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Research Article

Observation on analgesic efficacy and adverse effects of intrathecal administration of bupivacaine versus bupivacaine-midazolam combination in lower limb surgeries in a tertiary care hospital

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ABSTRACT

Background: Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life. Neuraxial blocks not only reduce the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding transfusion requirements and respiratory depressions but also provide effective postoperative analgesia. One of the methods of providing postoperative is to prolong the duration of intrathecally administered bupivacaine by using additives such as opioids such as midazolam, clonidine and ketamine. Intrathecal administration of midazolam induces antinociceptive effects in humans. The present study was undertaken to evaluate the additive analgesic effects of intrathecal midazolam in combination with bupivacaine in lower limb surgeries in a tertiary care hospital and to compare the results with the use of bupivacaine alone. The aim of this study was to observe and compare the quality of spinal anaesthesia and occurrence of side effects in thirty cases administered with bupivacaine and thirty cases administered with bupivacaine-midazolam combination.
Methods: Sixty cases admitted for lower limb surgery were divided into equal groups I and II. Cases in group I received intrathecal bupivacaine while those in group II received intrathecal combination of bupivacaine and midazolam. Data regarding quality of anesthesia and side effects were recorded and compared.
Results: There was a significantly higher duration of a pain-free period in cases administered with intrathecal combination of bupivacaine and midazolam.
Conclusions: Addition of preservative free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block prolongs the duration of effective analgesia as compared to bupivacaine alone. The utilization of intrathecal midazolam also decreases the incidence of postoperative nausea-vomiting.

Keywords: Anaesthesia, Bupivacaine, Combination, Intrathecal, Midazolam

INTRODUCTION

Dr. August Bier carried out the first spinal anaesthesia in 1899 and his anaesthetic technique has become the standard practice for lower extremity and abdominal surgery worldwide.[1] Nowadays, the most commonly used drugs for spinal anaesthesia are local anaesthetics. However, a major disadvantage of single injection spinal anaesthesia is its limited duration of action. In clinical practice, a number of adjuvants have been added to intrathecal local anaesthetics for supplementation of intraoperative anaesthesia and postoperative analgesia. They have advantages as they reduce the dose of local anaesthetic; 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 anaesthesia.[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] Benzodiazepines commonly used in the perioperative period include diazepam, midazolam, and lorazepam, as well as the selective benzodiazepine antagonist flumazenil. 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). Anaesthesiologically 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 anaesthetics in that their action can readily be terminated by administration of their selective antagonist flumazenil.[11,12] 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 extra hepatic sites. This has been demonstrated by the discovery of metabolites following intravenous injection of midazolam during the an hepatic 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 and this lipophilicity is responsible for its rapid CNS effect and large volume of distribution.[27,28] 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.

METHODS

After prior approval from the Institutional Ethics Committee (IEC), this randomized study was conducted in the Department of Anaesthesiology of Katihar Medical

College, Bihar, India. Sixty adult cases of either sex and between the ages of 20 to 70 years of ASA grade I and II that were admitted in the hospital for lower limb surgeries were included in this study. Data pertaining to age, sex and impending surgery of the patient was documented and each patient was clinically examined. Cases not falling in the age group and cases with diabetes mellitus, hypertension, hypotension, respiratory diseases, cardiac diseases, renal diseases, epilepsy, spinal defects, coagulopathy, increased intracranial tension and sepsis were excluded from the study. Pre-anaesthetic evaluation was performed. The sixty cases were divided into two groups of thirty cases each. The groups were I and II. Cases in group I received intrathecal 2.5 ml of 0.5% hyberbaric bupivacaine 12.5 mg with 0.4ml of midazolam. Cases in group II received intrathecal 2.5 ml of 0.5% hyberbaric bupivacaine 12.5 mg with 0.4ml (2 mg) of midazolam. No premedication was administered and spinal block was performed with 25G spinal needle in the L_3-L_4 intervertebral space in the sitting position.

The following parameters were recorded and monitored every two minutes for the first twenty minutes and then every five minutes till the completion of the surgery.

(1) Clinical parameters

(2) Level of sensory blockade

(3) Quality of intraoperative analgesia

(4) Motor power

(5) Time of two segments regression

(6) Side effects

Postoperatively, the cases were monitored within four hours of intrathecal injection or upon complete recovery of the sensory and motor functions whichever of the two was longer. Duration of total analgesia was recorded as the time between onset of analgesia to that of rescue analgesia. Duration of motor blockade was recorded as the time between onset to resolution of motor blockade.

RESULTS

Both the groups were comparable to each other in age, weight, gender and type of surgery involved. No significant difference in heart rate and blood pressure was observed. Time taken between administration of the drug and onset of motor block was less in group II. All sixty cases required anaesthesia during twenty four hours after surgery. However, the total number of oral administrations was significantly less in group II. There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients. Few patients from each group developed urinary retention and time for the first self-voiding was almost similar in both groups. No neurological deficits were detected at discharge.

Table 1: Duration for onset of sensory blockade in minutes.

Time in minutes	Group I	Group II
3-5	02	14
6-8	20	14
9-11	07	01
12-14	01	01
Total	30	30

Table 2: Duration for onset of motor blockade in minutes.

Time in minutes	Group I	Group II
6-8	00	00
9-11	18	17
12-14	11	12
15-17	01	01
Total	30	30

Table 3: Duration of motor blockade in minutes.

Time in minutes	Group I	Group II
111-120	00	00
121-130	01	01
131-140	05	04
141-150	06	05
151-160	09	08
161-170	05	09
171-180	04	03
Total	30	30

Table 4: Level of analgesia.

Spinal Level	Group I	Group II
T_4	00	00
T_5	00	00
T_6	00	00
T_7	04	03
T_8	09	12
T_9	06	05
T_{10}	11	10
Total	30	30

Table 5: Time for two segment sensory regression.

Time in minutes	Group I	Group II
41-60	02	00
61-80	10	01
81-100	13	01
101-120	03	06
121-140	01	19
141-160	00	02
161-180	01	01
181-200	00	00
Total	30	30

Table 6: Duration of analgesia.

Time in minutes	Group I	Group II
121-140	02	00
141-160	08	00
161-180	10	00
181-200	10	02
201-220	00	02
221-240	00	13
241-260	00	13
261-280	00	00
281-300	00	00
Total	30	30

Table 7: Post-operative side effects.

Spinal level	Group I	Group II
Hypotension	01	02
Nausea	02	01
Shivering	02	03
Heavy headedness	02	01
Pruritus	00	00

DISCUSSION

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 γ_2 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 α_1 GABA receptors and anxiolysis and centrally acting muscle relaxant properties are mediated by α_2 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] Spinal anesthesia is the most commonly used regional anaesthetic technique. Local anaesthetic 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 available 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), chronic and cancer pain.[36-39] 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 pen-tameric gammaaminobutyric acid (GABA-A) receptor. Agonist occupancy of the benzodiaze- pine 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. 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] Addition of preservative free midazolam to hyperbaric bupivacaine for spinal anaesthesia 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 haemodynamics. A small diluted dose of preservative-free intrathecal midazolam appears to have few systemic side effects and is free of short term neurotoxicity.

CONCLUSION

Spinal anaesthesia 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 anaesthesia are important disadvantages. On the other hand, the impediments to the effective use of spinal anaesthesia 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 anaesthesia. 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 haemodynamics and respiration during spinal anaesthesia. 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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