Original Research Article

Comparison of the effect of intrathecal 0.5% hyperbaric bupivacaine with dexmedetomidine and 0.5% hyperbaric bupivacaine with midazolam in patients undergoing elective lower abdominal surgeries - A prospective randomised controlled double blinded study

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Abstract

Background: Postoperative pain relief is an important issue. In recent years. Use of intrathecal adjuvant has gained popularity with aim of prolonging the duration, intensity of block and postoperative analgesia for better success rate, patient's satisfaction, and faster recovery and less complications with decreased resources utilization compare to general anaesthesia. This study evaluates to compare the effect of intrathecal 0.5% bupivacaine with dexmedetomidine and 0.5% bupivacaine with midazolam. **Methods:** A prospective randomized double blind study will be conducted on 80 adult patients of physical status ASA grade I and II in the age group of 18-60 years, posted for elective lower abdominal surgeries in lower abdominal surgeries. They were randomly divided into 2 groups of 40 each, whereas group BD receives will receive 2.8 ml of hyperbaric bupivacaine (0.5%) + 5µg Dexmedetomidine 0.1 ml (50 mcg ampule (1;10 dilution) + 0.3 ml of Normal Saline and group BM receives 2.8 ml of hyperbaric bupivacaine (0.5%) + 0.4 ml (2mg) of midazolam. **Results:** Duration of motor blockade was significantly prolonged in the dexmedetomidine group (356.35mins) when compared midazolam group (208.85 mins. The time for two segment regression was prolonged in dexmedetomidine group (143.70mins) compared to midazolam group (111.90mins). **Conclusion:** The addition of dexmedetomidine (5 mcg) to intrathecal hyperbaric bupivacaine (0.5%) significantly prolongs the duration of effective analgesia and motor blockade in comparison to 2 mg midazolam to intrathecal bupivacaine (0.5%) without any hemodynamic instability.

Key Words: Dexmedetomidine, Midazolam, Spinal anesthesia, Postoperative analgesia, Motor blockade. Lower abdominal surgeries.

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INTRODUCTION

Spinal anaesthesia with lignocaine was highly popular earlier for short surgical procedures as it had a predictable onset and provided dense sensory and motor blockade of moderate duration. The phenomenon of 'transient neurological symptoms' may be associated with all local anaesthetics; but it is 7-9 times more common with lignocaine than with bupivacaine.[1] In view of controversy and uncertainty with the use of spinal lignocaine, hyperbaric bupivacaine (0.5 %) has replaced lignocaine as the gold standard drug for the safe conduct of spinal anaesthesia in recent times. Sensory and motor blockade is

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satisfactory. But its duration of action, though longer than that of lignocaine, is limited. Post-operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal hyperbaric bupivacaine (0.5 %) by adding various drugs such as opioids[2], ketamine[3], neostigmine[4] etc. However each drug has its own limitations and a need for alternative method or drug always exists. Another group of drugs including clonidine[5], dexmedetomidine [6]and epinephrine provide neuraxial analgesia via α adrenergic receptors and are mainly used as adjuvants to local anaesthetics and opioids. Other drugs that are used for providing neuraxial analgesia include drugs such as neostigmine, ketamine, midazolam and conotoxin ziconotide. The latter drug has recently gained registration for intrathecal use in specific chronic pain conditions.[7] Discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam for analgesia.[8] Several studies have shown that intrathecal or epidural administration of midazolam produces a dose dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory depression or significant sedation. Antinociception produced by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors.[9] It has been found to prolong analgesia when used as an adjuvant to local anaesthetics for subarachnoid block. Analgesic action of α_2 -AR agonists is a result of the depression of the release of presynaptic C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.[6] Preservative free midazolam is also being used in recent times as an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. It is associated with less side effects compared to neuraxial opioids. As there are only a handful of studies comparing intrathecal dexmedetomidine with midazolam, the present study was undertaken to compare the effects of intrathecal dexmedetomidine 5µg and midazolam (2 mg) as adjuvant to intrathecal hyperbaric bupivacaine (0.5 %) for spinal anaesthesia.

