



Intrathecal Midazolam: A Review on the Drug's Pharmacological Features, as Well as Its Therapeutic Efficacy and Side Effects

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Spinal anaesthesia with lignocaine was highly popular earlier for short surgical procedures as it had a predictable onset and provided dense sensory and motor blockade of moderate duration. Unfortunately, some reports of neurotoxicity had cast doubts on the intrathecal use of lignocaine. Post operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal hyperbaric bupivacaine (0.5%) by adding various drugs such as opioids, midazolam, clonidine, ketamine, neostigmine etc. Discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam for analgesia.

Methodology: This review article was prepared after a thorough study of the literature using data search engine such as 'Pubmed'. This article referred to prior Randomized Controlled Trial (RCT) on Intrathecal Midazolam.

Review Findings: Midazolam is a potent short acting benzodiazepine that has been shown to have

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anti-nociceptive effects when administered intrathecally both in laboratory animals and in humans. Preservative free midazolam is also being used in recent times. As an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. It is said to be associated with less side effects compared to neuraxial opioids.

Conclusion: Intrathecal midazolam can be used for postoperative pain relief. It can prolong the duration of analgesia and prolonged motor and sensory block without any significant hemodynamic compromise.

Keywords: Intrathecal; midazolam; spinal anaesthesia; pain; post-operative.

1. INTRODUCTION

Midazolam was the first benzodiazepine that was produced primarily for use as a pre- anaesthetic. It is a water soluble short acting benzodiazepine with potency 2-3 times that of diazepam [1,2]. Post operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal hyperbaric bupivacaine (0.5 %) by adding various drugs such as opioids, clonidine, ketamine, neostigmine etc. However each drug has its own limitations and a need for alternative method or drug always exists.

Discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam for analgesia. Several studies have shown that intrathecal or epidural administration of midazolam produces a dose dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory depression or significant sedation. Intrathecal midazolam caused spinally mediated antinociception involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. Preservative free midazolam is also being used in recent times as an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. It is associated with fewer side effects compared to neuraxial opioids [1,2].

Midazolam belongs to the benzodiazepine group but unlike most drugs of this group it is water soluble. This is because its formula includes an imidazole ring which opens at pH values below 4.0, imparting water solubility. At the pH of plasma, the ring closes and lipid solubility is enhanced [1]. Its pka is 6.15. In solution it is buffered to an acidic pH of 3.5. It is more lipid soluble compared to diazepam and lorazepam.

2. METHODOLOGY

This review article was prepared after a thorough study of the literature using data search engine

such as 'Pubmed'. The time period was taken for 20 years from 2000 to 2020. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews are also hand-searched and the process above is performed repeatedly until no further article is identified. The inclusion criteria are as follows: (1) the study population is patients undergoing surgery (below the umbilicus); (2) the intervention treatments are intrathecal midazolam intervention versus placebo; and (3) the study design is RCT (Randomized Controlled Trial). No ethical approval and patient consent are required, because all analyses are based on previous published studies. On our search, we found 15 RCTs from 2000 to 2020 that comes under the inclusion criteria of this study.

3. REVIEW FINDINGS

1. In 2001, A Sen, A Rudra, S K Sarkar, B Biswas [3] conducted a study in which 40 women of ASA I/II to evaluate postoperative pain relief using intrathecal midazolam in caesarean section delivery. Group A patients (n=20) received 1.5 ml of 5% lignocaine only and group B patients (n=20) received mixture of 1.5 ml 5% lignocaine with 2 mg midazolam (preservative free) through intrathecal route at L3.4 interspace; vital parameters were monitored intra-operatively and postoperatively and Apgar score of baby in 1st and 5th minute of delivery was assessed. It was observed intrathecal midazolam produced highly significant ($p < 0.001$) postoperative pain relief together with anti-emetic effect and tranquillity of patients of caesarean section delivery.
2. M H Kim, Y M Lee [4] in 2001 conducted a study entitled "Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy", where they found that 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.

