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Comparative study of hyperbaric bupivacaine and bupivacaine with midazolam in subarachnoid block for postoperative analgesia in perianal surgeries

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Abstract:

Subarachnoid block with bupivacaine is routinely administered for perianal surgeries. The ensuing nerve blockage is sufficient to facilitate the surgeon's work and also provides effective pain relief during the initial postoperative period. A number of adjuvants have been added to intrathecal bupivacaine to maximize postoperative analgesia. Intrathecal supplements for postoperative pain relief is becoming more popular as they eliminate the need for intravenous and intramuscular analgesics and their associated complications. Perianal surgeries are extremely painful and hence chosen for this study. Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecally administered bupivacaine by additives such as opioids, clonidine, ketamine, midazolam etc. Intrathecal opioids were used with success but with high incidence of side effects. Midazolam was taken as an alternative for opioids in this study. The duration of analgesia was significantly prolonged in the midazolam group ($p < 0.005$).

Key words: Bupivacaine; Intrathecal; Midazolam; Perianal Surgeries; Postoperative analgesia

Introduction

Spinal anesthesia with bupivacaine is routinely administered for perianal surgeries. Bupivacaine is a long acting, amide group, local anesthetic agent that is four times more potent than lignocaine. The maximum dose of bupivacaine is 2 mg/kg body weight and the minimal toxic blood concentration is 2 – 4 µg/ml which is 15 times more toxic when compared to lignocaine [1]. Bupivacaine provides effective pain relief in the initial postoperative period. Inorder to maximize the postoperative analgesia, a number of adjuvants have been added to bupivacaine. Discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam [2]. Intrathecal administration of midazolam produced anti-nociceptive effects in rats and humans [3]. GABA-A receptors in the spinal cord have been reported to be involved in nociceptive mechanisms [4]. Midazolam is a water soluble benzodiazepine with sedative, amnesic, anxiolytic, muscle relaxant and anti-convulsant properties [5,6]. Midazolam given by

intrathecal or epidural injection can also produce an anti-nociceptive effect. This may be Gamma Amino Butyric Acid (GABA) mediated. GABA has been shown to have analgesic properties. In human beings no adverse or irreversible effects have been observed after intrathecal or epidural administration of midazolam till date [7]. The present study was undertaken to evaluate the additive analgesic effects of intrathecal midazolam in combination with bupivacaine for perianal surgeries and to compare the results with bupivacaine alone.

Materials and Methods

This study was conducted at a Government Hospital in Chennai after obtaining approval from the ethical committee. A written informed consent was obtained from patients for participation in our study. Forty patients (ASA 1 & 2) in the age group of 20-50 years, height (155-170 cms) scheduled for perianal procedures were enrolled in this study. The patients were evaluated and those with contraindications to regional anesthesia were excluded from the study. Pre anesthetic evaluation was done for all the patients. Visual Analogue Scale (VAS) consisting of 100mm line with '0' representing no pain and '100' worst possible pain was explained to all the patients during the pre operative visit. Oral diazepam 0.2mg/kg was given to all the patients one and a half hours before the surgery.

In the operating room Boyle's apparatus was checked. Baseline electrocardiogram (ECG), non invasive blood pressure (NIBP), heart rate (HR), respiratory rate (RR) and arterial oxygen saturation (SpO2) were recorded before initiating spinal anesthesia.

The patients were randomly allocated into two groups of 20 patients each. After preloading the patients with Ringer lactate solution (15ml/kg), subarachnoid block was performed with patient in the lateral position using 25G Quincke's needle at L3-L4 interspace. Group 1 (n=20) received 1.6ml of 0.5% hyperbaric bupivacaine + 0.4ml of saline while Group 2 (n=20) received 1.6ml of 0.5% hyperbaric bupivacaine + 0.4ml (2mg) of preservative free midazolam (5mg/ml). After five minutes the patients were put in lithotomy position. ECG, SpO2, NIBP, RR and HR were monitored intraoperatively. The following parameters were analysed (a) time of injection of study solution (b) time of onset of sensory blockade (c) time of onset of motor blockade (d) time required for complete motor recovery (e) time for the VAS score to reach 50 (f) complications if any like hypotension, bradycardia, nausea, vomiting etc. Postoperatively VAS score was recorded half hourly. Duration of postoperative analgesia, defined as the time taken in the postoperative period for the patient to demand analgesia or when the VAS score was > 50 was recorded. Rescue analgesia was provided with injection diclofenac sodium 75mg intramuscularly. Duration from the time of completion of spinal injection to the time of rescue analgesic administration or VAS score greater than 50 was recorded in both the groups. Results obtained were subjected to statistical analysis.

Results

Total No of patients: 40.

Group 1: 20 (1.6ml of 0.5% hyperbaric bupivacaine with 0.4ml saline)

Group 2: 20 (1.6ml of 0.5%hyperbaric bupivacaine with 0.4ml ie 2mg of preservative free midazolam)

The male female ratio in both the groups were 3:1.

