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Comparison of 0.5% Hyperbaric Bupivacaine with Midazolam Versus 0.5% Hyperbaric Bupivacaine Alone Intrathecally: Prospective Observational Study

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Abstract

Context: Neuraxial anesthesia is the preferred choice for infraumbilical surgeries due to its advantages. The incorporation of midazolam alongside local anesthetic drugs in spinal anesthesia has demonstrated positive outcomes. This study was undertaken to assess the effectiveness of midazolam in terms of analgesic and anesthetic efficacy, as well as potential adverse effects, in patients undergoing infraumbilical surgeries.

Aims: To compare the analgesic and anaesthetic effect of mixture of midazolam - bupivacaine as compared to bupivacaine alone in patients undergoing infra-umbilical surgeries under spinal anaesthesia.

Settings and Design: The present study is a prospective, observational study.

Methods and Material: Fifty patients posted for elective infra-umbilical surgery were randomly divided into two groups of 25 each for intrathecal drug administration. (n=25). After administration of block, patients were assessed for analgesic and anesthetic effect of the drug.

Statistical Analysis used: The study analyzed through the statistical programming software SPSS-22 and it involved the application of the student's t-test, with a significance threshold set at a P value of <0.05.

Results: Analgesic duration of patients in Midazolam Group was significantly longer compared to Bupivacaine Group for sensory block. More patients in the midazolam group were sedated and easily arousable.

Conclusions: This study concludes that the addition of intrathecal preservative-free midazolam to hyperbaric bupivacaine improved intra - operative anaesthesia and prolonged duration of analgesia. Also, it was observed that there was a significant reduction in the consumption of analgesics during the post-operative period in patients undergoing infra-umbilical surgeries without causing any significant haemodynamic changes.

Keywords: Infra-umbilical surgery; hyperbaric bupivacaine; midazolam; spinal anaesthesia.

Key Messages: The addition of 1mg of preservative free midazolam as an adjuvant to hyperbaric bupivacaine during intrathecal administration has been shown to extend the duration of post-operative

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analgesia. This approach not only minimizes adverse effects but also reduces the requirement for intraoperative and post-operative rescue analgesics. This effect is comparable to the benefits observed with the use of intrathecal opioids.

INTRODUCTION

Spinal anesthesia is a safe, affordable method providing surgical anesthesia and extended post-operative pain relief for infra-umbilical surgeries with benefits including rapid onset, effective sensory and motor blockade. Hyperbaric bupivacaine has side effects like hypotension; intrathecal adjuncts such as neostigmine and opioids are used but have limitations due to associated side effects. Midazolam enhances local anesthetic effects in spinal anesthesia by binding to GABAA-BZD-Cl- complexes in the spinal cord, resulting in analgesia without neurotoxicity.

This study examines the effects of intrathecal midazolam - bupivacaine versus bupivacaine alone, evaluating sensory block onset, anesthesia quality, pain relief duration, analgesic requirements, side effects, and complications.

MATERIALS AND METHODS

The study was a Prospective Observational Study conducted for a period of 18 months in a study population of patients who underwent infraumbilical surgeries in the department of Anaesthesia in a reputed Medical College in South Kerala, India during September 2019 to October 2021. This study included a sample size of (50) divided into 2 groups randomly by the consultant anesthesiologist – group B (which received only bupivacaine) and group M (which received bupivacaine and midazolam). Group B was administered 2 mL of 0.5 % heavy bupivacaine with 0.2 mL saline. Group M was administered 2 mL 0.5% heavy bupivacaine and 0.2 mL (1 mg) midazolam mixture.

The inclusion criteria for this study were as follows: participants falling under ASA (American Society of Anesthesiology) physical statuses 1 and 2, encompassing normal and healthy individuals (ASA 1) as well as those with mild systemic disease without functional limitations (ASA 2). The age range for inclusion was between 18 and 60 years. Additionally, participants with a BMI falling within the range of 18.5 to 24.9 were considered. Both genders were eligible for participation, ensuring a diverse representation in the study. exclusion criteria for this study encompassed a range of conditions and situations. Patients who refused to participate were excluded, along with those undergoing lower segment cesarean section (LSCS). Individuals with a history of bleeding disorders or currently on anticoagulants, those on benzodiazepines as a part of their regular medication were not included, as were patients with a known allergy to local anesthetic drugs. Additionally, individuals with psychiatric conditions, on going local infections, or chronic pain were excluded from the study to ensure a specific and manageable participant pool.

