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Midazolam administered intrathecally augments the analgesic effects of spinal blocking with bupivacaine in patients undergoing lower limb orthopaedic surgeries.

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Abstract

Bupivacaine is one of the most often utilised intrathecal drugs. If the analgesic effect is prolonged by adding midazolam to intrathecal bupivacaine, it will be of great benefit to the patient.60 patients between 18-60 years of age, belonging to ASA 1 and ASA 2 categories, scheduled to undergo elective or emergency lower limb orthopaedic surgeries were randomly allocated to one of the two groups: the control group BS receiving 2ml of 0.5% Bupivacaine plus 1 ml of 0.9% saline intrathecally and the BM group receiving 2 ml of 0.5% Bupivacaine plus 1ml(1mg) of preservative free midazolam. Two parameters have been assessed in this study, Duration of effective analgesic time from the spinal anaesthesia and the Visual analogue scales (VAS) at first analgesia. Chi square test and analysis of variance has been used to analyse the results. Time to first analgesia in group BM was significantly longer than that in the control group. There were no significant differences in the Visual analogue scales (VAS) at first analgesia among the two groups. In this study, we found that the analgesic effect of intrathecal bupivacaine was potentiated by intrathecal midazolam.

Keywords: Spinal, Intrathecal Midazolam, Bupivacaine, Post Operative Analgesia, Visual Analogue Scale.

Introduction

For analgesia following lower limb orthopaedic procedures, many patients require parenteral or oral opioids and/ or non-steroidal anti – inflammatory Medi cations (NSAIDs). Opioid-induced side effects, such as respiretory depression, nausea, vomiting, urinary retention and pruritus, limit their use. The purpose of our study was to assess the effects of intrathecal midazolam as an adjunct to intrathecal bupivacaine after lower limb orthopaedic surgeries. [1]

The benzo diazepine/ gamma-amino butyric acid (GABA) a receptor com bination in the spinal cord mediates the analgesic effect of midazolam. Gamma-amino butyric acid type A receptors are traditionally believed to exist on primary afferent terminals in the spinal cord and to participate in presynaptic inhibition via primary afferent depolarization. [2,3]

The highest density of GABA/ benzo diazepine receptors has been found in the superficial layers of the spinal dorsal horn, especially lamina II (substantia gelatinosa [SG]). The inhibition of poly synaptic EPSCs (Excitatory Post Synaptic Complexes) by midazolam has considerable effects on nociceptive transmission in the superficial dorsal horn, given that more than 70% of SG neurons exhibit polysynaptic EPSCs. The augmentation of GABAergic inhibition located on soma to dendritic sites of excitatory interneurons in the SG is the most likely mechanism of action for midazolam. [3]

Mida zolamanimidazo benzo diazepine derivative is utilized as a premedicate, sedative, and an anesthetic induction agent [6,7]. The high lipophilicity of midazolam at physio logic PH causes it to have a rapid onset of activity after intravenous administration. The volume of distribution generally averages between 1 and 2.5 l/ kg. After the distribution equilibrium is achieved elimination of midazolam proceeds rapidly, with half-life ranging from 1 to 4hr in healthy individuals. The elimination half-life on the other hand is similar or identical to that observed after intravenous administration, indicating that the rate of elimination is in dependent of route of administration.

Bupivacaine is an amino amide local anesthetic [8]. The mechanism by which local anesthetics block sodium conductance is as follows

a. Local anesthetics in the cationic form act on the receptors within the sodium channels on cell membrane and block it. The local anesthetics can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anesthetics.

b. The second mechanism of action is by membrane expansion. This is a non-specific drug receptor interaction.

Absorption of local anesthetics is determined by site of injection, dosage, and addition of a Vaso constrictor. Ab sorption is faster in regions of higher vascularity.

According to the International Association for the Study of Pain, pain is a distressing sensory and emotional experience linked to real or potential tissue damage or characterised in terms of such damage. [4,5]

There are two components of pain. Neurophysiological mediated sensory component and an emotional component.

There are two types of pain

1. Physiological pain is a transient sensation due to noxious mechanical, thermal, chemical stimulus each

with a clearly defined threshold and without causing damage to the nervous system.

2. Pathological pain is an inflammatory response to tissue injury or damage to central nervous system with an alteration in perception. Pain following surgery is pathological.