There were no significant difference in both the groups with respect to age, bodyweight, height, and ASA status. There were no statistical differences in the duration of surgery (p=0.9068), the onset of sensory blockade (p=0.89), motor blockade (p=0.989) and recovery from motor blockade (p=0.423) (Table 1). However there was a significant difference in the duration of analgesia which was 329.40± 33.28 minutes in Group 2 while it was 225.71 ± 13.42 minutes in Group 1 (p< 0.001).

Table 1: Comparision table of two groups

	Group 1 (in Mins)	**Group 2 (In Mins)**	**P Value**
Duration of Surgery	21.77 ± 5.57	21.65 ± 5.21	=0.9068
Duration of Analgesia	225.71 ± 13.42	329.40 ± 33.38	< 0.001
Duration of motor blockade	5.35 ± 1.30	5.35 ± 1.30	= 0.989
Duration of sensory blockade	3.45 ± 1.05	3.45 ± 0.94	=0.89
Recovery from motor blockade	156.75 ± 4.17	155.25 ± 4.67	=0.423

P < 0.005 is significant

Hypotension was observed in 3 (15%) of patients and 2 (10%) of patients in Groups 1 and 2 respectively. The incidence of nausea and vomiting was equal in both the groups 2 (10%) each. There was no incidence of bradycardia, dizziness, sedation or urinary retention in both the groups. (Table 2).

Table 2: Comparision table of two groups based on side effects

	Group 1	Group 2
Hypotension	3(15%)	2 (10%)
Bradycardia	0	0
Dizziness/ Sedation	0	0
Nausea / Vomiting	2 (10%)	2 (10%)
Urinary retention	0	0

Discussion

Bupivacaine a potent long acting amide local anesthetic blocks generation, propagation and oscillation of electrical impulses in the peripheral or central nervous system [8]. The sodium channel is the key target of bupivacaine [9]. Bupivacaine blocks sodium currents and rapidly inactivates potassium currents in the spinal horn neurons [10].

Every surgical procedure produces pain. Perianal surgeries are extremely painful postoperatively. Hence it was considered for our study. Intraoperative pain which continues into the postoperative period, is a matter of major concern as far as anesthetists are concerned. The importance of spinal anesthesia is well established, as it reduces the severity of postoperative pain and prolongs analgesia even after recovery from sensory and motor blockades. The main aim of our study was to prolong the period of postoperative analgesia by using additives to bupivacaine. Kim et al [11] and Prakash et al [12] administered intrathecal bupivacaine along with midazolam in either 1mg or 2mg doses and observed that the duration of postoperative analgesia was significantly prolonged with the addition of midazolam and the effect was dose dependent. Our study also demonstrated significant prolongation of postoperative analgesia with addition of 2mg of intrathecal midazolam. The time to first rescue analgesic was 329.40± 33.28 minutes in Group 2 as compared to 225.71 ± 13.42 minutes in Group 1 ($p< 0.001$).

Midazolam acts on benzodiazepine receptors (GABA-A receptors) which are found not only throughout the central nervous system including the spinal cord, but also in many other tissues like kidneys, liver and lungs [13]. The GABA-A receptors in the spinal cord have been reported to be involved in nociceptive mechanisms [14] and are found in highest concentration in lamina 2 or dorsal horn ganglia [15]. The administration of the benzodiazepine antagonist flumanezil and the GABA-A antagonist bicuculline has been reported to reverse the analgesic effect of intrathecal midazolam, suggesting that the anti-nociceptive actions are mediated via the benzodiazepine GABA-A receptor complexes. Intrathecal midazolam has also been suggested to be involved in the release of an endogenous opioid which acts at spinal delta receptors [16]. Midazolam 2mg given intrathecally has been found to be the optimum dose to relieve pain without causing any side effects [7,17,18]. Yegin et al [19] demonstrated postoperative analgesic effect of 2mg intrathecal midazolam was longer than that of the control group after perianal surgeries. Safety of neuraxial administration of midazolam in humans has been demonstrated by several studies [7,17,20]. Various other histopathological studies in animals [21,22] have shown that intrathecal midazolam does not cause any morphological changes in the spinalcord which are suggestive of midazolam induced neurotoxicity. Borg and Krijnen [23] also reported that the continuous intrathecal administration of midazolam and clonidine produced almost immediate and nearly complete pain relief without tolerance or side effects.

Intrathecal midazolam 1mg and 2mg have been reported to decrease postoperative nausea and vomiting [12]. However our study found 10% incidence in both the groups.

In a cohort study, Tucker et al [24] evaluated patients who received intrathecal midazolam and observed the patients for neurotoxicity. They concluded that the administration of 2mg midazolam did not increase the occurrence of neurological symptoms. Our study was mainly concentrated on the analgesic efficacy of bupivacaine midazolam combination. Moreover a larger study is required to study the side effect profile of midazolam.

Conclusion

Addition of preservative free midazolam 0.4ml (2mg) to 1.6ml of 0.5% hyperbaric bupivacaine intrathecally provides very good and prolonged postoperative analgesia without significant intraoperative and postoperative side effects in comparison with plain bupivacaine for perianal surgeries.

No significant alternations in the onset of sensory and motor blockades were noticed.

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