In a study by Prakash S *et al.*[1], the analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing Cesarean delivery was investigated. The study involved three groups: Group 1 received 0.5% hyperbaric bupivacaine, Group 2 received 0.5% hyperbaric bupivacaine + 1mg midazolam, and Group 3 received 0.5% hyperbaric bupivacaine + 2mg midazolam intrathecally. Sample size calculations of our study were based on data from the first two groups. The calculated sample size for each group was 25, resulting in a total sample size of 50. The desired level of statistical significance (Z) was 1.96, and the desired power (Z1-β) was 0.84. Standard deviations ($\sigma1 = 0.5$, $\sigma2 = 0.7$) and means ($\mu1 = 3.8$, $\mu2 = 4.3$) of the groups were used in the calculations. The sampling technique employed was convenient, with consecutive patients meeting inclusion criteria being selected by the consultant anaesthesiologist. The study consisted of two groups: Group M (25 Patients receiving spinal anesthesia with hyperbaric bupivacaine and preservative free intrathecal midazolam) and Group B (25 patients receiving spinal anesthesia with hyperbaric bupivacaine alone).

The study focused on several variables to assess its outcomes. The primary outcome variable was the duration of sensory blockade, which was evaluated through various measures, including the loss of pin prick sensation reported by patients, sedation levels using the Ramsay sedation scale, post-operative analgesia measured by the visual analog scale (VAS), the requirement for rescue medication, and the maintenance of hemodynamic stability as indicated by the usage of injection Atropine/Ephedrine. The study also considered two independent variables: Age and Sex. The data collection process involved explaining the study protocol to participants and obtaining their written informed consent. A proforma was utilized as a data collection tool.

Clearance from the Institutional Research

Committee and Ethics Committee was obtained. All patients were visited the day before their surgery. They were given detailed explanations about the anesthesia procedure, and informed written consent was obtained from each patient. A 6 hours period of nil oral in take was observed before surgery. Upon arrival in the operating theater, a wide bore venous cannula was inserted under sterile precautions, and intravenous fluids were initiated. Standard monitoring, including non-invasive blood pressure (NIBP), Electrocardiography (ECG), Heart Rate (HR), and Oxygen (O_2) Saturation, was performed, with baseline parameters recorded. Oxygen supplementation at 5L/minute was provided through a simple face mask. Subsequently, patients were positioned for the SAB (Subarachnoid Block). The block was administered in the L3 - L4 interspace using a 25 G Quincke's spinal needle with the patient in a left lateral position, following institution protocols. During the surgery, the sensory blockade's onset, height, duration, and regression were assessed through pin prick sensation loss. The assessment occurred every 5 minutes for the initial 30 minutes and then every 15 minutes until two dermatome regressions were achieved. Recovery time for sensory blockade was defined as the regression of anesthesia by 2 dermatomes from the maximum block level.

Sedation levels were evaluated using the Ramsay level of sedation scale every 15 minutes during surgery:

1. Conscious or Agitated
2. Cooperative or Tranquilized
3. Drowsy but Responding to Commands
4. Asleep but Responding to Glabellar Tap
5. Asleep with Sluggish Response to Tactile Stimulation
6. Asleep and Unresponsive

A Ramsay sedation score of 4 or more was considered excessive.

Post-operative pain was assessed using the visual analogue scale (VAS) every 15 minutes until the first analgesic was administered, and then every 4 hours for the next 24 hours. All patients received 1g of paracetamol as the initial rescue analgesia when pain was reported, followed by subsequent doses every 8 hours. If the VAS score exceeded 5, rescue analgesia in the form of 50mg intravenous Tramadol was administered.

Intraoperatively, if patients complained of pain, they were given 1 g of intravenous paracetamol as rescue medication. If severe pain persisted despite paracetamol, 50 mg of intravenous Tramadol was administered.

Hemodynamic parameters were monitored closely. Hypotension, defined as systolic blood pressure below 90 mmHg, was treated with a bolus administration of 300 ml of ringer lactate over 10 minutes and 6 mg IV Ephedrine. A heart rate below 50bpm was treated with 0.6 mg of IV atropine.

The collected data was meticulously entered into an MS Office Excel sheet. After undergoing thorough validation and error checks, it was processed and analyzed through the statistical programming software SPSS-22. Frequencies and proportions were employed to represent qualitative variables, while mean and standard deviation were utilized for quantitative variables. The statistical analysis for this study involved the application of the student's t-test, with a significance threshold set at a P value of <0.05.

