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Original Research Article

A comparative study of intravenous dexmedetomidine and midazolam on prolongation of spinal anesthesia

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ABSTRACT

Background: The present study was conducted to compare the efficacy and safety of intravenous dexmedetomidine and midazolam on prolongation of spinal anesthesia.
Methods: The study population included people who were undergoing for spinal anesthesia for various surgeries. A total of 90 subject were randomized equally to Dexmedetomidine, Midazolam and saline groups using a computer generated random number sequence. Three study groups were compared with respect to all the baseline variables. The key outcome parameters and hemodynamic parameters were compared among the three study groups.
Results: No statistically significant differences were observed in baseline paramters across study groups. The median values of patient satisfaction score and anesthesiologist satisfaction score were almost equal among three study groups, but the association was statistically not significant. The median VAS and the median HSL were slightly lower in dexmedetomidine group than other two groups (VAS-1,2,3 respectively and HSL -4,6,6 respectively) with statistically significant association (P<0.001). The proportion of Bradycardia and hypertension was slightly higher(13.3%) in dexmedetomidine group than other two groups whereas patients with excessive sedation 16.7% in midazolam group. The proportion of patients requiring analgesic for the first 24 hours was 36.7% in saline group, 33.33% in midazolam group. The association between symptoms and study groups was statistically not significant (P value>0.05) except with number of patients requiring analgesic for the first 24 hours (P value<0.05).
Conclusions: Measurement of patient and anesthesiologist satisfaction scores are more or less similar in midazolam and dexmedetomidine groups compare to saline group.

Keywords: Dexmedetomidine, Midazolam, Spinal anesthesia

INTRODUCTION

Although spinal anaesthesia has been established as simple and safe anaesthesia+ technique for short to intermediate duration of infra umbilical surgeries, it may not be very comfortable for all, especially those with high level of anxiety, prolonged surgeries with uncomfortable positions and inadequate level of spinal block. These patients at times may need supplementation with sedative-analgesic or conversion to general anaesthesia, with potential risk of respiratory depression and consequent hypoxemia.

Dexmedetomidine being a sedative with analgesic without respiratory depressant property provides, intraoperative sedation, alleviates position related discomfort and to an extend can cover up inadequate block height along with prolonging the postoperative analgesia. Adequate sedation after spinal anaesthesia reduces patient anxiety level, physiological and

psychological stress, and increases the patient and surgeon satisfactions.[1-3]

Different adjuvants have been used to prolong spinal anesthesia, with the possible advantages of delayed-onset of postoperative pain and reduced analgesic requirements. Dexmedetomidine, a highly selective a 2-adrenoreceptor agonist, has been used for premedication and as an adjunctto general anesthesia. Intravenous dexmedetomidine pre-medication before general anesthesia provides preoperative sedation, analgesia, and hemodynamic stability and reduces requirements for intraoperative inhalational agents and postoperative analgesics. Also, it has been used safely as premedication or as a sedative agent in patients undergoing surgical procedures under regional anesthesia. Although a synergistic interaction between intrathecal dexmedetomidine and local anesthetics has been observed in previous studies, there are no clinical data regarding the effect of intravenous dexmedetomidine premedication on the duration of sensory and motor block during spinal anesthesia.[4]

Dexmedetomidine is a selective alpha-2-adrenoceptor agonist. It exerts both sedative and analgesic effects via mechanisms different from other sedatives such as midazolam and propofol, and provides sedation characterized by prompt response to stimuli with no respiratory depression.[5]

Recently, dexmedetomidine, a selective a2-adrenoreceptor agonist, was a focus of interest for sedation during regional anesthesia due to its rapid offset, prolongation of spinal anesthesia, and excellent postoperative analgesia characteristics.[3,4] In addition, dexmedetomidine has a biphasic hemodynamic effect, whereby an initial increase in blood pressure by a 2-receptor-mediated peripheral vasoconstriction is followed by a decrease due to norepinephrine release and sympathetic activity inhibition in central nervous system.

