Minireview Article

Title:- Intrathecal midazolam: A review on the drug's pharmacological features, as well as its therapeutic efficacy and side effects.

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 motorblockade of moderate duration. Unfortunately, some reports of neurotoxicity had castdoubts 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[2], ketamine[3], neostigmine[4] 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 engines such as 'Scopus',' Pubmed', 'Web of Science', and 'Google Scholar'. This article referred to prior Intrathecal Midazolam observational studies and case reports.

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

INTRODUCTION:

Midazolam was the first benzodiazepine that was produced primarily for use in anaesthesia. It is a water soluble short acting benzodiazepine with potency 2-3 times that of diazepam.

Chemical structure and physiochemical properties-

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]

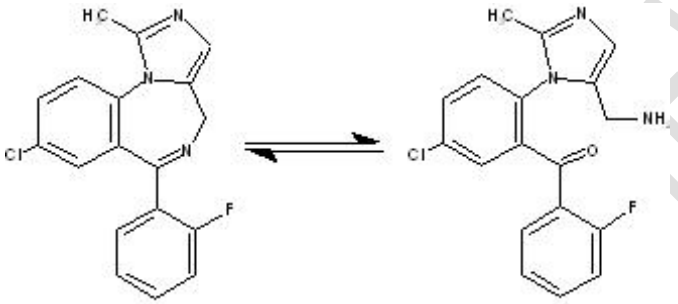

Figure 1: Chemical structure of midazolam.

Its pka is 6.15. In solution it is buffered to an acidic pH of 3.5. It is more lipid solublecompared to diazepam and lorazepam.

Pharmacokinetics[1] -

Midazolam is rapidly absorbed from gastro intestinal tract and promptly pass acrossblood brain barrier. Midazolam is highly protein bound (approximately 95 %), thoughnot as highly bound as diazepam. The practical implication of this is that patients witha low plasma albumin from any cause will have an enhanced response to it. The drugfollows the usual distribution pattern to vessel-rich tissues and later to the poorlyperfused fat. Elimination is then dependent on hepatic biotransformation, whichconverts it into 4-hydroxymidazolam, a

metabolite almost devoid of pharmacologicalactivity. The initial redistribution is shorter than that of diazepam, contributing to themore rapid recovery from the newer drug. The elimination phase (t½ β = 2-3 hours) isalso more rapid than with diazepam, though slower than thiopentone or propofol.Elimination is prolonged in elderly patients and following any major surgery (t1/2 β =approximately 5 hours), the latter presumably by interfering with hepatic blood flow.Placental transmission, as judged by the fetal / maternal plasma ratio in animals, isless for midazolam than for diazepam.

Pharmacodynamics[1,2] **-**

CENTRAL NERVOUS SYSTEM

This group of drugs acts on specific benzodiazepine receptors which are concentratedin the cerebral cortex, hippocampus and cerebellum. Their action is produced bypotentiation of specific depressant interneurons which use gamma aminobutyric acid(GABA) as a transmitter. The release of GABA opens the Cl- channel, resulting inhyperpolarization of the nerve cell. In this connection it should also be noted that thespecific benzodiazepine antagonist, flumazenil acts by competitive inhibition of thesebenzodiazepine receptors, thereby blocking the action of midazolam.

The onset of action is slow and the onset of sleep takes 2-5 minutes but with wideinterpatient variation. Similarly, the dose required to induce sleep ranges widelyaround 0.3 mg / kg. However, lower doses (0.05-0.1 mg / kg) will produce drowsinessand amnesia, which is often all that is required in the clinical situation. Amnesiawhich is an effect common to all benzodiazepines can be undesirable, but in dentalpractice, for instance, may be a valuable adjunct to therapy. Other CNS effects ofmidazolam which may be required include an anticonvulsant action (e.g., in statusepilepticus) and an antihallucinatory action (e.g., after ketamine or in deliriumtremens).

CARDIOVASCULAR SYSTEM

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

RESPIRATORY SYSTEM

Intravenous injection 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 safealternative to anaesthesia, permitting the presence of an anaesthetist to be dispensedwith.