RESULTS

During an 18 months prospective observational study involving patients who underwent infraumbilical surgeries, two groups were examined – Group B, receiving only bupivacaine, and Group M, receiving a mixture of bupivacaine and midazolam. In Group B, 2 ml of 0.5% heavy bupivacaine with 0.2 ml saline was administered, while Group M received 2 ml of 0.5% heavy bupivacaine and 0.2 ml (1 mg) midazolam mixture.

Socio-demographic Characteristics: The mean age in Group M was 42.44 years, and in Group B, it was 44.28 years. The age difference between the groups was not significant (p=0.622).

The gender distribution was comparable between the groups (p=0.396), with 56.0% males and 44.0% females in both Group M and Group B.

There was no significant difference in the duration of surgery between the two groups.

Comparison of the Analgesic and Anaesthetic Effect:

1. Level of Sensory Block at Regular Intervals: The sensory level was assessed using dermatome regression. Group M showed slightly higher sensory block levels, but the differences were not significant.
2. Time for Regression by 2 Dermatome Levels: The time to reach two dermatome regression was higher in Group M (99.60±14.92 minutes) compared to Group B (90.60±14.01 minutes). (Table 1) (fig. 1).

Table 1: Time for regression by 2 dermatome level

Parameter	Group M (n=25)				Group B (n=25)				P
Time to Regress By 2 dermatome level (minutes)	Mean	SD	Min	Max	Mean	SD	Min	Max	0.033
	99.6	14.92	75	120	90.6	14.01	60	120	

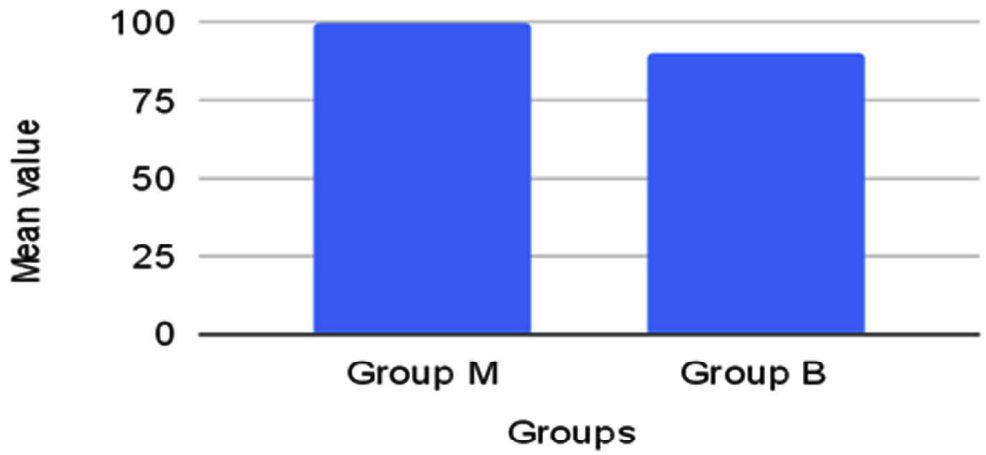

Fig. 1: Bar diagram showing comparison of two dermatome regression

3. Comparison of Sedation at Regular Time Intervals in Both Groups: Patients in Group M were well sedated with RSS scores of 3 and 4, while Group B had lower sedation levels with RSS scores of 1 and 2 (Table 2) (fig. 2).
4. Post-operative Pain Comparison Using VAS Scale: Post-operative pain, assessed using the VAS scale, was significantly lower in Group M compared to Group B at various time intervals.
5. Time to Reach VAS>5 in Both Groups: The time for rescue analgesia (VAS>5) was significantly longer in Group M (196.80±26.09 minutes) compared to Group B (108.60±10.85 minutes). (Table 3)(fig. 3).

i. Hypotension (Systolic BP <90 mmHg):

In Group M, 12% of patients experienced systolic blood pressure below 90 mmHg and were administered 6 mg IV Ephedrine (categorized as "yes"). Mean while, 88% of patients in Group M maintained hemodynamic stability and did not need Ephedrine (categorized as "no"). In Group B, 28% of patients had systolic blood pressure below 90 mmHg and were given 6mg IV Ephedrine (categorized as "yes"). Conversely, 72% of patients in Group B remained hemodynamically stable and did not require Ephedrine (categorized as "no"). The observations suggest that there was no statistically

