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Comparative Study of Dexmedetomidine and Midazolam in Sedation for Patients Undergoing Lower Abdominal Surgeries Under Spinal Anesthesia

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ABSTRACT

A comparative study was conducted for evaluating the efficacy of two different class of drugs in patients undergoing lower abdominal surgery with spinal anesthesia. A total 50 patients belonging to ASA grade I & II were randomly divided into 2 groups with each group comprised of 25 patients. After obtaining clearance from the department's ethical committee, the patients were explained about the study and a written informed consent was obtained from all the participants. For Group I patients Midazolam was administered in 100 ml saline whereas Group II subjects were supplied with intravenous Dexmedetomidine 5 µg per Kg in 100 ml normal saline infused over 20 minutes. Continuous data was represented as mean, median and standard deviation. Independent 't test' or Mann Whitney U test was used as test of significance to identify the mean difference between two groups. Paired 't test' or Wilcoxon Signed Rank test was used as test of significance to determine paired data such as before and after surgery. *P* value < 0.05 was considered as statistically significant. The mean age of study subjects supplied with Midazolam and Dexmedetomidine group were found to be 41.32 ± 8.46 and 37.76 ± 12.16 respectively. Majority of the subjects in both the groups were females with the mean weight found in Midazolam and Dexmedetomidine group were 68.6 ± 12.12 and 64.16 ± 7.94 respectively. Dexmedetomidine was found to be superior in all aspects except for the fact that it produced biphasic response and bradycardia.

Keywords: Comparative study; Spinal anaesthesia; Preoperative Anxiety; Midazolam; Dexmedetomidine; Sedation.

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INTRODUCTION

Anaesthesia and surgery cause significant fear and anxiety in patients. It induces sympathetic nervous system stimulation that leads to adverse cardiovascular effects like tachycardia and hypertension. Preoperative anxiety has been a challenging concept in the preoperative care of patients and almost all patients undergoing surgery experiences varying level of anxiety. The incidence of preoperative anxiety has been found in 60–80 % of surgical patients. Drugs like phenothiazine, barbiturates, opioids and benzodiazepines are used to relieve anxiety preoperatively[1]. Premedication involves the administration of anaesthetic adjuvant drugs to allay anxiety, decrease post-operative pain, nausea and the risk of pulmonary aspiration. Clinically used routes of administration of premedication comprises of oral, rectal, intramuscular, intravenous and intranasal. The process of administering medication before anaesthesia was generally considered as premedication. They are performed in order to prepare the patient for anaesthesia and also to provide optimal conditions for surgery. In the past, Opioid analgesics were used as premedication, as they possessed good sedative and analgesic effects. Opioids enhanced the effects of other anaesthetic agents. For this quality, opioids were preferred largely in premedication, when no potent inhalational agents were available. But certain disadvantages were observed in opioid premedication. They caused euphoria when given to patients who did not have any pain and caused delay in gastric emptying. In addition, augmentation of central nervous system (CNS) depressant effect of other anaesthetic agents was undesirable.

Pharmacology of Midazolam

Midazolam, a benzodiazepine has started becoming the drug of choice as premedicant to decrease anxiety. Other classes of drugs used for anxiolysis and sedation are barbiturates and α-2 agonists[2]. Fryer and Walser's in 1976 synthesized Midazolam, the first clinically used water–soluble benzodiazepine[3]. Available in an acidified (pH 3.5) aqueous formulation, it produces minimal local irritation after intravenous (IV) or intramuscular (IM) injection. All benzodiazepines have anxiolytic, amnestic, sedative, hypnotic, anticonvulsant and spinally mediated muscle relaxant properties. It was observed that premedication with benzodiazepines such as Midazolam has reduced the release of cortisol, intraoperative epinephrine and norepinephrine. Stability of Midazolam in solution and rapid metabolism are due to the presence of an imidazole ring. The rapid CNS effect and large volumes of distribution are due to high lipophilicity[3]. Midazolam 0.04 to 0.08 mg/Kg IV/IM was the most common dosage used for premedication[4]. They are given in the dose of 0.5 mg/kg orally and as 5 mg/ml prefilled syringes with 2.5, 5, 7.5 and 10 mg through buccal area. However, the cardiovascular depressant effects of benzodiazepines are frequently masked by laryngoscopy and intubation.

