Original Research Article

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Comparative Study of Intrathecal Bupivacaine 0.5% with Midazolam 2mg and Bupivacaine 0.5% with Clonidine 50 μg for Postoperative Analgesia in Infra-Umbilical Surgeries

Kiran Nelamangala[1], Nikila Devarayasamudram Gopal[2], Ravi Madhusudhana[3], Dinesh Krishnamurthy[4]

[1]Associate Professor, [2]Senior Resident, [3]Professor, [4]Professor & Head, Department of Anaesthesiology, Sri Devaraj URS Medical College, RL Jalappa Hospital, SDUAHER, Tamaka, Kolar, Karnataka 563101, India.

Abstract

Background: Spinal anaesthesia is safe, reliable and inexpensive technique of providing surgical anaesthesia. The intrathecal use of clonidine is shown to be effective and safe. Several studies indicate that clonidine extends duration of local anaesthetics action and can decrease the dose of local anaesthetic drug. Midazolam, a benzodiazepine when added to local anaesthetic bupivacaine has significant synergistic effect in terms of quality of spinal anaesthesia, duration and prolong post-operative analgesia without having any significant side effects. *Aims:* To evaluate the synergistic effect and safety of adding 50μg clonidine to intrathecal 0.5% hyperbaric bupivacaine in spinal anaesthesia compared to 2mg of midazolam to intrathecal 0.5% hyperbaric bupivacaine for infra-umbilical surgeries *Material and Methods:* Mean onset of sensory blockade in Group A was 151.8±36.8 sec and in Group B was 170±53.5 sec. Mean time taken for two segment regression in Group A was 210.5±62.1 min and in Group B was 162.7±54.9 min which was statistically significant. Mean Duration of analgesia in Group A was 312.4±53.8 min and in Group B was 404.5±63.6 min. *Results:* Mean onset of sensory blockade in Group A was 151.8±36.8 sec and in Group B was 170±53.5 sec. Mean time taken for two segment regression in Group A was 210.5±62.1 min and in Group B was 162.7±54.9 min which was statistically significant. Mean Duration of analgesia in Group A was 312.4±53.8 min and in Group B was 404.5±63.6 min. *Conclusions:* Midazolam as an additive to intrathecal bupivacaine prolongs the duration of analgesia with minimal side effects when compared to clonidine.

Keywords: Anaesthesia; Analgesia; Bupivacaine; Clonidine; Midazolam; Spinal.

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Introduction

Infra-umbilical and Lower limb surgeries are commonly done under spinal anaesthesia. Sub arachnoid block blunts the somatic, autonomic and few endocrine responses and provides surgical anaesthesia with adequate post-operative analgesia [1]. It is a safe and reliable technique of providing anaesthesia and cost effective. 0.5% Hyperbaric bupivacaine is more potent compared to lignocaine , prolongs the duration of action but it has slower onset. Hence different additives are added to improve quality of spinal anaesthesia [2]. Drugs belonging to various classes like opioid, non opioids, benzodiazepine and α2-receptor agonists when used as neuraxial adjuvants improve the quality of perioperative analgesia, minimize the local anaesthetic dosage particularly in high risk procedures and in ambulatory patients [3].

Corresponding Author: Ravi Madhusudhana, Professor, Department of Anaesthesiology, Sri Devaraj URS Medical College, R L Jalappa Hospital, SDUAHER, Tamaka, Kolar, Karnataka 563101, India.
E-mail: ravijaggu@gmail.com

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Clonidine, a partial α2 adrenoceptor agonist when used as an intrathecal adjuvant has been shown to be effective and safe. It prolongs the duration local anaesthetic action and reduces the local anaesthetic dosage requirement [4].

Objectives of the Study

To evaluate the synergistic effect and safety of adding 50μg clonidine to intrathecal 0.5% hyperbaric bupivacaine in spinal anaesthesia for infra-umbilical surgeries compared to 2mg of midazolam to intrathecal 0.5% hyperbaric bupivacaine, with regards to

- Time to onset and duration of sensory blockade.
- Time to onset and duration of motor blockade.
- Time to rescue analgesia
- Any adverse effects like hypotension, bradycardia or sedation

Subjects and Methods

Institutional Ethical Committee Permission was obtained before starting the study.104 patients admitted for elective surgeries, to be done under spinal anaesthesia were divided into 2 groups of 52 each randomly via computer generated table. A prospective randomized double blind study was planned.