LOCAL EFFECTS

Midazolam, as an aqueous solution, has no irritant effects following intravenousinjection. This is seen both in the lack of pain on injection and the absence of venoussequelae.[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. These metabolites have pharmacological activity, although it is less than that of parent compound. In contrast to diazepam, H2 receptor antagonists do not interfere with the metabolism of midazolam. But the drugs that inhibit cytochrome P-4503A (erythromycin and (Ca+2 channel blockers) may decrease the hepatic clearance, resulting in CNS depression. Cytochrome P-4503A also influences the metabolism of fentanyl. In this regard, the hepatic clearance of midazolam is inhibited by fentanyl as administered during general anesthesia. Overall, the hepatic clearance rate of midazolam is five times greater than that of lorazepam and ten times greater than that of diazepam.[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 metabolism of midazolam.[1,2]

Clinical uses[1]**-**

1. Preoperative medication in pediatric age group 0.5 mg/kg orally 30 minutes before induction. 0.05–0.1 mg/kg IM 0.1 – 0.15 mg/kg by jet injection. The causes are:
    a) Sedation.
    b) Anxiolysis

c) Anterograde amnesia.

2. Intravenous sedation: Dose 1 – 2.5 mg IV for regional anesthesia as well as per brief therapeutic procedures.

3. Induction of anesthesia: Dose 0.1 – 0.2 mg/kg IV over 30 – 60 seconds.

METHODOLOGY:

This review article was prepared after a thorough study of the literature using data search engines such as 'Scopus',' Pubmed', 'Web of Science', and 'Google Scholar'. This article referred to prior Intrathecal midazolam observational studies and case reports.

REVIEW FINDINGS:

Edwards M, Serrao M Juliet and Goodchild CS in 1990 conducted a study to findout the mechanism by which midazolam causes spinally mediated analgesia. Theelectrical current thresholds for pain (ECTP) in the skin of the neck and tail weremeasured in rats with chronically implanted lumbar subarachnoid catheters. Theeffects of a benzodiazepine antagonist flumazenil and a gamma-aminobutyric acid(GABA) antagonist bicuculline on the analgesic effects of equivalent doses ofmidazolam, fentanyl and ketocyclazocine were studied. The authors concluded thatthe segmental analgesia produced by intrathecal midazolam is mediated by thebenzodiazepine-GABA receptor complex that is involved in other benzodiazepineactions.[(3)]

Serrao M Juliet, Marks L Ray, Morley J Stephen, and Goodchild CS (1992)carried out a prospective, randomized, double-blind comparative study of intrathecalmidazolam (2 mg) with epidural steroid (methyl prednisolone 80 mg) for chronicmechanical low back pain on 28 patients. It was observed that improvements in bothgroups were similar. However all the patients treated with the steroid methylprednisolone were either taking more or same amount of self-administered analgesicmedication after their treatment during 2 month follow up period, whereas betweenone third and one half of midazolam treated patients took less medication during the 2month follow up period. Thus, they concluded that intrathecal midazolam is aneffective treatment for chronic mechanical low back pain. This study demonstrates theantinociceptive effect of intrathecal midazolam and its comparison to theantinociceptive effect of epidural steroids.[(4)]

Naguib Mohammed, Gammal ME, Elhattab YS, and Seraj M in 1995 evaluatedthe analgesic efficacy of caudal administration of midazolam in children undergoingunilateral inguinal herniotomy. 45 children of ASA physical status 1and 2 weredivided into three groups of 15 each on a random basis. Group 1 received midazolam50 micrograms / kg alone, group 2 received bupivacaine 0.25 % 1 mg / kg alone, andgroup 3 received both. They concluded that times to first analgesic administration(paracetamol suppositories) were longer in bupivacaine midazolam group than inother two groups. Further, the bupivacaine midazolam group received fewer doses ofrescue analgesics than the other two groups. They concluded that caudal midazolamin a dose of 50 micrograms / kg provides equivalent analgesia to bupivacaine 0.25 %,when administered post operatively in a volume of 1 ml / kg for children followingunilateral inguinal herniotomy.(5)

JMJ Valentine, Lyons G and Bellamy MC (**1996**) evaluated the efficacy ofintrathecal midazolam as a post operative analgesic in parturient posted for electivecaesarean section. They conducted a study on 52 patients of ASA physical status 1scheduled for elective caesarean section, randomly allocated to receive eitherbupivacaine, bupivacaine with diamorphine, bupivacaine with midazolam or all thethree bupivacaine, midazolam and diamorphine (BMD) intrathecally. Patientcontrolled analgesia system (PCAS) usage was significantly greater in bupivacainegroup than in the other groups. There was not much side effects attributed tointrathecal midazolam. Intrathecal midazolam thus appeared safe and had clinicallydetectable analgesic properties.(6)