The cardiovascular depressant effects are directly related to the plasma concentration where a plateau appears to exist in the concentration above which the changes in blood pressure are found less[4]. Benzodiazepines depress the swallowing reflex and decrease the upper airway reflex activity by reducing the tonic and phasic contraction of airway muscles[5].

Pharmacology of Dexmedetomidine

There are number of reasons for the renewed interest in the use of Dexmedetomidine, a newer alpha 2 agonist, as sedative premedication. They belong to the imidazole subclass of alpha 2 receptor agonists. The loading dose for IV infusion is 0.5 to 1 mic/kg over 10 minutes followed by 0.2 to 0.7 mic/kg/hr. The effect starts after 5–10 minutes and lasts for 30–60 minutes. Dexmedetomidine has a rapid distribution and extensive metabolism in the liver. They are normally excreted both in urine as well as faeces and undergoes glucuronide conjugation. The pharmacokinetic parameters appear to be unaltered by age, weight or renal failure but clearance has been based on function of height. The concentration ratio observed between whole blood and plasma has been around 0.66[6]. Time required to peak plasma concentration after intramuscular injection was around 1.6 to 2.4 hours[7]. The metabolism of Dexmedetomidine follows zero order kinetics, i.e., every hour a constant amount of drug will be eliminated from the body and not a constant fraction of the drug within the body, following the first order kinetics[8]. Currently the teratogenic effects of Dexmedetomidine has not been adequately investigated, but the drug has been known to cross the placenta and its use in pregnancy is warranted only if the benefits outweigh the risk to the foetus. No studies concerning side effects have been conducted in children[9]. Considering its actions on alpha2 receptors, the most common side effect of Dexmedetomidine are bradycardia and hypotension. If the drug is used in higher concentrations, there is potential for pulmonary and systemic hypertension and direct or reflex bradycardia[10-11].

MATERIALS AND METHOD

The comparative study was carried out at the department of Anaethesiology and Critical care. After obtaining clearance from the institute's ethical committee, a total of 50 patients were chosen for the study. After explaining about the procedures involved, a written informed consent was obtained from all the patients. The study group comprised patients of different age group, either sex, belonging to American Society of Anesthesiologists (ASA) physical status I and II and scheduled for elective surgical procedures under Spinal Anaesthesia.

Inclusion criteria

1. Patients of either sex
2. Patient with ASA grade I and II
3. Adults aged 18-50

4. Patient willing for surgery and given informed consent

Exclusion criteria

1. Patients on antidepressants and hypnotics
2. Patients on anti hypertensives and sedative drugs
3. Patients with contraindications to regional anaesthesia

Anaesthesia Procedure

50 patients belonging to ASA grade I & II were randomly divided into 2 groups with each group consisting of 25 patients. After shifting the patients to the operation theatre (OT), an IV line of different sizes were secured according to patient age and basic monitors were connected. Following this, while Group A [Midazolam] patients received 100 ml saline infused over 20 minutes, Group B [Dexmedetomidine] patients received IV Dexmedetomidine 5µg per Kg in 100 ml normal saline infused over 20 minutes. At the end of 20 minutes duration patients positioned for spinal anaesthesia were administered with spinal drug 0.5 % Bupivacaine. The patient sedation score was recorded at 5, 10, 15, 20, 25, 30, 60, 90 and 120 minutes.