Table 2: Comparison of sedation levels at regular intervals

Sedation	Group M (n=25)		Group B (n=25)		P
	Mean	SD	Mean	SD	
0 min	0.0	0.0	0.0	0.0	_
15 min	1.0	0.0	1.0	0.0	_
30 min	1.44	0.50	1.04	0.20	<0.001
45 min	1.88	0.66	1.44	0.50	0.011
60 min	2.40	0.76	1.40	0.50	<0.001
75 min	2.52	0.71	1.52	0.51	<0.001
90 min	2.92	0.75	1.68	0.47	<0.001
105 min	3.08	0.64	1.60	0.50	<0.001
120 min	3.92	0.66	1.52	0.51	<0.001

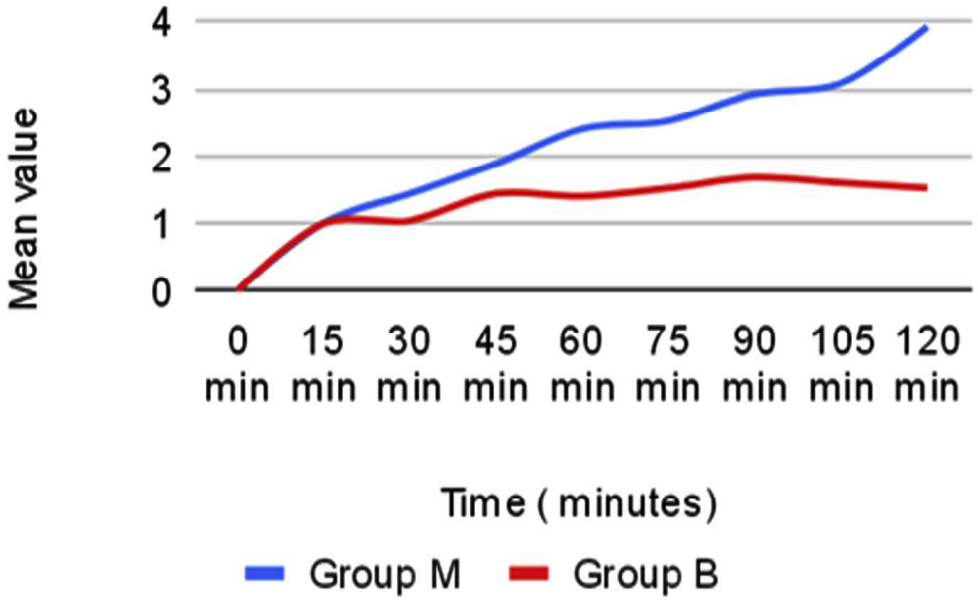

Fig. 2: Line diagram showing comparison of sedation levels

Table 3: Comparison of Postoperative Pain

Parameter	Group M (minutes) (n=25)				Group B (minutes) (n=25)				P value
Time to Reach VAS >5 (minutes)	Mean	SD	Min	Max	Mean	SD	Min	Max	<0.001
	196.8	26.09	150	240	108.6	10.85	90	120	

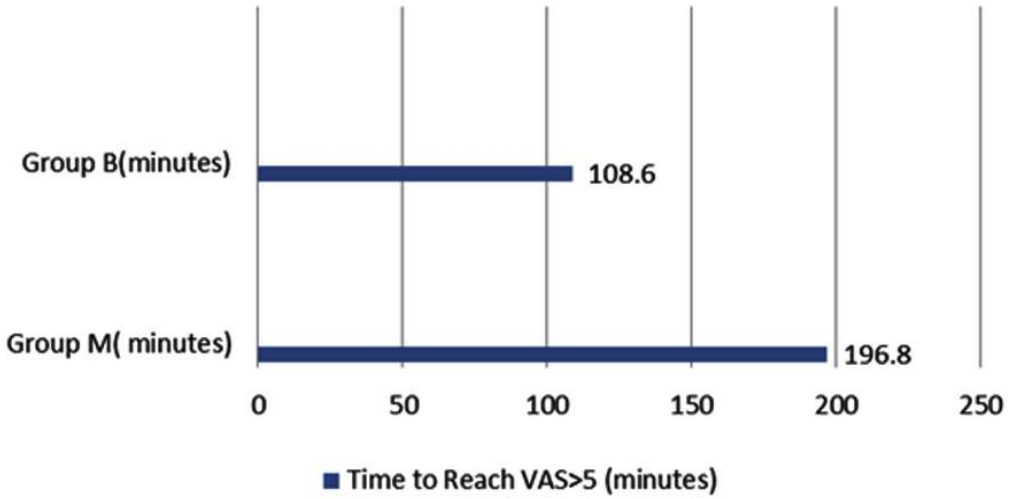

Fig. 3: Bar diagram showing Comparison of Postoperative Pain

significant difference in systolic blood pressure between the two groups. (p=0.157).