3. F R Shah , A R Halbe, I D Panchal, C S Goodchild, [5] in 2003 found in their study that intrathecal midazolam 2 mg improves the quality and duration of postoperative pain relief afforded by intrathecal buprenorphine and bupivacaine.
4. N Bharti, R Madan, P R Mohanty, H L Kaul, [6] in 2003 conducted a study in which forty ASA I or II adult patients undergoing lower abdominal surgery were selected for the study. The patients were randomly allocated to receive 3 ml of 0.5% hyperbaric bupivacaine intrathecally either alone or with 1 mg of midazolam using a combined spinal epidural technique. The duration and quality of sensory and motor block, perioperative analgesia, haemodynamic changes, and sedation levels were assessed. They concluded from 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 significant side-effects.
5. Adam P Tucker , Joseph Mezzatesta, Raymond Nadeson, Colin S Goodchild, [7] in 2004 conducted a study entitled "Intrathecal midazolam II: combination with intrathecal fentanyl for labor pain". In the study thirty parturients with cervical dilations 2-6 cm were randomized to receive either intrathecal midazolam 2 mg, fentanyl 10 micro g, 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, respiratory rate, sensory changes to ice, motor impairment, cardiococograph, and Apgar score were also recorded. The parturients were assessed after 2 days and 1 mo 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 cardiococograph. They concluded that intrathecal midazolam enhanced the analgesic effect of fentanyl without increasing maternal or fetal adverse effects.
6. A Yegin , S Sanli, L Dosemeci, N Kayacan, M Akbas, B Karsli, [8] in 2004 conducted a study "The analgesic and sedative effects of intrathecal midazolam in perianal surgery", where it was found that the use of intrathecal midazolam combined with intrathecal bupivacaine produces a more effective and longer analgesia with a mild sedative effect in perianal surgery.
7. Yu-Wha Wu, Jieh-Min Shiau, Chao-Chun Hong, Chih-Peng Hung, Hsiao-Feng Lu, Chia-Chih Tseng, [9] in 2005 conducted a study entitled "Intrathecal midazolam combined with low-dose bupivacaine improves postoperative recovery in diabetic mellitus patients undergoing foot debridement", where they found that the combination of intrathecal midazolam and bupivacaine was a safe and effective anesthetic technique, and it also provided early recovery of motor function and reduced the requirement of analgesics postoperatively.
8. In 2006, Mehdi Boussofara, Michel Carlès, Marc Raucoules-Aimé, Mohamed Riadh Sellam, Jean-Louis Horn, [10] in their study "Effects of intrathecal midazolam on postoperative analgesia when added to a bupivacaine-clonidine mixture", found that addition of midazolam to an intrathecal bupivacaine-clonidine mixture does not potentiate postoperative analgesia but prolongs the motor blockade.
9. In 2006, Smita Prakash, Nandita Joshi, Anoop R Gogia, Sunil Prakash, Rajvir Singh, [11] in their study found that Intrathecal midazolam 2 mg provided a moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine in patients undergoing

- cesarean delivery. Intrathecal midazolam, 1 mg and 2 mg, decreased postoperative nausea and vomiting.
10. In 2008, T Murali Krishna, N B Panda, Y K Batra, S Rajeev, [12] conducted a study entitled "Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery". They concluded from their study that a low dose of midazolam and ketamine with bupivacaine intrathecally results in prolonged analgesia and less haemodynamic fluctuations.
 11. H Talebi, B Yazdi, S Alizadeh, E Moshiry, A Nourozi, P Eghtesadi-Araghi, [13] in 2010 made an assessment of the effect of combination of intrathecal midazolam and lidocaine on postoperative pain. This randomized controlled trial was performed on forty five male patients who were candidates for elective inguinal herniorrhaphy and randomly divided into three groups of control (lidocaine 5% plus normal saline), M 0.5 (lidocaine 5% and midazolam 0.5 mg) and M 1.0 (lidocaine 5% and midazolam 1 mg) according intrathecal solution injected for spinal anesthesia. The findings of their study suggest that administration of intrathecal midazolam (especially 1 mg) together with lidocaine is effective in reducing post-operative pain in patients undergoing open inguinal herniorrhaphy and is not associated with adverse effect.
 12. G P Dureja, Hammad Usmani, Mozaffar Khan, Mohd Tahseen, Aslam Jamal, [14] in 2010 conducted a study where they wanted to quantify the effectiveness of a single intrathecal injection of midazolam 2 mg with and without epidural methylprednisolone 60 mg for management of pain and allodynia in 150 adult patients with postherpetic neuralgia of 3-6 months duration involving lumbosacral dermatomes. The study concluded that the combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with post herpetic neuralgia of lumbosacral dermatomes due to the complementary anti nociceptive action of intrathecal midazolam with epidural methylprednisolone on spinal nerve roots.
 13. B K Shadangi, R Garg, R Pandey, T Das [15] in 2011 conducted a study in which a total of 100 patients scheduled for elective lower abdominal, lower limb and gynaecological procedures were selected to participate in this prospective, randomised, double-blind study. Patients were randomly allocated into two groups for intrathecal drug administration. Group B received 3 mL 0.5 percent bupivacaine with 0.4 mL saline, and group BM received 3 mL 0.5 percent bupivacaine and 0.4 mL (2 mg) midazolam mixture. The onset, duration of sensory/motor block, time to first rescue analgesia and side effects were noted. They concluded from their study that the addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block.
 14. Aloka Samantaray, Natham Hemanth, Karunakar Gunnampati, Hemalatha Pasupuleti, Madhusudan Mukkara, Mangu Hanumantha Rao [16] in 2015 conducted a study entitled "Comparison of the effects of adding dexmedetomidine versus midazolam to intrathecal bupivacaine on postoperative analgesia", where they found the addition of dexmedetomidine (5 mcg) to 3 mL of intrathecal hyperbaric bupivacaine (0.5%) significantly prolongs the duration of effective analgesia in comparison to 1 mg midazolam or placebo (0.9% normal saline) with a comparable incidences of side effects.
 15. Francis Codero, Mung'ayi Vitalis, Sharif Thikra [17] in 2016 conducted a study where a total of 40 patients undergoing lower limb orthopaedic surgery under spinal anaesthesia were randomized to two groups. Group 1: 2.6mls 0.5% hyperbaric bupivacaine with 0.4mls (20micrograms) fentanyl Group 2: 2.6mls of 0.5% hyperbaric bupivacaine with 0.4mls (2mg) midazolam. They found that there was no significant difference in the duration of effective analgesia between adjuvant intrathecal 2 mg midazolam as compared to intrathecal 20 micrograms fentanyl for patients undergoing lower limb orthopaedic surgery.