Statistical Analysis

Data obtained for various parameters were analyzed using Statistical Package for Social Sciences (SPSS) version 22 software. Categorical data was represented in the form of frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean, median and standard deviation. Independent 't test' or Mann Whitney U test was used as test of significance to identify the mean difference between two groups. Paired 't test' or Wilcoxon signed Rank test is the test of significance for paired data such as before and after surgery. *P* value < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

In the present study, 50 patients divided into 2 groups (Midazolam and Dexmedetomidine) were assessed for sedation at different time intervals. Apart from this, several parameters such as age distribution, mean age and weight determination among the study subjects of both the groups were carried out. Midazolam and Dexmedetomidine were administered 36 % and 48 % respectively for the patients of < 40 years, whereas 64 % and 52 % respectively for the patients of > 40 years (Table 1). While the mean age of patients in Midazolam group was 41.32 ± 8.46, in Dexmedetomidine group it was 37.76 ± 12.16. There was no significant difference in age between two groups (Table 2). Mean weight of the patients found in Midazolam and Dexmedetomidine group was 68.6 ±12.12 and 64.16 ± 7.94 respectively. There was no significant difference observed in weight between two groups (Table 3). Similarly, in gender distribution also no significant difference was found among both the groups. Majority of subjects in both the groups were females (Table 4).

However, a significant difference was found in the median score for sedation levels between two groups. In particular, higher sedation scores were seen in the group administered with Dexmedetomidine than Midazolam at all the intervals except at 120 minutes where sedation scores remained the same (Table 5). A line diagram representation of the median score obtained for the sedation levels among both the groups are depicted in Figure 1. The results clearly show that at time interval 120 minutes the median score was found to be same for both the groups (Figure 1). Furthermore, by using Wilcoxon Signed Ranks test, differences in sedation levels were separately analyzed for each group. For the study subjects representing Midazolam group, significant difference was observed in median sedation score at various intervals when compared to 5 minutes score. The score remained at 3 starting from 15 to 30 minutes and later on reduced to 2 at 60, 90 and 120 minutes (Table 6). The corresponding Z and *P* values obtained at each interval have also been given in the table 6. A line diagram representation of the sedation median score obtained for the study subjects administered with Midazolam are represented in Figure 2.

Table 1: Age Distribution of Subjects in the Study

		Group			
		Midazolam		Dexmedetomidine	
Age Distribution		Count	%	Count	%
Age	< 40 years	9	36.0 %	12	48.0 %
	41 to 50 years	16	64.0 %	13	52.0 %

$\chi 2 = 0.739$, df = 1, $P = 0.390$

Table 2: Mean Age in Subjects between Two Groups

Group								
Midazolam				Dexmedetomidine			T value	*P* value
	Mean	SD	Median	Mean	SD	Median		
Age	41.32	8.46	44.00	37.76	12.16	42.00	1.201	0.235

Table 3: Mean Weight in Subjects between Two Groups

Group								
Midazolam				Dexmedetomidine			T value	*P* value
	Mean	SD	Median	Mean	SD	Median		
Weight	68.60	12.12	70.00	64.16	7.94	65.00	1.532	0.132

Table 4: Gender Distribution of Subjects in the Study

Gender Distribution		Group			
		Midazolam		Dexmedetomidine	
		Count	%	Count	%
Gender	Female	13	52.0	14	56.0
	Male	12	48.0	11	44.0

$\chi 2 = 0.081$, df = 1, $P = 0.777$

Table 5: Sedation Score between Two Groups at Various Time Interval after Anaesthesia

Time Interval (Minutes)	Group						Z value	*P* value
	Midazolam			Dexmedetomidine				
	Mean	SD	Median	Mean	SD	Median		
5	2	0	2	3	0	3	-4.802	< 0.001*
10	2	0	2	3	0	3	-4.216	< 0.001*
15	3	1	3	4	1	3	-4.058	< 0.001*
20	3	1	3	4	0	4	-4.273	< 0.001*
25	3	0	3	4	1	4	-5.674	< 0.001*
30	3	0	3	4	1	4	-5.702	< 0.001*
60	2	0	2	3	1	3	-5.425	< 0.001*
90	2	0	2	2	0	2	-3.042	0.002*
120	2	0	2	2	0	2	-1.000	0.317