ii. Bradycardia (Persistent HR<50/min):

In Group M, 4% of patients exhibited a heart rate below 50 bpm and received treatment with 0.6 mg IV Atropine (denoted as "yes"). Contrarily, 96% of patients in Group M did not experience a heart rate drop to 50 bpm or below (denoted as "no"). Within Group B, 8% of patients had a heart rate below 50 bpm and were administered 0.6mg IV Atropine (denoted as "yes"). In Group B, 92% of patients did not encounter bradycardia (denoted as "no"). The analysis indicated no statistically significant

difference in heart rate between the two groups (p=0.552).

In conclusion, the study demonstrated that the mixture of midazolam - bupivacaine provided better sensory block duration, sedation, and post-operative pain relief, with no significant differences in age, gender, surgery duration, or hemodynamic stability between the two groups.

DISCUSSION

Ineffective management of post-operative pain can have significant emotional and physiological consequences for patients, leading to prolonged hospital stays and increased costs for both patients and healthcare facilities. Spinal anesthesia is a widely used regional anesthesia technique for infraumbilical surgeries, offering advantages such as early ambulation and shorter hospital admissions.[2] This technique has been particularly beneficial for critically ill patients, improving respiratory and bowel functions, mental status, and overall patient comfort.[3] Moreover, certain upper abdominal laparoscopic surgeries have also been performed under regional anesthesia due to benefits such as reduced airway manipulation, preservation of spontaneous respiration, effective post-operative pain relief, minimal nausea and vomiting, and quicker recovery.[4,5]

To enhance the duration of spinal anesthesia, various adjuvant drugs, including opioids, ketamine, dexmedetomidine, soda bicarbonate, and neostigmine, have been explored. Among these, opioids like fentanyl and morphine are common, though their spinal administration can lead to side effects such as nausea, vomiting, respiratory depression, and pruritus.[6] Recent studies have highlighted the effectiveness of intravenous, intrathecal, and oral administration of midazolam. Intrathecal midazolam, by modulating GABA at GABAA receptors, triggers the release of endogenous opioids, which in turn act on δ opioid receptors.[7] Importantly, sedative action of midazolam doesn't compromise airway reflexes, induce significant autonomic, hormonal, or circulatory changes, and is associated with anterograde amnesic properties.[8]

This present study aimed to compare the effects of intrathecal midazolam combined with bupivacaine against bupivacaine alone for spinal anesthesia in infraumbilical surgeries. The study encompassed 50 patients aged 18 to 60 years, falling under ASA I/II category. The first 25 consecutive patients meeting inclusion criteria received 2 ml of 0.5% hyperbaric bupivacaine with 0.2 ml of preservative free midazolam, forming Group M. The subsequent 25 patients fitting inclusion criteria received 2 ml of 0.5% hyperbaric bupivacaine with 0.2 ml of saline, composing Group B. The two groups were compared in terms of demographic and surgical outcomes.

Dermatome Regression Duration

The study found that the mean time for regression of sensory blockade by two dermatomal levels was significantly longer in Group M (99.60±14.92 mins) compared to Group B (90.60±14.01 mins), signifying statistical significance (p=0.033). This finding aligns with the results of a study by N. Bharti *et al.*[9], where the addition of intrathecal preservative free midazolam to hyperbaric bupivacaine led to a significantly prolonged duration and quality of spinal blockade. Similar conclusions were reached by other studies as well. Shandangi *et al.*[10] and Prakash *et al.*[1] both reported a significant increase in the mean time required for regression of sensory blockade by two dermatomal levels in patients who received intrathecal midazolam, confirming the consistency of our findings.

