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ORIGINAL RESEARCH

Comparison of the Effect of Adding Dexmedetomidine versus Midazolam to Intrathecal Bupivacaine on the Post-Operative Analgesia

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ABSTRACT

Background: Dexmedetomidine and midazolam both affects duration of spinal analgesia by different mechanisms, and yet, no studies are available to compare them for postoperative analgesia after neuraxial administration. We investigated the addition of dexmedetomidine or midazolam to intrathecal bupivacaine on the duration of effective analgesia.

Materials and Methods: The patient posted for elective procedure under spinal anaesthesia were randomly allocated in to three group of 20 patient and each group. Group D- Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 5mcg Dexmedetomidine the total volume is 3.5ml. Group M - Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 1mg of Midazolam, the total volume is 3.5 ml. Group B-: Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 0.5 ml of normal saline, the total volume is 3.5 ml. The groups were compared to the regression time of sensory block, duration of effective sedation score, and side effects.

Results: The mean duration of sensory and motor block was quite prolonged in group D patients The results were, statistically highly significant (P<0.0l) There is significant difference between all the three groups in group D the sensory duration block is 226 minutes while in group M is 158.7 minutes, In group B this Is 134.8 minutes which is much less than the above groups. The motor block in group D 202.35 minutes, in group M is 110.5 minutes and in group B is 96.8 minutes.

Conclusion: Dexmedetomidine (5mcg) when used as an adjunct to 3 ml of 0.5% hyperbaric bupivacaine and prolongs the duration of effective analgesia in the immediate postoperative period without any significant hemodynamic instability in comparison to 1 mg midazolam.

Keywords: Dexmedetomidine, midazolam, intrathecal, spinal anaesthesia, subarachnoid block, postoperative pain

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INTRODUCTION

Subarachnoid block is a safe and effective alternative to general anaesthesia when surgical site is located on the lower extremities, perineum and lower abdominal wall. The patient undergoing lower abdominal as well as lower limb surgery usually experience mild to

moderate degree of pain in immediate postoperative period, adding neuraxial adjuvant prolongs the duration of sensory block thereby extended postoperative pain relief. Various adjuvant have been tried and tested for their post-operative pain relief property. Both Dexmedetomidine and Midazolam are shown to be effective in this regard. These drugs modulate spinal analgesia by different mechanism.Dexmedetomidine is selective Alfa 2 adreno-receptor-agonist that modulate-antinociception by inhibiting peripheral norepineprine release thus terminating the propagation of pain spinal At same time post synaptic activation of Alfa 2 adrenoreceptor in the central nervous system inhibit sympathetic activity and may result in hypotension and bradycardia.Midazolam a benzodiazepine derivative modulate antinociception through gamma amino butyric acid (GABA) receptor present in the dorsal horn of spinal cord and through activation of spinal delta-opiod receptor. In contrast to dexmedetomidine, Midazolam keeps the central nervous system intact.In the present study we have tried to prospectively compare of the effect of adding dexmedetomidine versus midazolam to intrathecal bupivacaine on the duration post-operative analgesia, post-operative sedation and obvious adverse effect.

MATERIALS & METHODS

After approval of Institutional ethics committee, a prospective and randomized comparative study was conducted on 60 patients undergoing elective surgery under spinal anaesthesia, having ASA physical status I and II, aged 20-60 years were included in study.Written informed consent was obtained from all patients. Patients were randomly allocated by online computer-generated randomizer (http://www.randomizer.org) to one of three Groups comprising 20 patients in each: Group D- Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 5mcg Dexmedetomidine the total volume is 3.5ml. Group M - Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 1mg of preservative free Midazolam, the total volume is 3.5 ml, Group B-: Patient in the group receiving 3 ml of 0.5% hyperbaric Bupivacaine with 0.5 ml of normal saline, the total volume is 3.5 ml.