Batra YK, Chari P, Dhillon MS, Shaheen B, Reddy GM and Jain K in 1999designed a study to evaluate the post operative analgesic effect of intrathecalmidazolam-bupivacaine mixture on 30 healthy patients undergoing knee arthroscopy,divided into 2 groups of 15 each to receive either bupivacaine alone or midazolam-bupivacainemixture. Visual analogue score, time to block regression, recovery toambulation and ability to void were recorded. The results suggested that addition ofmidazolam to bupivacaine provided better post operative analgesia than the controlgroup with lower VAS score. They concluded that intrathecal administration ofmidazolam along with bupivacaine enhances the quality and duration of postoperative analgesia without any side effects.(7)

MH Kim and YM Lee (**2001**) conducted a double-blind study to evaluate theanalgesic effects of intrathecal midazolam bupivacaine combination in comparisonwith bupivacaine in 45 patients undergoing haemorrhoidectomy. Patients weredivided into 3 groups, control group receiving 1 ml of 0.5 % bupivacaine with 0.2 mlof 0.9 % saline, BM1group receiving 1 ml of bupivacaine 0.5 % + 0.2 ml ofpreservative free midazolam and group BM2 receiving

0.5 % bupivacaine 1 ml + 0.4ml of 0.5 % midazolam. The following parameters were assessed in the study -duration of effective analgesia from the time of administration of spinal anaesthesia,

visual analogue scores at first analgesia and total consumption of analgesics in 24hours after spinal anesthesia. They concluded that the analgesic effect of intrathecalbupivacaine was potentiated by intrathecal midazolam. The addition of 1 or 2 mg ofmidazolam prolonged the post operative analgesic effect of bupivacaine by 2 hoursand 4.5 hours respectively. In addition, midazolam treated patients used less analgesics in the first 24 hours after surgery.[8]

Choi DH, Choi HS and Ahn HJ in 2001 carried out a study to compare the analgesiceffects of intrathecal bupivacaine fentanyl combination with epidural bupivacaine incombined spinal epidural anaesthesia for caesarean section. Spinal anaesthesia viaCSEA technique was performed with 6 mg 0.5 % hyperbaric bupivacaine plus 20micrograms fentanyl in 75 parturient. Study group (n=38) received epidural injectionof 10 ml of 0.25 % bupivacaine 5 min after intrathecal injection and was comparedwith the control group (n=37). Recovery times from sensory and motor block and theduration of analgesia were assessed between the two groups. Supreme analgesiawithout higher blocks and more side effects was obtained afterepidural injection of 25mg bupivacaine.[9]

Dr BN Biswas, A Rudra, JK Saha and Karmakar S in 2002 conducted a study toevaluate the analgesic effect of intrathecal midazolam and fentanyl as additives to intrathecal hyperbaric lignocaine after inguinal herniorrhaphy. Sixty male patients ofage 40 to 60 years belonging to ASA 1and 2 were selected for study. These weredivided into three groups. Group A received intrathecal hyperbaric lignocaine (5 %)1.5 ml (75 mg), Group B received intrathecal hyperbaric lignocaine (5 %) 1.5 ml (75mg) with 2 mg midazolam intrathecally, and Group C received intrathecalhyperbaric lignocaine (5 %) 1.5 ml (75 mg) with fentanyl 25 microgramsintrathecally. They concluded that both intrathecal midazolam and fentanyl prolonged theduration of post operative analgesia significantly compared to hyperbaric lignocaine (5 %) alone, but the differences in the duration of post operative analgesiawere not very much significant in fentanyl and midazolam groups.[10]

FR Shah, AR Halbe, ID Panchal and CS Goodchild in 2003 conducted aprospective double-blind study to evaluate the effects of intrathecal midazolam onaddition to a combination of buprenorphine and bupivacaine used for spinalanesthesia in 60 patients of ASA 1 and 2 physical status undergoing minor and lowerabdominal surgery under spinal anaesthesia. Patients were randomized into twogroups. The control group received hyperbaric bupivacaine of 0.5 % 3 ml plusbuprenorphine 0.15 mg. The test group received the same 2

drugs supplemented withintrathecal midazolam 2 mg.The duration of post operative analgesia in the controlgroup was 9.24 ± 2.57 hours and 21.33 ± 12.69 hours in the midazolam treated group.Patients in midazolam group had better pain relief judged by visual analogue score oncoughing and a nursing mobility score. Adverse effects were minor and theirincidence was similar in both groups. Thus, they concluded that intrathecal midazolam2 mg improves the quality and duration of post operative analgesia afforded byintrathecal combination of buprenorphine and bupivacaine.[11]