Sedation Score

In our study, we assessed intra operative sedation using the Ramsay sedation score. The patients who received intrathecal midazolam along with bupivacaine (group M) demonstrated significantly higher sedation scores compared to the control group, which received spinal anesthesia with bupivacaine alone (group B). Among the patients in group M, 88% (22 out of 25) achieved effective sedation, while patients in group B did not exhibit notable sedation. The Ramsay sedation scores in group M predominantly ranged from 3 to 4, where as in group B, they were mainly within the range of 1 to 2. Yegin *et al.*[11] conducted a study that observed a similar significant increase in sedation scores in the group receiving intrathecal midazolam. In 2012, Karbasfrushan *et al.*[12] reported an expedited onset of sedation in the group that received intrathecal midazolam in comparison to the group that received only bupivacaine. It is important to note that our findings contrast with studies by Shandangi[10] and Batra[13], where no significant difference in sedation scores was observed between the study groups.

Post-operative Analgesia

In our study, we found that the addition of Intrathecal midazolam was found to enhance post-

operative analgesia, as evidenced by lower VAS scores and extended time before rescue analgesia was required. Similar findings were reported in other studies, corroborating our results. Kim and Lee[14], in a trial conducted in 2001 on patients under going haemorrhoidectomy, investigated the impact of intrathecal midazolam as an adjuvant to bupivacaine. They found that the analgesic effect of intrathecal bupivacaine was not only enhanced but also prolonged by the addition of midazolam. Their study showed that the addition of 1 mg of intrathecal midazolam extended the post-operative analgesic effect by 2 hours, and with 2 mg of midazolam, this effect was prolonged to 4.5 hours, compared to control groups after haemorrhoidectomy. Additionally, they observed a reduced need for rescue analgesia in the midazolam receiving groups during the first 24 hours. Further support comes from Bharti *et al.*[9] whose study in 2003 investigated the impact of intrathecal midazolam in patients under going lower abdominal surgeries. Their findings highlighted that the combination of intrathecal midazolam and hyperbaric bupivacaine not only extended the duration and quality of spinal blockade but also prolonged the period of post-operative analgesia. Agrawal and colleagues[15] also conducted a study in 2005 that examined the effects of adding 1 mg of intrathecal midazolam to hyperbaric bupivacaine. Consistent with our study, they reported that this combination increased the duration of post-operative analgesia without affecting the time of dermatomal regression. Prakash *et al.*[1] observed in their study that intrathecal midazolam significantly increased the time before patients requested their first post-operative analgesic ($P < 0.001$ compared to bupivacaine alone). Notably, they found that analgesia was extended in the group that received 1 mg of intrathecal midazolam and further prolonged in the group that received 2 mg of intrathecal midazolam, thus indicating a significant impact on post-operative analgesia. Adding to the body of evidence, a meta-analysis conducted by Ho and Ismail[16] in 2008 indicated that intrathecal midazolam indeed improved perioperative analgesia and led to a reduced incidence of post-operative nausea and vomiting among patients.

Collectively, these findings underscore the potential benefits of intrathecal midazolam as an adjuvant to enhance post-operative analgesia and alleviate pain, thus contributing to improved patient outcomes.

Haemodynamic Parameters

In our study, we closely examined the hemodynamic parameters between the two study groups and found that these differences were not statistically significant (P=0.157 for hypotension and P=0.552 for the incidence of heart rate <50/ min). The requirement for ephedrine to manage hypotension showed no significant variance between the two groups. These findings are consistent with other research studies[15,9] that compared the effects of a bupivacaine - midazolam mixture to bupivacaine alone. For instance, in 2006, Lee J.M. and colleagues[17] conducted a study to explore the impact of intrathecal midazolam combined with bupivacaine. While they observed an extended duration of spinal anesthesia in the midazolam group, they found no notable differences in hemodynamic parameters between the study groups. These findings collectively suggest that the addition of intrathecal midazolam to bupivacaine does not appear to significantly affect hemodynamic stability.

Drawback: In our study, other side effects like changes in the arterial saturation or respiratory rate were not observed and sample size was small.

CONCLUSION

This study aimed to investigate the impact of intrathecal midazolam on the duration of anesthesia and post-operative pain relief in patients undergoing infraumbilical surgeries under spinal anesthesia at our hospital. A prospective observational approach was employed to compare the administration of spinal anesthesia using bupivacaine with saline and bupivacaine with intrathecal midazolam. The objective was to demonstrate the analgesic properties of midazolam in enhancing the duration of post-operative pain relief and the over all quality of anesthesia.

The findings of the study revealed that the addition of 1mg intrathecal midazolam to 2 ml of 0.5% hyperbaric bupivacaine resulted in an extended duration of analgesia, increased sedation scores and improved post-operative pain relief. Further more, the study demonstrated that there were no significant hemodynamic changes and minimal side effects observed between the two groups.

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