Objectives

to compare the effect of intrathecal 0.5% bupivacaine with dexmedetomidine and 0.5% bupivacaine with midazolam **IN PATIENTS UNDERGOING ELECTIVE LOWER ABDOMINAL SURGERIES.**

MATERIALS AND METHODS

A Prospective Randomized double blind controlled study was done in the department of Anaesthesiology at Adichunchanagiri Hospital and Research center, B.G. Nagara, Mandya district from November 2016 to April 2018. Sample size is calculated by considering two sided significance level of 95%, power of study as 80%, and Using results of the previous studies, pilot study-percentage of exposed with outcome (group BM) 56% and unexposed with outcome (group BD) 25% gives a sample size of 80. A total of 40 Patients in both the group were selected based on the random number generated by computerized Random Number software.

1. Group "BD" (n=40) will receive 2.8 ml of hyperbaric bupivacaine (0.5%) + 5µg Dexmedetomidine 0.1 ml (50 mcg ampule (1:10 dilution) + 0.3 ml of Normal Saline.
2. Group "BM" (n=40) will receive 2.8 ml of hyperbaric bupivacaine (0.5%) + 2mg (0.4 ml) of preservative free midazolam.

METHOD OF COLLECTION OF DATA

80 patients aged between 18 years and 65 years of physical status ASA grade I and ASA grade II undergoing elective lower abdominal surgery were included in the study after ethical clearance from the college ethical committee. All patients were visited preoperatively and detailed pre anesthetic evaluation was done and procedure was explained and written informed valid consent was obtained. All routine laboratory investigations was done and radiological investigations if needed. All patients were kept nil per orally prior day of surgery and received Tab Rantac 150mg and Tab Anxit 0.5mg as premedication.

INCLUSION CRITERIA

All patients willing to give consent between the age group of 18 to 65 years posted for elective lower abdominal surgery

1. ASA physical status I and II
2. Age between 18 to 60 years.
3. Weight between 50 to 80 kg.
4. Patients with valid informed consent.
5. Those patients scheduled to undergo elective lower abdominal surgeries under subarachnoid block.
6. Height of the patient >150 cms

EXCLUSION CRITERIA

1. Patient refusal.
2. Patients belonging to ASA Grade 3 and Grade 4.
3. Patients with gross spinal abnormality, localized skin infection, sepsis, hemorrhagic diathesis or neurological diseases.
4. Patients physically dependent on benzodiazepines.
5. Patients with history of drug allergy.
6. Pregnancy.
7. Patients with cardiac, pulmonary, hepatic or renal disorders.
8. Patients with peripheral neuropathy.
9. Patients having inadequate subarachnoid blockade and who are later supplemented by general anesthesia.

Pulse rate, NIBP, spo2 will be recorded every 5mins for first 30mins, every 10mins for next half an hour and then every 15mins till end of surgery. No other sedative or analgesic will be administered in the study period. The occurrence of adverse events like hypotension, bradycardia, pruritus, nausea and vomiting will be noted. Hypotension [10] (<30% from basal) and bradycardia (heart rate < 50 bpm) are most common side effects of spinal anesthesia, these are corrected by using injection Ephedrine 6mg IV and injection Atropine 0.02mg/kg respectively. A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.

Data was entered into MS Excel and analyzed using SPSS VERSION 20.0.

Data obtained will be categorized and will be expressed in terms of rates, ratios, and percentage and continuous data which will be expressed as mean ± standard deviation (SD).

The comparison between two groups will be done by use of Students unpaired 't' test. A probability value (p value) of less than or equal to 0.05 will be statistically significant. Chi square/ Fischer Exact Test will be been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

A comparative clinical study with 80 patients, randomized into two groups, 40 in each group, were undertaken to study the addition of intrathecal dexmedetomidine to hyperbaric bupivacaine and midazolam under subarachnoid block for lower abdominal surgeries.

