkurt et al. [28] in 1997 studied the histological change following epidural administration of midazolam in neonatal rabbit and showed that 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. The toxic effects of acidic saline and midazolam are similar; in view of these results the epidural use of acidic midazolam (commercially available preparations) in neonates should be avoided. Bahar et al. [29] in 1997 examined in an animal model whether intrathecal midazolam, alone or with fentanyl, can achieve anaesthesia sufficient for laparotomy, comparable to lidocaine and concluded that midazolam, when injected intrathecally, produces reversible, segmental, spinally mediated antinociception, sufficient to provide balanced anaesthesia for abdominal surgery without any adverse effect.

In 1999, Nishiyama et al. [30] conducted histopathological study in cats with intrathecal midazolam. The purpose of this study was to investigate whether spinally administered midazolam induces acute-phase histopathological or inflammatory reactions of the spinal cord and concluded that up to 6 h after direct exposure to midazolam, no acute histological damage or inflammatory reaction of the spinal cord was seen in the cats.

7. Human Clinical Evidence

In 1998, Nishiyama et al. [31] 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 side effects in patients undergoing laparotomy. Nishiyama et al. [32] 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. These results do not suggest that clinically useful doses of intrathecal or epidural midazolam are neurotoxic. In the same year, Güleç et al. [33] showed that caudal administration of a bupivacaine-midazolam mixture produces a longer duration of postoperative analgesia than a bupivacaine-morphine mixture and bupivacaine alone with sedation for 8–12 h postoperatively.

In 1999, Batra et al. [34] conducted study on postoperative analgesia following intrathecal administration of midazolam

with hyperbaric bupivacaine in combination, in patients undergoing knee arthroscopy. Results showed higher VAS score in patients received bupivacaine alone than patients received midazolam and bupivacaine combination. Requirement for recue analgesic was also delayed in midazolam group. Time to regression of sensory analgesia to L_5-S_2 level was longer in midazolam-bupivacaine group (267 ± 67.38) as compared to bupivacaine group (299.9 ± 41.4). They concluded that intrathecal administration of midazolam along with bupivacaine produces better postoperative analgesia.

In 2001, Kim and Lee [35] conducted a study to evaluate the postoperative analgesic effect of intrathecal midazolam when coadministered with bupivacaine in patients undergoing haemorrhoidectomy. The authors 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. The result suggested a dose-dependent effect of intrathecal midazolam.

In the same year, Sen and coworkers [36] reported that intrathecal midazolam produced significant postoperative pain relief together with antiemetic effect and tranquillity of patients of caesarean section delivery. Mahajan et al. [37] studied the effect of caudal bupivacaine and midazolam-bupivacaine mixture for postoperative analgesia in children undergoing genitourinary surgery and showed that caudal administration of midazolam-bupivacaine mixture significantly prolongs postoperative analgesia compared to bupivacaine alone.

In 2003, Shah et al. [38] conducted a study on intrathecal midazolam and they demonstrated augmented postoperative pain relief by the addition of midazolam to an intrathecal injection of buprenorphine and bupivacaine in patients undergoing lower abdominal surgery and adverse effects were minor and their incidence was similar in both groups.

In 2003, Bharti et al. [39] reported in their study that intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia in patients undergoing lower abdominal surgery. The duration of sensory block (i.e., time to regression to the S_2 segment) was significantly longer in the midazolam group than the bupivacaine group (218 min versus 165 min, $P < 0.001$) and duration of motor block was also prolonged in midazolam group than in the control group (on 180 min versus 250 min, $P < 0.001$). The duration of effective analgesia was longer in the midazolam group than in the control group (199 min versus 103 min, $P < 0.001$) and no significant adverse effects were recorded in midazolam group. They concluded in their study that the addition of intrathecal midazolam to bupivacaine significantly improves the duration and quality of spinal anaesthesia and provides prolonged perioperative analgesia without any significant side effects.

In 2004, Tucker et al. [40] conducted a cohort study to investigate the safety of use of intrathecal midazolam. They investigated the potential of intrathecal midazolam to produce symptomatology suggestive of neurological damage. This study compared two cohorts of patients who received intrathecal anaesthesia with or without intrathecal midazolam (2 mg). Eighteen risk factors were evaluated with respect to symptoms representing potential neurological complications. The definitions of these symptoms were made wide to maximize the chance of counting patients with neurological sequel after intrathecal injections. Eleven-hundred patients were followed up prospectively during the first postoperative week by a hospital diagram review and 1 month later by a mailed questionnaire. Symptoms suggestive of neurological impairment, including motor or sensory changes and bladder or bowel dysfunction, were investigated. They concluded that intrathecal midazolam was not associated with an increased risk of neurologic symptoms and the administration of intrathecal midazolam, 2 mg, did not increase the occurrence of neurologic or urologic symptoms, as suggested by some preclinical animal experimentation.