METHODS

The study was conducted with an objecteive of comparing efficacy and safety of intravenous dexmedetomidine, midazolam and normal saline on prolongation of spinal anesthesia. The study was a randomized open labelled controlled trail, conducted in the department of anaesthesiology, Velammal medical college & research institute, Madurai, Tamil Nadu. The data collection for the study was done between June 2016 to June 2017, i.e. for a period of One year. The study population included people who were undergoing for spinal anesthesia for various surgeries.

The study population were randomized to intervention group dexmedetomidine, midazolam and saline groups using a computer generated random number sequence. The allocation sequence was concealed from the investigator by serially numbered opaque envelops, which were kept in the custody of an independent statistician. The investigator blinding was not possible in the study. The participant involved in the study and the statistician analysing the data were blinded for the intervention. The sample size included 30 subjects in each of the intervention groups, which was assessed basing on the published data, assuming 80% power of study and 5% alpha error, using STAT IC software version 13.

The study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants, after explaining the risks and benefits involved in the study and voluntary nature of participation. All the personal data of the participants was kept confidential throughout the study. After obtaining informed written consent, thorough history and clinical examination was done on each participant

The subjects in dexemedetomidine group received 1µg/kg over 10min the participants in Midazolam group received midazolam 0.05mg/kg and the participants in saline group received normal saline the key outcome variables assessed were highest sensory level (min), duration of surgery (min), regression of sensory block (min), regression o motor block (min) and request for analgesia (min). Three study groups were compared with respect to all the baseline variables. The key outcome parameters and hemodynamic parameters were compared among the three study groups. Quantitative variables were compared by mean and standard deviation, using Independent sample t-test. Categorical variables were compared by using Chi square test. P value < 0.05 was considered as statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

The mean age of patients in Bupivacaine and dexmedetomidine group was 43.70 years, in Bupivacaine and midazolam group was 45.33 years and in Bupivacaine and saline group it was 41.60 years. The association among the anesthesia agent group and age was statistically not significant (P value >0.05). The proportion of males in bupivacaine and dexmedetomidine group was 73.33% compare to female (26.66%). Similarly, the proportion of male in bupivacaine and midazolam and bupivacaine and saline group was 80% and 73.33% respectively. The association of Gender with anesthesia agent groups was statistically not significant (P value > 0.05). The mean Height of patients in 3 study groups was almost same as in Bupivacaine and dexmedetomidine group it was 152.50cm, in Bupivacaine and midazolam group it was 152.30cm and in bupivacaine and saline group it was 152.47cm. The association among the anesthesia agent group and Height of patient was statistically not significant (P value >0.05). The mean weight was little high in bupivacaine and midazolam group as 58.57kg whereas mean weight of patients in bupivacaine and dexmedetomidine group and

bupivacaine and saline group was 56.73 and 56.90 respectively. The association of weight of patients with anesthesia agent groups was statistically not significant (P value >0.05). The proportion of Grade I ASA patients was more in all 3 study groups compared to Grade II ASA as in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and bupivacaine and saline group proportion of ASA grade I patients was 53.3%, 53.3% and 50% respectively.

The association of ASA grades with anesthesia agent groups was statistically not significant (P value >0.05). The mean duration of surgery in minutes was little high in bupivacaine and dexmedetomidine group as 41.2min where as in bupivacaine and midazolam group and bupivacaine and saline group it was 40.60 and 39.67min respectively. The association of duration of surgery with anesthesia agent groups was statistically not significant (p value >0.05). The mean fluids intake by patients was 856.67ml, 862ml and 873.67ml in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and bupivacaine and saline group respectively. The association among study groups and fluids was statistically not significant (P value >0.05). The mean heart rate of patients in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and bupivacaine and saline group was 77.43, 76.47 and 75.47 respectively. The association of heart rate with study groups was statistically not significant (P value >0.05). The mean MAP of patients in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and bupivacaine and salinegroup was 102.10, 97.53 and 101.53 respectively. The association of MAP with study groups was statistically not significant (P value>0.05) (Table 1).

Table 1: Comparison of baseline parameters among the 3 study groups (N=90).