The intrathecal (IT) injections were given at the L3-L4 or L4-LS intervertebral space using 25 G QUINKE spinal needles in sitting position to all the patients of three groups. The intrathecal injection was given after the confirming the free flow of CSF. All patients received supplemented oxygen at rate of 6lit per min through face mask. An infusion of ringer solution is given 2ml/kg/hr during anaesthesia and rate of infusion was altered depending upon the hemodynamic response. Blood pressure recorded at every 5min.for the first 15min and there after every 15 min until the end of surgery. Hypotension is defined as decrease in systolic blood pressure by more than 20% of base line blood pressure or below 90mm of Hg. Hypotension is treated with addition of intravenous fluid 4ml/kg repeated 2 times. If failed to reverse then bolus dose of i.v. ephedrine 1mg/kg. Bradycardia is defined as an absolute decrease in heart rate below 55 beats per min. Bradycardia is treated with I.V. Atropine 6 mg at repeated dose.

Sensory block onset time (Time interval between the completion of intrathecal drug injection to the onset of complete loss of pinprick sensation), level of sensory blockade, the time to reach this level from the time of injection and duration of sensory blockade (defined as the time interval from completion intrathecal drug injection) and two segment regression of sensory block by pin prick method was recorded. The degree of sensory blockade assesed by visual analogue score.Onset of motor block (time elapsing from intrathecal injection to failure to raise the lower limb on comment) and degree of motor block (assessed by bromage score- 0: No motor loss, 1: Inability to flex the hip, 2: Inability to flex the knee joint, 3: Inability to flex the ankle) was noted. Degree of motor blockis assesed by (the time interval between completion of IT injection to the onset of Bromage score 1) was recorded.

Level of sedation assist by Ramsay Sedation Score- 1-Anxious, agitated and restlessness, 2-Oriented and cooperative, 3-Respond to command only, 4- Brisk response to loud voice , 5-Sluggish to no response to loud voice, 6 - No response even to pain. The level of sedation assessed before giving SAB and then assessment was repeated every 15 min intra-operatively and postoperatively using following score.

All calculations of durations were done considering the time of subarachnoid injection as time "zero." Heart rate, mean arterial pressure (MAP), SpO2, were recorded every 5 min for 1 h and then every 15 min till 2 segment regression of sensory block. All the patients were assessed for post procedural complication like hypotension and bradycardia-Hypotension, Bradycardia, Respiratory depression (RR< 8/min), Shivering, Nausea and Vomiting.

RESULTS

Table 1: Patients Demographic and Intra-Operative Data.

Variables	Group M (n=20)		Group D		Group B		P value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	34.25	11.55	36.85	12.20	36.75	9.62	>0.05
Weight (kg)	62.20	8.2	61.05	9.2	64.2	10.2	>0.05
Duration of surgery (min)	109	25.73	91.85	42.27	108.5	26.59	>0.05

Values are expressed as mean ± SD. #Values are expressed as numbers. SD = Standard deviation.

Table 2: Characteristic of Sensory and Motor Blockade.

Variables (min)	Group M (n=20)		Group D		Group B		P value
	Mean	SD	Mean	SD	Mean	SD	
Mean onset of sensory block(seconds)	227	39.38	141.35	27.35	262.35	40.09	<0.001
Mean onset of motor block(seconds)	254.5	66.68	205	27.38	320.25	41.94	<0.001
Peak onset of sensory block(seconds)	396.5	85.22	394.5	92.47	484.5	51.75	<0.001
Two segment regression (sensory block)	103.5	18.7	158.75	11.11	75.25	10.32	<0.01
Regression up to S2 level (sensory block)	158.75	11.11	226	23.8	134.8	16.92	<0.01
Motor effect to bromage 1 (Motor Block)	110.5	10.35	202.35	20.38	96.8	14.20	<0.01
Time of 1st analgesia requirement (min)	179.0	11.2	300.0	15.4	161.4	6.83	<0.001

Table 3: Comparison of Sedation Score (Ramsay Sedation Score).

Time of observation	Group M (n=20)		Group D		Group B		P value
	Mean	SD	Mean	SD	Mean	SD	
0 min	1.8	0.615	2.3	.571	1.8	.615	>0.05
15 min	2.6	.5026	2.4	.502	2.8	.410	>0.05
30min	2.6	.5026	2.6	.502	2.7	.470	>0.05
1hr	2.35	.489	2.75	.444	2.4	.502	>0.05

4hr	2	0	2	0	2	0	>0.05
6hr	1.9	.4472	2.05	.22	1.9	.44	>0.05

Table 4: Adverse Effects.