Group A received clonidine 50 mcg added to 3ml of 0.5% hyperbaric bupivacaine.

Group B received 2mg midazolam added to 3ml of 0.5% hyperbaric bupivacaine

Source of Data: 104 patients admitted for elective surgeries, to be done under spinal anaesthesia.

Method of Collecting Data

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software (IBM). Categorical data is represented in the form of frequencies and proportions. Chi-square is the test of significance. Continuous data is represented as mean and standard deviation. Independent t test is the test of significance to identify the mean difference between two groups. p value <0.05 is considered as statistically significant.

Sample size was estimated by using the difference in Mean Duration of Sensory block in clonidine and midazolam groups from studies by Raj Bahadur Singh et al. and Ravichandra Dodawad et al. as 295.2±81.17 min and 260.6±22.45 min respectively [5,6]. Using these values at 95% Confidence limit and 80% power sample size of 47 was obtained in each group by using the below mentioned formula and Med calc sample size software. With 10% nonresponse sample size of 47 + 4.7 = 52 cases were included in each group.

Inclusion Criteria

The patients scheduled for lower abdominal surgeries, aged 18-65 years with physical status American Society of Anesthesiologists (ASA) class I and II were recruited for the study.

Exclusion Criteria

Patient's refusal, history of allergies to any study medications, gross spinal abnormality, localised skin sepsis, hemorrhagic diathesis, neurological involvement/diseases, with head injury, raised intra cranial pressure, raised intra ocular pressure, psychiatric disorders, asthma, epilepsy and, thyroid diseases.

After taking informed consent, Preoperative assessment was done for each patient on the previous day of surgery and written informed consent was taken. Patients were kept nil by mouth for solids for 8 hrs and clear fluids 2 hrs before surgery. Premedication on the night before surgery: tablet ranitidine 150mg and tablet alprazolam 0.25mg. In the preoperative room, on the day of surgery an intravenous access was secured with 18 gauge cannula and patients were preloaded with Ringer lactate 15ml/kg half an hour before surgery. Pulse oximeter, ECG and NIBP were connected .

Spinal anaesthesia was administered for all patients in left lateral position. Under aseptic precautions, sub arachnoid block was given at level of L3-L4 through a midline approach using 25G Quinckespinal needle and hyperbaric bupivacaine 3.0 ml (15mg) with inj clonidine either 50 μg or inj midazolam 2mg . The total volume made up to 3.5 ml will be injected with operative table kept horizontal. Patient was turned to supine posture immediately and supplemental oxygen given.

The parameters which were noted were onset of sensory blockade and motor blockade, maximum level of sensory and motor blockade attained and the time taken for the same, time to two segments sensory regression, total duration of analgesia which was determined by time to rescue analgesia (VAS ≥4), total duration of sensory blockade and motor blockade and side effects like nausea, vomiting, hypotension and bradycardia will be noted.

Quality of analgesia was assessed by visual analogue scale.

Visual analogue scale for pain:

0 No pain

1-3 Mild pain

4-6 Moderate pain

7-10 Severe pain

Motor blockade was assessed using modified Bromage scale.

Bromage scale: Grade Definition

0- Full flexion of knee and feet.

1- Inability to raise extended leg; able to move knee and feet

2- Inability to raise extended leg and move knee; able to move feet

3- Complete block of lower limb

Results

Mean age of subjects in Group A was 43.8±15.1 years and in Group B was 48.6±19.4 years. There was no significant difference in mean age between two groups. Mean weight in Group A was 61.1±8.4 Kgs and in Group B was 59.2±7.1 Kgs. There was no significant difference in mean weight between two groups. Demographic variables such as age and weight were comparable between two groups in our study.

Mean onset of sensory blockade in Group A was 151.8 ± 36.8 sec and in Group B was 170±53.5 sec. There was significant difference in mean Onset of sensory blockade between two groups. Mean onset of motor blockade in Group A was 189±48.6 sec and in Group B was 186.4±54.7 sec. There was no significant difference in mean Onset of motor between the two groups as shown in Table 1.

Mean time taken for two segment regression in Group A was 210.5±62.1 min and in Group B was 162.7± 54.9 min. There was significant difference in mean time taken for two segment regression between two groups. Mean Duration of analgesia in Group A was 312.4±53.8 min and in Group B was 404.5±63.6 min. There was significant difference in mean duration of analgesia between two groups as shown in Table 2.