The threshold for the perception of pain is the lowest intensity of stimulus recognized as pain. The conscious awareness or perception of pain occurs at the thalamic level and thalamic pain occur when the thalamocortical pathway is destroyed.

Somatosensory cortex is essential for the accurate localization, appreciation of intensity and other discriminative aspects of pain. Prefrontal cortex subserves the unpleasant affective and emotional reaction to pain.

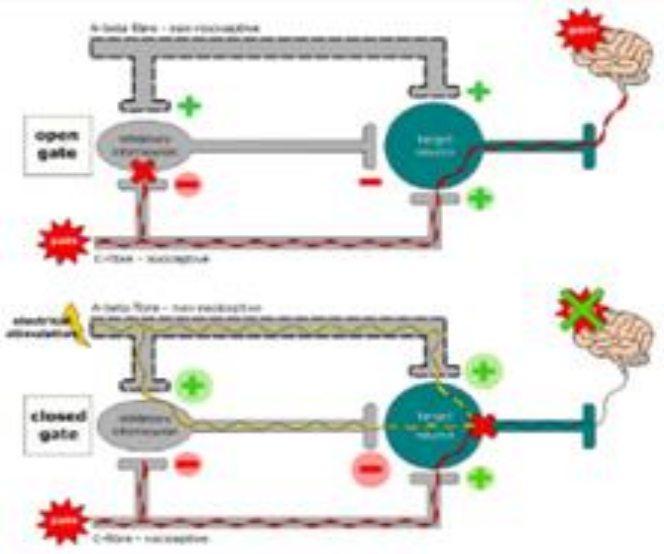

Figure 1: Gate control theory of pain.

This part of the theory accounts for why rubbing an injured area reduces the amount of pain felt. The rubbing stimulates Aβ fibres and this leads to a closing of the gate.

Materials and Methods

Data was collected from 60 patients undergoing lower limb orthopedic surgeries under subarachnoid block at Katuri Medical College and Hospital. Both study group and control groups were selected from these patients.

Inclusion criteria

a. ASAI and II patients.

b. 18 – 60 years of age

c. Elective & Emergency lower limb orthopedic surgery.

Exclusion criteria

a. ASA III and ASA IV

b. Increased intracranial tension

c. Inability of patient to main Tain stillness.

d. Skin/s Ott issue infection at the site of subarachnoid block.

e. Coagulopathy

f. Severe Hypovolemia

g. Pre-existing neuro logic disease

h. Opioid intolerance

i. Patient refusal

Method of collection of data

The 60 patients scheduled to undergo elective or emergency orthopedic surgeries were enrolled in this double blinded, randomized trial. They were randomly allocated to one of the two groups: the control group BS receiving 2ml of 0.5% Bupivacaine plus 1 ml of 0.9% saline intrathecally and the BM group receiving 2 ml of 0.5% Bupivacaine plus 1ml(1mg) of preservative free midazolam. Spinal anesthesia was performed in the sitting position using a 25 G spinal needle in the L3 – L4 space. The patients were kept in the sitting position for 5 minutes, tested for sensory loss and then placed in the supine position.

Two parameters were assessed in this study

1. Duration of effective analgesic time from the spinal anesthesia.

2. Visual analogue scales (VAS) at first analgesia.

Hemodynamic monitoring

1. ECG
2. Noninvasive blood pressure – Systolic and diastolic blood pressure, Mean arterial pressure.
3. Heart rate
4. SpO2

Patient Characteristics

1. Gender (male/female)
2. Age (year.)
3. Height (cm)
4. Weight (kg)

Sensory level was checked post sub-arachnoid block, at intervals of

1. 5 min.
2. 10 min.
3. 20 min.
4. 60 min.

Post operative side effects evaluated were

1. Nausea/vomiting
2. Sedation
3. Urinary retention

Post operative analgesia parameters

1. Time to first pain medication (min.)
2. VAS (Visual Analogue Scales) at first pain Medi cation (0-10)

Surgery Characteristics

1. Duration of Surgery (min.)
2. Type of Surgery – Elective or Emergency lower limb orthopedic surgery.

Results

A comparative prospective double blind randomized study with 30 patients in control group BS (Bupivacaine + Normal saline) and 30 patients in Group BM (Bupivacaine + Midazolam) was undertaken to study the analgesic effect of spinal blockade.