Side Effects	Group M	Group D	Group B	P value
Nausea-Vomiting	1	2	1	>0.005
Bradycardia	-	3	-	>0.005
Hypotension	6	6	3	>0.005
Dry Mouth	1	-	2	>0.005
Shivering	2		4	>0.005

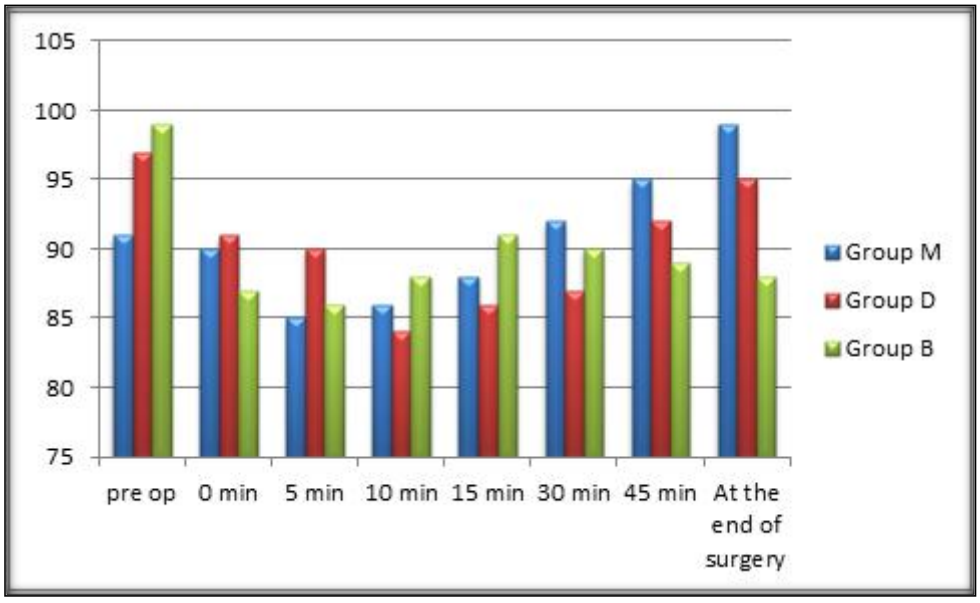

Figure 1: Mean Arterial Blood Pressure

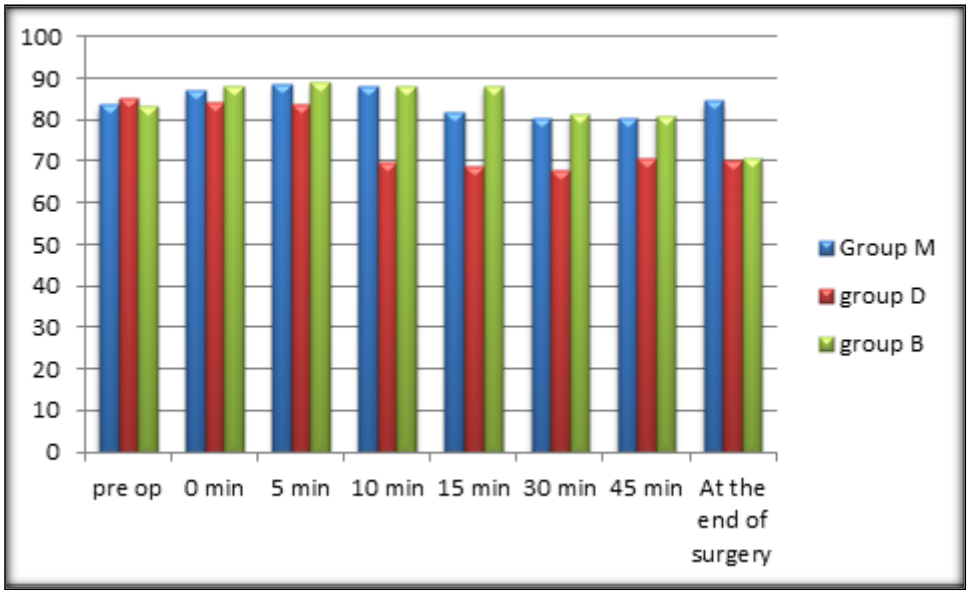

Figure 2: Variation in Pulse Rate

The study was conducted in sixty patient of either sex undergoing lower abdominal and lower limb orthopaedic surgeries under spinal anaesthesia. The sixty patients were randomly allocated to into 3 groups and there were no dropouts from the study after randomization. The

study groups (Group D, M and B) were found to be comparable with respect to patient's characteristics such as age, weight and duration of surgery [Table-1]. Spinal anaesthesia was successful in all the patients in both groups and no patient in either group required rescue analgesia (fentanyl) or general anaesthesia.