Parameter	Group			P value
	Bupivacaine and dexmedetomidine (N=30)	Bupivacaine and midazolam (N=30)	Bupivacaine and saline (N=30)	
Age	43.70± 13.75	45.33± 12.34	41.60± 13.84	0.56
Gender				
Male	22 (73.33%)	24 (80%)	22 (73.33%)	0.79
Female	8 (26.66%)	6 (20%)	8 (26.66%)	
Height	152.50 ± 6.20	152.30 ± 7.23	152.47 ± 6.84	0.99
Weight	56.73 ± 11.52	58.57 ± 8.77	56.90 ±11.55	0.76
ASA				
Grade1	16 (53.33%)	16 (53.33%)	15 (50%)	0.96
Grade2	14 (46.66%)	14 (46.66%)	15 (50%)	
Duration (min)	41.2± 03.87	40.60 ± 4.99	39.67 ± 5.25	0.45
Fluids (ml)	856.67± 35.56	862.00± 43.50	873.67± 47.38	0.29
HR	77.43± 6.93	76.47± 8.29	75.47± 10.15	0.67
MAP	102.10± 9.68	97.53± 8.22	101.53± 8.78	0.26

Table 2: Comparison of regression parameters among the 3 study groups (N=90).

Parameter	Group			P value
	Bupivacaine and dexmedetomidine (N=30)	Bupivacaine and midazolam (N=30)	Bupivacaine and saline (N=30)	
Regression of Sensory block (min)	149.63±22.95	105±33.52	104.67±15.6	<0.001
Regression of Motor block (min)	205.33±17.01	183.23±28.91	187.63±14.36	<0.001
Request for analgesia (min)	203.03±37.68	140.9±20.61	120.5±26.66	<0.001

The mean regression of sensory block in bupivacaine and dexmedetomidine group was 149minutes, in bupivacaine and midazolam group was 105minutes and in bupivacaine and saline group was 104minutes, the association of regression of sensory block among study groups was statistically significant (P value <0.001). The mean regression of motor block was little high in bupivacaine and dexmedetomidine group as 205.33 and the same was 183 minutes in bupivacaine & midazolam group and 187minutes in bupivacaine and saline group, the association of regression of motor block among study groups was statistically significant (P value <0.001). The mean request for analgesia in bupivacaine and dexmedetomidine group was 203minutes, in bupivacaine

and midazolam group was 140minutes and in bupivacaine and saline group was 120minutes, the association of request for analgesia (minutes) among study groups was statistically significant (P value <0.001) (Table 2).

Among 30 patients in bupivacaine & dexmedetomidine group only 11 patients with patient satisfaction score as 2 and in bupivacaine & midazolam group there were only 10 whereas in bupivacaine and saline group there were 15 people with the same score, the association of patient satisfaction score among the study groups was statistically not significant (P value >0.05). Among 30 patients in bupivacaine & dexmedetomidine group and in bupivacaine & midazolam group only 11 patients with anesthesiologist satisfaction score as 2 and in bupivacaine and saline group there were 13 people with same score, the association of anesthesiologist satisfaction score among the study groups was statistically not significant (P value >0.05) (Table 3).

Table 3: Comparison of satisfaction scores of patient and anesthesiologist among the 3 study groups (N=90).

Parameter	Group			P value
	Bupivacaine and dexmedetomidine (N=30)	Bupivacaine and midazolam (N=30)	Bupivacaine and saline (N=30)	
Patient satisfaction score				
2	11 (36.66%)	10 (33.33%)	15 (50%)	0.38
3	19 (63.33%)	20 (66.66%)	15 (50%)	
Anesthesiologist satisfaction score				
2	11 (36.66%)	11 (36.66%)	13 (43.33%)	0.83
3	19 (63.33%)	19 (63.33%)	17 (56.66%)	

Table 4: Comparison of satisfaction scores of patient, anesthesiologist, VAS and HSL among the 3 study groups (N=90).

Parameter	Group			(Kruskal-Wallis Test) P value
	Bupivacaine and dexmedetomidine (N=30) Median (IQR)	Bupivacaine and midazolam (N=30) Median (IQR)	Bupivacaine and saline (N=30) Median (IQR)	
Patient satisfaction score	3 (2,3)	3 (2,3)	2.5 (2,3)	0.38
Anesthesiologist satisfaction score	3 (2,3)	3 (2,3)	3 (2,3)	0.83
VAS	1 (1, 2)	2 (2, 3.25)	3 (2,4)	<0.001
HSL	4 (4, 5)	6 (4.75, 7)	6 (5, 7)	<0.001

Table 5: Comparison of HSL among the 3 study groups (N=90).