4. DISCUSSION

Midazolam is rapidly absorbed from gastro intestinal tract and promptly pass across blood brain barrier. Midazolam is highly protein bound (approximately 95%), though not as highly bound as diazepam. The practical implication of this is

that patients with a low plasma albumin from any cause will have an enhanced response to it. The drug follows the usual distribution pattern to vessel-rich tissues and later to the poorly perfused fat. [1,2] Elimination is then dependent on hepatic biotransformation, which converts it into 4-hydroxymidazolam, a metabolite almost devoid of pharmacological activity. The initial redistribution is shorter than that of diazepam, contributing to the more rapid recovery from the newer drug. The elimination phase ($t_{1/2\beta} = 2-3$ hours) is also more rapid than with diazepam, though slower than thiopentone or propofol [1,2].

4.1 Intrathecal Effect of Midazolam

4.1.1 Central nervous system [1,2]

This group of drugs acts on specific benzodiazepine receptors which are concentrated in the cerebral cortex, hippocampus and cerebellum. Their action is produced by potentiation of specific depressant inter neurons which use gamma aminobutyric acid (GABA) as a transmitter. The release of GABA opens the Cl⁻ channel, resulting in hyperpolarisation of the nerve cell. Amnesia which is an effect common to all benzodiazepines can be undesirable, but in dental practice, for instance, may be a valuable adjunct to therapy. Other CNS effects of midazolam which may be required include an anticonvulsant action (e.g., in status epilepticus) and an anti hallucinatory action (e.g., after ketamine or in delirium tremens).

4.1.2 Cardiovascular system [1,2]

Even in large doses the benzodiazepines have little depressant effect on the heart or circulation. Midazolam causes a fall in systemic vascular resistance rather than the rise as seen with thiopentone, thus reducing pre and afterload. While this effect may benefit the patient with a failing heart, it does introduce hazards in hypovolaemic patients. Because of the slow onset of action, any cardiovascular depression with the benzodiazepines is often underestimated, though in clinical practice, if used in a fullgeneral anaesthetic technique, tracheal intubation may counterbalance any cardiovascular depression.

4.1.3 Respiratory system [1,2]

Intravenous injection and intrathecal use of the benzodiazepines in general can cause respiratory depression, in contrast to the notable

safety of this group for oral medication. The depression includes loss of sensitivity to carbon dioxide and this is accentuated by the concomitant use of opioids. These effects in turn are more marked in patients with chronic obstructive airway disease. The use of intravenous benzodiazepines by those not skilled in airway management can lead to unrecognized respiratory obstruction. It is therefore, highly dangerous to assume that sedation with midazolam is a safe alternative to anaesthesia, permitting the presence of an anaesthetist to be dispensed with.

4.1.4 Local effects [1,2]

Midazolam, as an aqueous solution, has no irritant effects following intravenous injection. This is seen both in the lack of pain on injection and the absence of venous squeal [1].

Metabolism- Midazolam undergoes extensive hydroxylation by hepatic microsomal oxidative mechanisms (Cytochrome P 450 3A) to form 1 hydroxy midazolam and 4-hydroxy midazolam (smaller amounts). These water-soluble metabolites are excreted in urine as glucuronide conjugates [1,2].

Renal Clearance- The elimination half-time, volume of distribution (Vd) and clearance of midazolam are not altered by renal failure. This is consistent with the extensive hepatic.

Some of the side effects of midazolam are:- [1,2]

- Headache
- Drowsiness
- Shallow breathing
- Nausea
- Vomiting
- Hiccups
- Coughing
- Pain, redness, or hardening of the skin at the injection site

Some of the other routes of administration of midazolam are as follows – Intramuscular, intranasal, intravenous and via nebulization [1,2].

5. CONCLUSION

Midazolam, despite of being the commonest benzodiazepine used in anaesthesia and perioperative care, is a relatively newer addition to the list of adjuvants 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. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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