Dr P Rudra and Dr A Rudra in 2004 did a comparison between intrathecalmidazolam and fentanyl for prevention of post operative nausea and vomiting duringcaesarean section under spinal anaesthesia. 120 parturient of ASA physical status 1were selected for study. The incidences of intra operative and early post operativenausea and vomiting were recorded. They found out that incidence of intra operativeand early post operative nausea and vomiting was 75% with placebo group, 40% withmidazolam group, and 25% with fentanyl group. They concluded that coadministrationof 12.5 micrograms of fentanyl or 2 mg of midazolam in thesubarachnoid injectate avoid intra operative discomfort during peritoneal traction andexteriorization of uterus and there by significantly minimize the incidence of intraoperative and early post operative nausea and vomiting in caesarean delivery underspinal anaesthesia.[12]

Dr Nidhi Agrawal, Dr A Usmani, Dr R Sehgal, Dr Rakesh Kumar, and DrPoonam Bhadoria(2005) carried out a study on 53 healthy adult patients to comparethe efficacy of intrathecal bupivacaine with intrathecal bupivacaine midazolamcombination for post operative pain relief by randomly allocating patients into 2groups. Group B (n=24) received 3 ml (15 mg) 0.5 % heavy bupivacaine and 0.2 ml0.9 % saline as control group and study group BM (n=25) received 3 ml (15 mg) of0.5 % heavy bupivacaine and 0.2 ml (1 mg) midazolam. The groups did not differsignificantly as regards to the duration of surgery, time of onset of sensory block andtime to achieve maximum sensory block. The time of first rescue analgesic was 4 ±

3.5 hrs in group B and significantly longer in group BM (17.6 ± 8.87 hrs). The timefor regression of sensory block to S1 in group B was 164 ± 67 mins and in group BM158.6 ± 32.16 minutes. There were no episodes of bradycardia, hypotension, sedation,vomiting, pruritus and urinary retention. Thus, they concluded that the intrathecalcombination of midazolam and bupivacaine provides longer duration of post operativeanalgesia as compared to intrathecal bupivacaine alone without prolonging duration ofdermatomal sensory block.[13]

Rajvir (2006) investigated the post operative analgesic efficacy of 2 different dosesof intrathecal midazolam as an adjunct to bupivacaine for spinal anaesthesia in 60patients undergoing elective caesarean delivery allocated into 3 groups. Group Breceived 2 ml of bupivacaine 0.5 %, group BM1 received 2 ml of 0.5 % bupivacaine +midazolam 1 mg (preservative free) and group BM2 received 2 ml of 0.5 %bupivacaine + midazolam 2 mg. The mean duration of post operative analgesiadetermined by the request for rescue analgesic was 3.8 ± 0.5 hrs in group B whencompared with 4.3 ± 0.7 hrs in group BM1 and 6.1 ± 1.0 hrs in group BM2.Supplemental analgesic requirement with diclofenac, was significantly less in groupBM2 compared to group B & BMI. Time to regression of sensory block was longer ingroup BM2 compared to other two groups. Group B had significantly high incidenceof nausea and vomiting than other two groups. Thus, they concluded that intrathecalmidazolam 2 mg provided a moderate prolongation of post operative analgesia whenused as an adjunct to bupivacaine.(14)

KM Ho and H Ismail in 2008 did a meta-analysis to evaluate intrathecal midazolamin perioperative and peripartum settings. They considered thirteen randomizedcontrolled studies involving 672 patients. They found out that addition of intrathecalmidazolam to other spinal medications reduce the incidence of nausea and vomitingand delayed the time to request for rescue analgesia. They concluded that intrathecalmidazolam improves peri operative analgesia and reduces the incidence of nausea andvomiting during intra and post operative period. The incidence of neurologicalsymptoms after intrathecal midazolam was uncommon and did not defer greatly fromplacebo group. Intrathecal midazolam did not affect the duration of motor blockade.(15)

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.

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