In Group A, height of sensory blockade was T4 in 1.9%, T5 in 13.5%, T6 in 71.2% and T8 in 13.5%. In Group B height of sensory blockade was T4 in 7.7%, T5 in 0%, T6 in 63.5% and T8 in 28.8%. This difference in height of sensory blockade between two groups was statistically significantas shown in Table 3.

Table 1: Onset of sensory and motor blockade comparison between two groups

	Group				P value
	Group A		Group B		
	Mean	SD	Mean	SD	
Onset of sensory blockade (sec)	151.8	36.8	170.0	53.5	0.046*
Onset of motor blockade (sec)	189.0	48.6	186.4	54.7	0.798

Table 2: Two segment regression and duration of analgesia between two groups

	Group				P value
	Group A		Group B		
	Mean	SD	Mean	SD	
Two segment regression (min)	210.5	62.1	162.7	54.9	<0.001*
Duration of analgesia (min)	312.4	53.8	404.5	63.6	<0.001*

Table 3: Height of sensory blockade comparison between two groups

		Group			
		Group A		Group B	
		Count	%	Count	%
Ht of sensory blockade	T4	1	1.9%	4	7.7%
	T5	7	13.5%	0	0.0%
	T6	37	71.2%	33	63.5%
	T8	7	13.5%	15	28.8%

÷ 2 = 11.93, df = 3, p = 0.008*

In our study there was significant difference in mean HR between two groups at various intervals (2, 5, 120, 180 minutes) as shown in Table 4.

In our study there was significant difference in mean MAP between two groups at various intervals as shown in table 5.

In Group A, 67.3% had VAS score of 1, 25% had Score of 2 and 7.7% had score of 3 and in Group B, 75% had score of 1, 25% had score of 2 and none had score of 3. There was no significant difference in VAS score between two groups.

In Group A, 3.8% had Bradycardia, 1% had Bradycardia, Hypotension, 9.6% had Hypotension and 1.9% had Hypotension + nausea. In Group B, 7.7% had hypotension. There was no significant difference in side effects between two groups.

Discussion

Spinal anaesthesia is most extensively used anaesthetic technique for infra-umbilical surgeries. It is a simple technique, reliable, less time consuming, avoids polypharmacy and is cost effective. This technique is aimed at providing optimal surgical anaesthesia with good post- operative analgesia.

Table 4: Heart rate comparison between two groups at various intervals

	Group				P value
	Group A		Group B		
	Mean	SD	Mean	SD	
Basal	81.3	10.5	77.9	8.6	0.07
Immediately	77.5	11.4	73.6	8.3	0.052
2 min	74.4	11.2	70.5	6.7	0.034*
5 min	73.4	11.6	69.5	7.2	0.041*
10 min	72.1	9.5	69.9	6.7	0.179
15 min	71.3	8.4	70.0	7.8	0.419
20 min	70.8	8.1	70.3	7.4	0.772
30 min	72.1	8.6	72.3	9.1	0.894
40 min	72.5	7.2	72.7	7.2	0.849
50 min	73.2	7.0	73.6	6.0	0.721
60 min	75.4	7.7	76.7	6.3	0.332
90 min	77.4	8.2	80.0	6.9	0.076
120 min	79.4	9.4	83.2	7.1	0.025*
180 min	79.3	8.8	84.3	7.0	0.002*
240 min	79.6	9.0	77.7	7.5	0.236
300 min	79.7	8.4	77.8	7.3	0.208
360 min	80.3	8.4	78.2	7.4	0.180
420 min	80.6	8.1	79.1	7.4	0.308

Table 5: MAP comparison between two groups at various intervals of follow-up

	Group				P value
	Group A		Group B		
	Mean	SD	Mean	SD	
Basal	97.6	8.3	91.3	7.1	<0.001*
Immediately	90.0	7.4	86.0	7.1	0.006*
2 min	87.1	8.5	82.7	8.1	0.007*
5 min	85.1	9.1	82.9	7.1	0.164
10 min	84.6	9.0	83.5	7.0	0.522
15 min	84.0	8.6	83.2	5.3	0.558
20 min	84.8	9.5	84.2	6.5	0.691
30 min	86.1	8.8	85.8	5.5	0.853
40 min	85.9	7.6	87.3	5.1	0.253
50 min	88.3	7.4	87.9	5.3	0.716
60 min	87.9	8.7	87.4	7.0	0.747
90 min	91.6	7.7	92.5	7.4	0.526
120 min	94.5	8.6	93.7	7.5	0.637
180 min	94.2	7.8	92.0	5.9	0.115
240 min	95.2	7.8	90.5	6.4	0.001*
300 min	95.7	6.8	90.6	6.1	<0.001*
360 min	95.6	7.2	90.5	6.9	<0.001*
420 min	96.1	7.2	91.0	7.1	<0.001*