Tucker et al. [41] investigated the use of intrathecal midazolam fentanyl combination for labour pain. In this study they assessed the ability of intrathecal midazolam to increase the potency and duration of the analgesic effects of intrathecal fentanyl without causing adverse effects. Thirty parturients with cervical dilations 2–6 cm were randomized to receive either intrathecal midazolam 2 mg, fentanyl 10 μg, or both combined to initiate analgesia. Pain scores were recorded before and at 5 min intervals for 30 min after the injection and then every 30 minutes until the patient requested further analgesia. The presence and severity of nausea, emesis, pruritus, headache, and sedation, in addition to arterial blood pressure, heart rate, and respiratory rate, sensory changes to ice, motor impairment, cardiotocograph, and Apgar score were also recorded. The parturient were assessed after 2 days and 1 month for neurologic impairment. Preinjection pain scores were unaltered by intrathecal midazolam alone and moderately decreased by fentanyl. Intrathecal midazolam increased the analgesic effect of fentanyl. No treatment altered cardiorespiratory variables or caused motor impairment. The addition of intrathecal midazolam to fentanyl did not increase the occurrence of any maternal adverse event or abnormalities on the cardiotocograph. They concluded that intrathecal midazolam enhanced the analgesic effect of fentanyl without increasing maternal or fetal adverse effects.

In 2004, Yegin et al. [42] conducted study on analgesic and sedative effects of intrathecal 2 mg preservative free midazolam in perianal surgery under spinal anaesthesia. They found that the postoperative VAS scores were significantly lower at the first 4 hours in patients who received bupivacaine-midazolam combination than bupivacaine alone and the average time until the first dose of rescue analgesic requirement was significantly longer. However, sedation scores were significantly higher in patients receiving midazolam. They concluded that the addition of bupivacaine produces a more effective and longer analgesia with a mild sedative effect in patient under spinal anaesthesia following use of 2 mg of intrathecal midazolam in experimental group.

In 2005, Agrawal et al. [43] conducted a study on postoperative pain relief following intrathecal administration of 1 mg preservative free midazolam with bupivacaine in patients scheduled for elective lower abdominal, lower limb, and

endoscopic urological surgeries. Time to first rescue analgesic in patients who received bupivacaine alone were significantly earlier than the patients who received bupivacaine and midazolam combination (4 ± 3.5 hours versus 17.6 ± 8.87 hours, $P < 0.0001$). They concluded that intrathecal midazolam and bupivacaine provides longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone without prolonging time for dermatomal regression. The authors also reported no episodes of bradycardia, hypotension, pruritus, urinary retention, and sedation related to midazolam.

In 2006, Prochazka [44] shared their experience of 10 years of using intrathecal midazolam. According to them intrathecal midazolam is able to assure good analgesia in most of the patients and is very useful and suitable supplement for postoperative and long-term analgesia without demand of expensive systems.

Prakash et al. [45] evaluated the efficacy of two dosage of intrathecal midazolam with bupivacaine in patients undergoing caesarean section. They concluded that intrathecal midazolam 2 mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine in patients undergoing caesarean delivery. Intrathecal midazolam, 1 mg and 2 mg, decreased postoperative nausea and vomiting also.

In 2007, Gupta et al. [46] investigated the effect of intrathecal midazolam in lower limb orthopedic surgery. In this study they investigated the postoperative analgesic efficacy of intrathecal midazolam 2.5 mg as an adjunct to bupivacaine for spinal anaesthesia in 80 patients undergoing lower limb orthopedic surgery. Mean duration of postoperative analgesia was significantly lower in patients who received bupivacaine alone in comparison to patients who received midazolam-bupivacaine combination (258 ± 37 min versus 412 ± 57 min, $P < 0.001$). Supplemental analgesic dose requirements with diclofenac were significantly less in midazolam-bupivacaine group (2.17 ± 0.50 versus 3.00 ± 0.39, $P < 0.001$). Time to onset of sensory analgesia, maximum level of sensory block, time to reach it, and time to two-segment regression were comparable. They concluded that intrathecal midazolam 2.5 mg provided moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine.

Yun et al. [47] studied the effect of 1 and 2 mg intrathecal midazolam added with bupivacaine on the duration of spinal anaesthesia up to T10 in orthopaedic surgery and concluded the prolongation of analgesia in midazolam group.

In 2008, Ho and Ismail [48] did a meta-analysis to evaluate the effectiveness and the side effects of intrathecal midazolam in postoperative and peripartum setting and found that intrathecal midazolam appears to improve perioperative analgesia and reduce nausea and vomiting during caesarean delivery.

In 2009, Jaiswal et al. [49] studied epidural midazolam and butorphanol for labour analgesia and concluded that epidural butorphanol and midazolam can be useful and safe adjuncts to bupivacaine used for epidural analgesia during labour.

In 2010, Dureja et al. [50] studied the efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of postherpetic neuralgia involving lumbosacral dermatomes. They concluded that the combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with postherpetic neuralgia of lumbosacral dermatomes due to the complementary antinociceptive action of intrathecal midazolam with epidural methylprednisolone on spinal nerve roots.

Shadangi et al. [51] in 2011 concluded that the addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block. Midazolam has been investigated as an adjuvant with lignocaine also. Talebi et al. [52] in 2010 found that administration of intrathecal midazolam (especially 1 mg) together with lidocaine is effective in reducing postoperative pain in patients undergoing open inguinal herniorrhaphy and is not associated with adverse effect. In a recent study published in 2012 Joshi et al. [53] found that midazolam provides superior analgesia to clonidine in subarachnoid block with fewer adverse effects.

8. Conclusion

Addition of preservative free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block in infraumbilical surgery 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). Intrathecal midazolam does not have any clinically significant effect on perioperative hemodynamics. A small diluted dose (1 to 2.5 mg, <1 mg/mL concentration) of preservative-free intrathecal midazolam appears to have few systemic side effects and is free of short-term neurotoxicity.

Conflict of Interests

The authors declare that they have no conflict of interests.

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