Table 1: Comparison of Basic characteristics of patients studied.

	Group BS	Group BM	P value
	Mean ± SD	Mean ± SD	
Age (in years)	42.7±14.6	44.7±12.1	0.565
Sex (M+F)	20+10	18+12	0.592
Height (in centimeters)	163±6.27	165.7±6.5	0.120
Weight (in kg.)	66.1±5.65	67.2±6.61	0.478
Duration of surgery (in min.)	63.6±10.2	65.3±8.6	0.488

Table 2: Comparison of type of surgery between two groups.

Type of surgery	Group BS (n=30)		Group BM (n=30)		P value
	No	%	No	%	
Elective	22	73.3	20	66.7	0.540+
Emergency	8	26.7	10	33.3	

Table 3: Comparison of haemodynamics of patients studied. Results are presented Mean ± SD (Min-Max)

Haemodyamics	Study period	Group BS	Group BM	P value
Heartrate	Initial	78.50±10.09 (36-90)	79.60±6.09 (68-88)	0.611
(rpm)	Final	82.90±6.53 (70-92)	82.67±5.90 (70-89)	0.885
	Initial	83.60±4.63 (77-92)	83.77±4.02 (78-90)	0.882
MAP (mmHg)	Final	85.63±4.41 (78-92)	84.90±3.56 (78-89)	0.481
SPO_2(%)	Initial	99.37±0.67 (98-100)	99.47±0.68 (98-100)	0.568
	Final	99.63±0.49 (99-100)	99.77±0.43 (99-100)	0.267

Table 4: Comparison of Sensory levels in two groups of patients

Study period	Sensory Level	Group BS (n=30)		Group BM (n=30)		P value
		No	%	No	%	
5min	L1	18	60.0	19	60.0	1.000
	L2	12	40.0	11	36.7	0.791
10min	L1	14	46.7	13	43.3	0.795
	L2	6	20.0	7	23.3	0.754
	T12	10	33.3	10	33.3	1.000
20 min	T10	12	40.0	12	40.0	1.000
	T11	18	60.0	18	60.0	1.000
60 min	T8	10	33.3	4	13.3	0.067+
	T10	20	66.7	26	86.7	0.067+

Table 5: Comparison of Time to 1st pain medication (min) of patients studied (Rescue Analgesia).

Time to 1st pain med (min)	Group BS (min)	Group BM (min)
Range	120-160	160-210
Mean±SD	133.27±8.29	152.9±11.25
Inference	Time to 1st pain med requirement is longer in Group BM when compared to Group BS with P <0.001	

Figure 2: Comparison of Time to 1st pain Medication (min) between two groups.

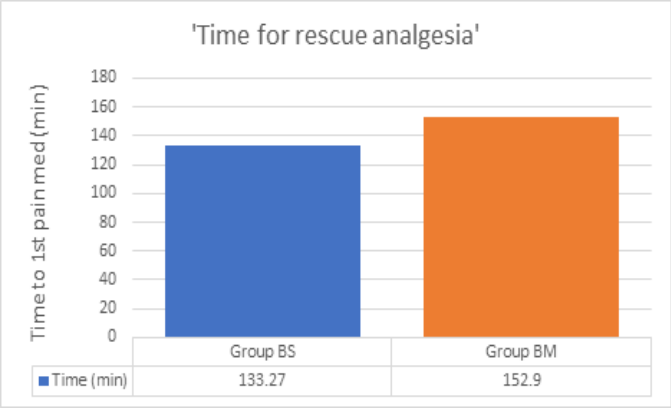

Table 6: Comparison of VAS score of patients studied.

VAS score	Group BS	Group BM
Range	2-9	2-9
Mean ± SD	5.34±1.65	5.65±1.79
Inference	VAS scores statistically similar between two groups with P = 0.4883	

Figure 3: Comparison of VAS score of patients studied between two groups.

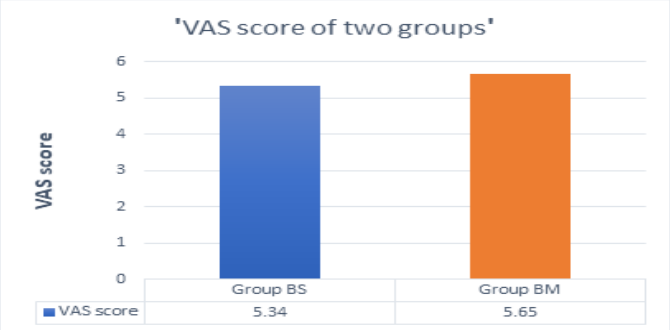

Table 7: Comparison of post - operative complications of patients studied.