Table 1: DEMOGRAPHIC VARIABLES

	GROUP BD	GROUP BM	*P* VALUE
No of patients	40	40	
Mean age (years)	41.38	40.60	0.760
male	20	20	1.000
female	20	20	1.000
Mean weight	55.45±6.388	57.30±6.135	0.360
Mean height	162.35±5.903	163.32±6.910	0.854
ASA 1	20	20	1.000
ASA 2	20	20	1.000

There is no significant difference among the groups with respect to Age, Height and Weight. The above groups shows that mean age (years) of patients in group BD is 41.38 And in group BM is 40.60 years. Both groups are comparable as suggested by *p* Value of 0.760. The Group BD had 50 % male patients and 50% female patients and Group BM shows 50% male and 50% female patients. Both groups are comparable as suggested by *p* value of 1.000. The Group BD patients with mean weight 55.45 ± 6.kg and Group BM patients with mean weight of 57.30 ± 6.135kg. Both groups are comparable as suggested by *p* value of 0.360. The Group BD has a patients with mean height of 162.35±5.903 cm and Group BM has patients with mean height of 163.32±6.910cm. both groups are comparable as suggested by *p* value of 0.854.

TABLE 2: Comparison of highest sensory level attained

	Group	HIGHEST SENSORY LEVEL						Total	*p* value
		T2	T3	T4	T5	T6	T8		
V1	**Group BD**	1	3	9	5	15	7	40	
	Group BM	1	3	8	3	16	9	40	0.828
Total	**Total**	2	6	17	8	29	16	80	

In both the groups only one patient attained highest sensory level of T2.

Table 3: Comparison of Mean time various parameters in both the groups

Variable	Group	N	Mean	Std. Deviation	Std. Error Mean	T	df	*p* value
TWO SEGMENT	Group BD	40	143.70	14.442	2.283	11.096	78	0.001
	Group BM	40	111.90	10.954	1.732			
Onset(sec)	Group BD	40	252.38	23.965	3.789	.632	78	.529
	Group BM	40	248.25	33.637	5.319			
Duration(Min)	Group BD	40	356.35	11.16	3.220	-.302	78	0.001
	Group BM	40	208.85	10.81	3.776			
Duration of Complete Analgesia(Min)	Group BD	40	300.10	22.430	3.547	12.139	78	0.001
	Group BM	40	238.18	23.189	3.667			

The two segment regression in group BM with mean value of 111.90 was faster than group BD with mean of 144.70 which was statistically significant with *p* value of 0.001. there were no statistically significant difference between two groups with respect to onset of motor blockade as significance value obtained from independent sample's t test was more than 0.05 (*p* value0.529). The motor blockade duration is significantly prolonged in Group BD with mean value of 356.35mins when compared to Group BM where it is 208.85 mins. The postoperative analgesia duration is significantly prolonged in Group BD with mean value of 300.10 min when compared to Group BM where it is 238.18 mins. there was strong statically significant difference between two groups as suggested by the *p* value of <0.001.

TABLE 4: Comparison of Sedation Grades in both the groups

SEDATION GRADE	Group		*p* value
	BD	BM	
GRADE 1	23	26	0.646
GRADE 2	13	12	
GRADE 3	4	2	
GRADE 4	0	0	
GRADE 5	0	0	
GRADE 6	0	0	
TOTAL	**40**	**40**	

There were no statistically significant difference between two groups with respect to sedation grade with significance value obtained from independent sample's t test was more than 0.05 (*p* value 0.646).