HSL	Group			P value
	Bupivacaine and dexmedetomidine (N=30)	Bupivacaine and midazolam (N=30)	Bupivacaine and saline (N=30)	
T3	6 (20%)	2 (6.666%)	0 (0%)	0.001
T4	11 (36.66%)	5 (16.66%)	4 (13.33%)	
T5	8 (26.66%)	2 (6.666%)	8 (26.66%)	
T6	5 (16.66%)	13 (43.33%)	10 (33.33%)	
T7	0 (0%)	8 (26.66%)	6 (20%)	
T8	0 (0%)	0 (0%)	2 (6.666%)	

The median score of patient satisfaction was 3 with interquartile range (2-3) in bupivacaine and dexmedetomidine group and bupivacaine and midazolam group whereas the same score median was 2.5 only with IQR (2-3) in bupivacaine and saline group, the association of Patient satisfaction score among study groups was statistically not significant (P value >0.05). The median score of anesthesiologist satisfaction was 3 with IQR (2-3) in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and in

bupivacaine and saline group, the association of anesthesiologist satisfaction score among study groups was statistically not significant (P value >0.05). The median VAS was 1 with IQR (1-2) in bupivacaine and dexmedetomidine group and the same was 2 with IQR (2-3.25) in bupivacaine and midazolam group and in bupivacaine and saline group it was 3 with IQR (2-4), the association of VAS among study groups was statistically significant (P value <0.001). The median HSL was 4 with IQR (4-5) in bupivacaine and dexmedetomidine group and the same was 6 with IQR (4.75-7) in bupivacaine and midazolam group and in bupivacaine and saline group it was 6 with IQR (5-7), the association of HSL among study groups was statistically significant (P value <0.001) (Table 4).

The proportion of T4, T5 was 36.66% and 26.66% respectively in Bupivacaine and dexmedetomidine group, In Bupivacaine and midazolam group the T6 sensory level was with maximum proportion as 43.33% but in Bupivacaine and saline group both T5, T6 occupies the high proportions as 26.66% and 33.33% respectively. The association among study groups and Highest sensory levels was statistically significant (P value <0.05) (Table 5).

Table 6: Comparison of side effects and analgesia required patients among the 3 study groups (N=90).

Parameter	Group			P value
	Bupivacaine and dexmedetomidine (N=30)	Bupivacaine and midazolam (N=30)	Bupivacaine and saline (N=30)	
Bradycardia	4 (13.3%)	1 (3.33%)	1 (3.3%)	0.20
Hypotension	4 (13.3%)	1 (3.33%)	2 (6.7%)	0.34
excessive sedation	2 (6.7%)	5 (16.7%)	0 (0.0%)	0.05
Number of patients requiring analgesic for the first 24 hours	2 (6.7%)	10 (33.3%)	11 (36.7%)	0.01

There were 13.3% patients with bradycardia in dexmedetomidine, 3.34% in midazolam group and saline both the groups. There was more proportion (13.3%) of patients with hypotension in dexmedetomidine group. There were patients with excessive sedation 16.7% in midazolam group and only 6.7% in dexmedetomidine group. The proportion of patients requiring analgesic for the first 24 hours was 36.7% in saline group, 33.33% in midazolam group. The association between symptoms and study groups was statistically not significant (P value >0.05) except with number of patients requiring analgesic for the first 24 hours (P value<0.05).

There were 13.3% patients with Bradycardia in dexmedetomidine, 3.34% in midazolam group and saline both the groups. There was more Proportion (13.3%) of patients with Hypotension in dexmedetomidine group. There were patients with excessive sedation 16.7% in midazolam group and only 6.7% in dexmedetomidine group. The proportion of patients requiring analgesic for the first 24 hours was 36.7% in saline group, 33.33% in midazolam group. The association between symptoms and study groups was statistically not significant (P value>0.05) except with number of patients requiring analgesic for the first 24 hours (P value<0.05) (Table 6).