The characteristics of spinal sympathetic and motor blockade are depicted in [Table 2]. The peak sensory levels reached, time to onset of sensory block, motor block, and peak sensory block were not significantly different among the groups. Time to 2-segment regression of sensory analgesia and duration of effective analgesia (time of the first rescue analgesic requirement) was significantly longer in the dexmedetomidine group (300± 15.4 minutes) in comparison to the midazolam group (179.0±11.2 minutes) and the control group (161.4±6.83minutes) (P = 0.001) with no significant difference between the midazolam and control group. Comparison of Sedation Score is depicted in [Table-3].

Incidences of hypotension, bradycardia, shivering, nausea, and vomiting were similar among the groups [Table 4]. All patients in both study groups had complete recovery of sensory and motor functions. No patient in either group had any neurological impairment like pain or numbness in leg, back or buttock, incontinence or retention of urine, headache in postoperative period or thereafter.

DISCUSSION

Statistical Analysis

Categorical variables were shown in number or as a percentage (%) and continuous variables were shown as mean _ SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test were used. Quantitative variables were compared using Independent t test/Mann-Whitney Test between the two groups. Qualitative variables were correlated using Chi-Square test. The p value of <0.05 was considered to be statistically significant. The data was entered in MS EXCEL spread sheet and analysis was done using SPSS (IBM Corp. Released 2013. IBM SPSS Statistical Package for Windows, Version21.0. Armonk, NY: IBM Corp).

Bupivacaine is well approved for intrathecal route. It has shown to produce good quality anaesthesia in all surgeries. Since hemodynamic parameters are well maintained and it is quite safer than the older drugs. It is been studied with interest worldwide Moreover property of sensory, motor dissociation and early disappearance of motor paralysis raises prospects of early discharge of the patient, making it an ideal drug for day care surgery Intrathecal Alfa 2 agonist are used as adjuvant drugs to local anaesthetics. They potentiate the effect of local anaesthetics and allow are decrease in the required dose. Its addition to anaesthetics prolong the duration both sensory and motor spinal block.

Dexmedetomidine is an Alfa 2 adreno receptor agonist that is approve as an intravenous sedative and co-analgesic drug. It has an Alfa 2 /Alfa 1 selectivity ratio higher. Both Midazolam and Dexmedetomidine are relatively newer additions to the list of adjuvant used in IT anaesthesia and may act synergistically with IT Bupivacaine to prolong the duration of postoperative analgesia However, both the drugs differ in their mechanism of action in mediating antinociception when introduced intrathecally.[1,2,3]

This is the study comparing Midazolam and Dexmedetomidine as neuraxial adjuvant with 0.5% hyperbaric bupivacaine in spinal anaesthesia. The current study results showed that the addition of 5 mcg Dexmedetomidine or 1 mg Midazolam as an adjunct to 3 mol of 0.5% hyperbaric Bupivacaine prolonged the duration of effective analgesia in the postoperative period compared to Bupivacaine alone.

Onset of sensory and motor block

In our study both 5 mcg of Dexmedetamidine and 1mg of Midazolam increased the duration of effective analgesia in the postoperative period but this reached statistical significance only between the Dexmedetomidine versus Midazolam and control group and not between the Midazolam and control group. The mean onset of sensory block is significantly shorter in group D 141.35 sec and in group M 227 sec than group B 262.35, P<O.OO1 These values also significantly differ between group D and group M. Similarly motor onset of block in group D is 205 sec and in group M is 254.5 sec while in group B is 320.25 These values also significantly differ between group D and group M and p value <001.

Peak Onset of Sensory Block

The mean time taken far the peak onset of sensory, block was quite low in group D patient. In group D this is 394.5 sec while in group B is 484.5 sec.The between group D and group B is less but variation is more there by showing statistically highly significant difference in peak onset of sensory block.