DISCUSSION

Bupivacaine is an amide type of local anaesthetic, a racemic (50:50) mixture of S and R enantiomers. Since its introduction is 1956, it has been used as drug of choice for spinal anaesthesia due to its longer duration of action (3 -7 hours), limited placental transfer and minimal neonatal effects compared to other local anaesthetics. Dexmedetomidine, a pharmacologically activated- isomer of medetomidine was first synthesized in late 1980's. Dexmedetomidine is a selective α2-adrenoceptors agonist that modulates antinociception by inhibiting peripheral norepinephrine release, thus terminating the propagation of pain signals. At the same time postsynaptic activation of α2-adrenoceptors in the central nervous system inhibits sympathetic activity and may result in hypotension and bradycardia. Dexmedetomidine is a highly selective α2 adrenergic agonist which has both analgesic and sedative properties when used as an adjuvant in regional anaesthesia. Dexmedetomidine became α_2 agonist of choice, due to its greatest $\alpha_{2:}\alpha_1$ affinity (8 times greater than clonidine). This increased selectivity results in more predictable and effective sedation and analgesia and fewer side effects. Dexmedetomidine when added with local anesthetics improves the quality of intra operative anesthesia, prolongs the duration and quality of postoperative analgesia with fewer side effects permitting the usage of lower doses of local anesthetics. It is also found to have synergistic effects with local anesthetics without intensifying or delaying the recovery of motor blockade. Midazolam, a benzodiazepine derivative, is a water soluble, short acting benzodiazepine with a potency of 2-3 times that of diazepam. modulates antinociception through gamma-amino butyric acid (GABA) receptors present in the dorsal horn of the spinal cord and through the activation of spinal δ-opioid receptor[11]. In contrast to sympatholytic effects of dexmedetomidine, intrathecal midazolam keeps the function of sympathetic nervous system intact, but may result in excessive sedation due to its GABA mimetic and opioid induced analgesia. [12,13] Choudhary B, Sharma N, *et al.*.[14] studied about 120 patients of ASA grade I and II undergoing lower abdominal surgeries. The duration of effective analgesia was significantly prolonged in the dexmedetomidine group (298.1±14.1 minutes) when compared with midazolam group (242.6±18.0 minutes) and the control group (223.4± 12.8 minutes). The time for two segment regression was significantly prolonged in Group B (143.1± 6.2 minutes) as compared to Other groups. Samantaray A, Hemanth N *et al.*.,[15] studied effects of adding midazolam versus dexmedetomidine to intrathecal bupivacaine on post-operative analgesia in patients undergoing endo-urological surgeries, In their study the duration of effective analgesia was significantly prolonged in dexmedetomidine group 281±64 mins when compared to midazolam group 236.9±64.9 mins and control group 212.7±+70.2 mins respectively clearly indicating dexmedetomidine prolongs post-operative analgesia compared to midazolam and control group. In this study there were no significant differences in the side effects. Gupta A *et al.*[16] conducted a study on 60 patients who were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 5 mcg dexmedetomidine (group D, *n*=30) or 12.5 mg hyperbaric bupivacaine plus 25 mcg fentanyl (group F, *n*=30) intrathecal. They found significant differences, the patients

with dexmedetomidine group (D) had a prolonged sensory and motor block time than patients in fentanyl group (F). Halder S, [17] studied 80 patients, 20-60yrs posted for elective lower limb orthopaedic surgery of traumatic origin under spinal anaesthesia were divided into 2 equal groups (group D5(n=40) 3ml 0.5% hyperbaric bupivacaine+5mcg dexmedetomidine in 0.5 ml of normal saline and group D10 (n=40) 3ml 0.5% bupivacaine+10mcg dexmedetomidine in 0.5 ml of normal saline were administered intrathecally. They found out that postoperative analgesia of group (D5) 227.00±19.85 mins was lower than group (D10) 241.80±42.10. The sensory regression time to T10 and S2 was significantly delayed in D10 group when compared to group D5 (160.63 vs. 130.12 and 216.50 vs. 189.10 min respectively) which means increased dexmedetomidine at subarachnoid space had produced more sustained sensory block. Shadangi B K, Garg R, Pandey R *et al.*. [18] had done a study on bupivacaine and bupivacaine with midazolam 2 mg the onset, duration of sensory/motor block, time to first rescue analgesia and side effects were noted. And concluded that duration of sensory block was prolonged without much increase in motor blockade when midazolam 2mg was given intrathecally. Similar results were obtained in our study with the midazolam group. Neerja Bhartia *et al.*. [19] comparing the effects of intrathecal midazolam 2 mg and fentanyl 25 mcg as additives to intrathecal bupivacaine 10 mg also found out that both intrathecal midazolam (284.2±18.2min) and fentanyl (272.4±15.6 min) prolonged the duration of postoperative analgesia significantly compared to bupivacaine alone (197.8±16.8 min), but the differences in the duration of postoperative analgesia were not very much significant between the groups.

CONCLUSION

Subarachnoid block is a widely employed technique. Despite excellent quality of anaesthesia and motor block that could be achieved with inthrathecal local anaesthetics, patient still needs prolonged post-operative analgesia. The present study shows that addition of 5 mcg dexmedetomidine intrathecally to 0.5 % bupivacaine prolongs motor blockade and post-operative analgesia without any hemodynamic instability and without any adverse effects when compared to intrathecal 2mg of midazolam to 0.5% bupivacaine.

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