Most commonly used intrathecal local anaesthetic agents are lignocaine and bupivacaine. Duration of action of 0.5% hyperbaric bupivacaine when used intrathecally is limited to 2-2.5 hrs with limited post operative analgesia. Hence various adjuvants are added to intrathecal bupivacaine to prolong the duration of anaesthesia, post-operative analgesia and reduce the local anaesthetic requirement.

The analgesic effect of Clonidine, an α-2 receptor agonist is mediated via activation of post synaptic receptors in the substantia gelatinosa of spinal cord, potentiates the blockade and duration of analgesia [7]. Midazolam, a benzodiazepine when added an adjuvant to bupivacaine for spinal anaesthesia improves the duration and quality of spinal anaesthesia with minimal side effects. It action is mediated by benzodiazepine-GABA receptor complex. These receptors are present in olfactory bulb, cerebral cortex, substantia nigra, inferior colliculus, brain stem and spinal cord.

To test our hypothesis, we designed this randomized study to evaluate the postoperative analgesic effect, sensory and motor blockade and hemodynamic effects of two different drugs clonidine and midazolam when added to bupivacaine intrathecally in patients undergoing lower abdominal surgeries.

Onset of sensory blockade was early in both the groups where as onset was early in group B (170± 53.5 sec) compared to group A (151.8±36.8 sec) which was statistically significant.Mean onset of duration of motor blockade in Group A and group B were 189 ± 48.6 sec and 186.4±54.7 sec respectively which was not significant statistically.

The difference in height of sensory blockade between two groups was statistically significant . With T4 in 1.9% and 7.7% and T5 in 13.5% and 0%, T6 in 71.2% and 63.5% and T8 in 13.5% and 28.8% in group A and group B respectively.

Singh RB et al. in their study showed that adding 50µg of clonidine intrathecally did enhance the onset of sensory and motor block when compared to plain bupivacaine [5]. Duration of post operative analgesia was significantly higher in clonidine group (551.06±133.64 min) with minimal side effects.

Thakur A et al. in their study showed that adding clonidine to intrathecal bupivacaine enhances onset, duration and quality of sensory and motor blockade and prolonging the duration of analgesia with higher incidence of hypotension [8].

Joshi SA et al. in the study have shown that the mean time of onset of sensory block and the peak sensory level was significantly earlier in midazolam group compared to clonidine group (p<0.05).

The duration of sensory block was also significantly longer in midazolam group (p<0.05) [9]. In contrast to our study the maximum level of sensory block and duration of motor block were comparable in both the groups.

In our study mean duration of analgesia in Group A was 312.4±53.8 min and in Group B was 404.5± 63.6 min. There was significant difference in mean duration of analgesia between two groups. Duration of analgesia was significantly prolonged in midazolam group.

It is similar to the studies done by Joshi SA et aland Gupta A et al, where in the duration of pain free period was significantly prolonged in midazolam group [9,10]. In contrast to our study Kothari N et al. have shown that adding 50µg of clonidine intrathecally prolongs the duration of analgesia [11].

In our study, we found that the mean heart rate and MAP in group A was lower at various intervals than in patients with group B which was statistically significant, but did not cause any significant bradycardia or associated hypotension. 5.7% of patients in group A and 0% in group B had Bradycardia, 13.4% in group A and 7.7% in group B had Hypotension. 1.9% in group A and 0% in group B had nausea.

There was no significant difference in side effects between two groups. This was similar to the studies done by Elfawal SM et al. and Siddiq S et al. where there was no significant side effects on adding midazolam intrathecally [12,13].

Strength & Limitations of our Study

Strength of our study was using midazolam 2mg intrathecally, we could achieve good postoperative analgesia. Limitations was we could have compared with still lesser doses of midazolam to standardise the dose.

Conclusion

Results from our study show that addition of 2mg of midazolam to intrathecal bupivacaine prolongs the duration of analgesia with minimal side effects when compared to intrathecal clonidine.

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