Mean Duration of Sensory Block

The mean duration of sensory and motor block was quite prolonged in group D patients The results were, statistically highly significant (P<0.0l) There is significant difference between all the three groups in group D the sensory duration block is 226 minutes while in group M js 158.7 minutes. In group B this Is 134.8 minutes which is much less than the above groups. The motor block in group D 202.35 minutes, in group M is 110.5 minutes and in group B is 96.8 minutes.

Duration of first analgesic requirement

Dexmedetomidine appears to be more analgesic efficient than midazolam as evidenced by a longer duration of effective analgesia or the time to first analgesic request/administration IT Midazolam and Dexmedetomidine influence the characteristics of spinal block in terms of prolonging the duration of sensory analgesia and time to first postoperative analgesic request.

In this study first analgesic requirement in group D is 300 min whereas in group M is 179 min and in group B is 161.40 mm Between group D and M this is significant and also significant from group B which shown by P value <0.001.Although between group M and group B this not much significant but the p value also near to<.001.

A study by Sanwal et al,[4] showed that it's the dose of Bupivacaine and not the dose of Midazolam that determine the time to onset of sensory or Motor block. In our study, we used an equal amount of hyperbaric bupivacaine (15mg) and all 3 groups were comparable regarding the time to onset of sensory and motor block and time to reach peak sensory block and the height of block.

Kim and Lee,[5] as well as Prakash et al,[6] in their dose finding study used 1mg or 2 mg of IT Midazolam along with a fixed dose bupivacaine. Both these studies concluded a prolongation of duration of effective analgesia in the postoperative period in either dose of midazolam.

Whereas studies using a very small dose of Dexmedetomidine (3 mcg) could demonstrate significantly longer duration of sensory block and the time to first analgesic request,[7,8] a finding also supported by other authors using Dexmedetomidine in the range of 5 - 15 mcg.[9,10]

The mean of pulse rate between all the three groups were almost similar and statistically not significant (P>0.05). Although in Group D the pulse rate is decrease comparable to group M and Group B. But the patient is haemodynamically stable throughout intraoperative period. The means of MAP (Mean Arterial Pressure) between all the three groups were almost

similar and statistically not significant P<0.005).Both Midazolam and Dexmedetomidine have a supra-spinal mechanism of action but their sedative effect after IT administration has not been reported in depth.

Yegin et al,[11] reported a mild but statistically significant sedative effect with IT Midazolam 2 mg, whereas, other authors did not find such difference in comparison to their respective control group.Hala et al,[12] concluded that higher doses of IT Dexmedetomidine (15 mcg) not only prolong the duration of effective analgesia but also result in lower Ramsay sedation scores (median score of 2 - 4). In our study the Dexmedetomidine group patients tended to be more sedated in the first 30 minutes after the IT injection However, all patients were oriented, cooperative, and promptly responded to verbal command at the end of surgery. The mean of Ramsay Scores at different time intervals between all the three groups were almost similar and statistically not significant (P>0.05).

The most significant hemodynamic side effects that can be expected with the use of IT alfa-2 adrenoreceptor agonists are bradycardia and hypotension in our study bradycardia and hypotension is noted with group D and group M. Side effects observed in our study, were almost similar in all the three groups statistically not significant (P<0.05)

Joshi et al,[9] in their study, compared 2 mg Midazolam to 30 mcg of Clonidine added to 15 mg: of O.5% hyperbaric bupivacaine and found a higher incidence of hypotension/bradycardia in the Clonidine group compared to the Midazolam group. Karbasfrushan et al,[13] reported a higher incidence of nausea and vomiting in the midazolam group compared to the Bupivacaine control group where as others did not find any difference in occurrence of postoperative nausea and vomiting in comparison to the control group.

In our study we did not account for the duration of the motor block. We have limited our observations to sensory black characteristics because the primary aim of the study was to identify whether Dexmedetomidine or Midazolam was more efficient in providing a longer pain-free period.

CONCLUSION

With this study we conclude that Dexmedetomidine (5mcg) when used as an adjunct to 3 ml of 0.5% hyperbaric bupivacaine and prolongs the duration of effective analgesia in the immediate postoperative period without any significant hemodynamic instability The mild sedation resulting from intrathecal Dexmedetomidine may be beneficial in procedures.

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