Post–op complications	Group BS	Group BM
Nausea/Vomiting Sedation	Nil	Nil
Urinary retention	Nil	Nil

Statistical Methods

Chi-square test has been used to find the significance of homogeneity of study characteristics between two groups of patients. An unpaired t test has been used to find the significance of hemodynamics between two groups. Chi-square has been used to find the significance of complications/sensory levels between two groups of patients. P value < 0.05 is considered significant.

Discussion

In this trial, we observed that intrathecal midazolam enhanced the analgesic efficacy of intrathecal bupivacaine. After elective or emergency lower limb ortho paedic procedures, the administration of 1 mg of intra thecal midazolam prolonged the postoperative anal gesia of bupivacaine by approximately 1 hour compared to controls. Intrathecal midazolam may cause neurotoxicity, which is the drug's most dangerous side effect. No harm was seen to the spinal cord, nerve roots, or meninges in any of the animals tested. There have been reports of midazolam spinal administration in humans. Patients with chronic low back pain reported considerable analgesia for 2 months following a single intrathecal injection of 2 mg midazolam, without experiencing any clinical neuro logical impairments. After leg surgery, intrathecal mida zolam was similarly efficacious and well tolerated.

Intrathecal midazolam has been shown to be beneficial against somatic pain, and it has also been shown to have an antinociceptive effect against visceral pain in rabbits subjected to intestinal distension and in people following caesarean delivery. Patients with refractory neurogenic and musculoskeletal pain have benefited from long-term, continuous intrathecal infusions of midazolam at doses of 6 mg/day. Clinically relevant dosages of intrathecal midazolam are probably not neurotoxic, according to in vitro investigations. In our research, we focused on the postoperative phase and its associated risks and problems. No neurological issues occurred. [1]

The clinical literature stresses the beneficial effects of adding midazolam to perioperative and chronic pain management at dosages of about 1-2mg IT. According to recent data, there appears to be no correlation between the use of midazolam and an increase in the occurrence of adverse events when the drug is administered in doses of 1-2 mg at concentrations of not more than 1 mg/mL, either alone or as an IT adjuvant.

When looking at the long-term effects of using midazolam during surgery on a broad patient population, there don't seem to be any obvious negative neurological consequences. [10]

Pain in the back or legs, numbness or weakness in the legs, urine incontinence or trouble voiding, fecal incontinence or difficulty voiding, numbness or burning sensation around the anal or vaginal area, and sedation are all symptoms that may indicate neurologic impairment after surgery. [9] In our research, we interpreted the presence of symptoms including nausea,

vomiting, drowsiness, and urinary in continence as signs of neurotoxicity. The BM group showed no occurrence of these symptoms.

Conclusion

A lot of people need parenteral opiates and/or non-steroidal anti-inflammatory drugs (NSAIDs) for pain management after they've had lower limb orthopedic surgeries. To provide sustained pain relief after their procedures, we chose to combine Bupivacaine with intrathecal midazolam. Patients undergoing orthopedic procedures on their lower limbs received Bupivacaine and 1 mg of midazolam intrathecally. The addition of 1mg of intra the calmidazo lampro longed the post operative analgesic effect of bupivacaine by approximately 1 hour as compared with controls after lower limb orthopaedic surgeries ($p < 0.001$).

Ethics approval and consent to participate: Approval was taken from Katuri Medical College and Hospital's Ethics Committee and written informed patient consents were also taken.

List of abbreviations

1. EPSCs: Excitatory Post Synaptic Complexes
2. GABA: Gaba-amino butyric acid
3. HR: Heart Rate
4. IV: Intravenous
5. MAP: Mean Arterial Pressure
6. NO: Nitric Oxide
7. NSAIDs: Non steroidalanti – in flammatory drugs
8. O_2: Oxygen
9. SG: Substantia Gelatinosa
10 SpO_2: Saturation of Oxygen
11 VAS: Visual Analogue Scale
12 IT: Intra Thecal

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