DISCUSSION

According to Kaya et al, mean blood pressure was high in dexmedetomidine group (104.4) compare to midazolam (98.9) and in saline group (101.9).[4] There were more or less similar results observed in our study as the mean MAP of patients in bupivacaine and dexmedetomidine group, bupivacaine and midazolam group and bupivacaine and saline group was 102.10, 93.90 and 101.53 respectively. The association of MAP with study groups was statistically significant (P value <0.05).

In the current study, the median score of patient satisfaction was 3 in dexmedetomidine group and it was same in midazolam group also, but it was 2.5 only in saline group. Among the study groups there was no statistically significant association of Patient satisfaction score (P value>0.05). Similar results were reported by Cheung CW et al, in both dexmedetomidine group and midazolam groups the median score of patient satisfaction was 8 and same in two groups.[7] Few of the existing studies in literature by Kaya FN et al, Demiraran Y et al and Liao W et al, did not show a significant difference in patient satisfaction between the drugs like current study.[4,8,9]

In present study, the median score of anesthesiologist satisfaction was 3 in dexmedetomidine group, midazolam group and saline groups the association of anesthesiologist satisfaction score among study groups was statistically not significant (P value >0.05). like current study in the study of Kaya FN et al, reported similar the median score of anesthesiologist satisfaction among three study groups and it was 3.[4] Similarly in literature few other studies by Cheung CW et al and Liao, W et al have reported equal clinician satisfaction scores

between dexmedetomidine group and midazolam groups.[7,9]

In our study, the median VAS was 1 in dexmedetomidine group and the same was 2 midazolam group and in saline group it was 3. There was a statistically significant association of VAS among study groups (P value <0.001). More or less similar results were shown in the study of Kaya FN et al.[4] In Kaya's study the median VAS of dexmedetomidine group was 2.1 and it was same in other two study groups (2.8) with statistically non-significant association among study groups.

In current study, the median HSL was 4 in dexmedetomidine group and the same was 6 in both midazolam group and saline groups, the association of HSL among study groups was statistically significant (P value<0.001). Almost similar results were reported by Kaya FN et al.[4] Kaya's have shown that in the dexmedetomidine group, the median HSL was 4.6 and it was 6.4 in other two study groups. The association of HSL among three study groups was statistically significant.

In our study, there were 4 with Bradycardia in dexmedetomidine and 1 in each with Bradycardia in midazolam and saline groups respectively, with the statistically non-significant p value =0.20. Similar results were reported by Kaya FN et al, in his study incidence of bradycardia was 2 in dexmedetomidine, none in midazolam group and 1 in saline group with no statistical significance between the groups.[4] Samantaray A et al, study findings also showed more are less similar incidence of Bradycardia to current study.[10] In Samantaray,'s study incidence of bradycardia was 5, 3, 3 in dexmedetomidine, midazolam and saline groups respectively.

In the present study, the incidence of hypertension was high in dexmedetomidine group than midazolam and saline groups. Hypertension was observed in 4 participants in dexmedetomidine group and in was seen in 1, 2 participants in midazolam and saline groups respectively. The difference in proportion among the groups was statistically not significant (P=0.34). Our study findings are similar to the findings of Kaya, F. N., et al, hypertension was seen in 2, 0 and 4 participants in dexmedetomidine group midazolam and saline groups respectively.[4] In Samantaray A et al, study findings hypertension was seen in 7 participants in dexmedetomidine group but it was found in 8 and 5 cases in midazolam and control groups respectively.[10]

In our study, there were 2 patients with excessive sedation in dexmedetomidine group, 5 patients in midazolam group and the association was statistically not significant. The patients requiring analgesic for the first 24 hours were 2,1 0, 11 in dexmedetomidine group, midazolam and saline groups respectively with statistically significant association among three study groups (P value<0.05). Similar findings were shown by Kaya FN et al.[4]

CONCLUSION

By comparing the different hemodynamic parameters, duration of surgery and regression of sensory block and motor block etc., present study proven the superiority of dexmedetomidine compare with midazolam and standard saline. Considering its unique properties, investigators used dexmedetomidine as the fundamental sedative, and additional sedatives and analgesics were added based on each patient's condition. Measurement of patient and anesthesiologist satisfaction scores are more or less similar in midazolam and dexmedetomidine groups compare to saline group.

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