Mann Whitney U test *

Table 6: Sedation Score with The Midazolam Group at Various Time Interval after Anaesthesia

Time Interval (Minutes)	Midazolam				
	Mean	SD	Median	Z Value	*P* Value
5	2	0	2	-	
10	2	0	2	-2.236[c]	0.025*
15	3	1	3	-3.690[c]	0.001*
20	3	1	3	-4.354[c]	0.001*
25	3	0	3	-4.716[c]	0.001*
30	3	0	3	-4.630[c]	0.001*
60	2	0	2	-2.236[c]	0.025*
90	2	0	2	-1.000[c]	0.317
120	2	0	2	-1.000[c]	0.317

Wilcoxon Signed Ranks test*

Table 7: Sedation Score with The Dexmedetomidine Group at Various Time Interval after Anaesthesia

Time Interval (Minutes)	Dexmedetomidine				
	Mean	SD	Median	Z Value	*P* Value
5	3	0	3	-	-
10	3	0	3	-2.236[c]	0.025*
15	3	1	3	-4.300[c]	0.001*
20	4	0	4	-4.388[c]	0.001*
25	4	1	4	-4.403[c]	0.001*
30	4	4	4	-4.276[c]	0.001*
60	3	1	3	-3.087[c]	0.002*
90	2	0	2	-1.604[d]	0.109
120	2	0	2	-4.000[d]	0.001*

Wilcoxon Signed Ranks test*

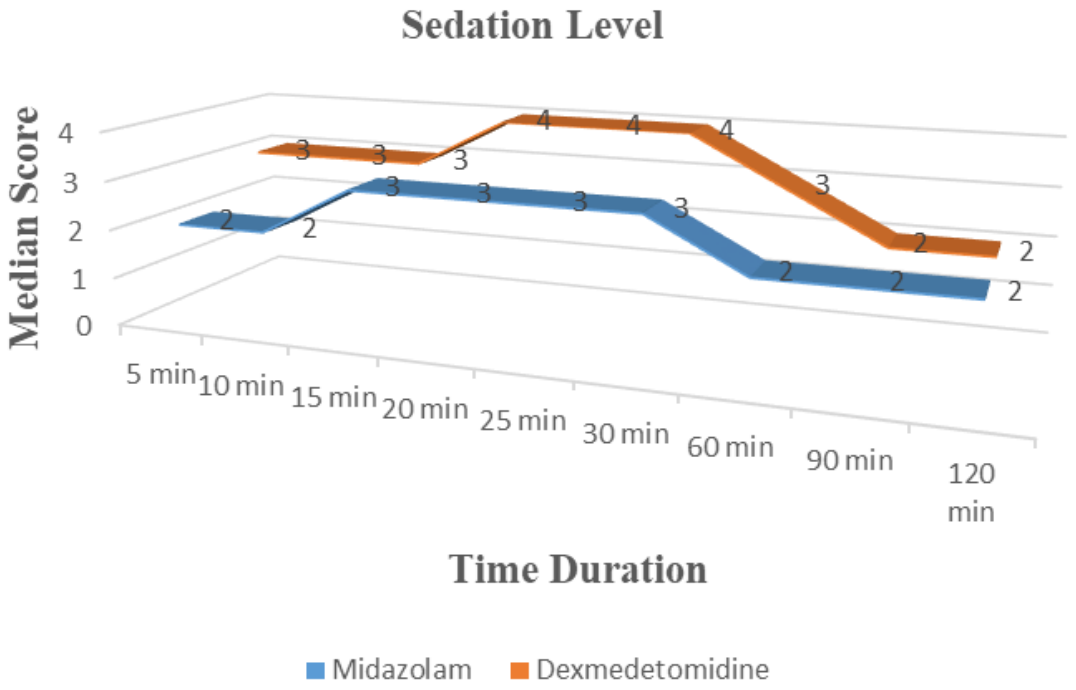

Figure 1: Line Diagram Showing Sedation Score Between Two Groups at Various Time Interval after Anaesthia

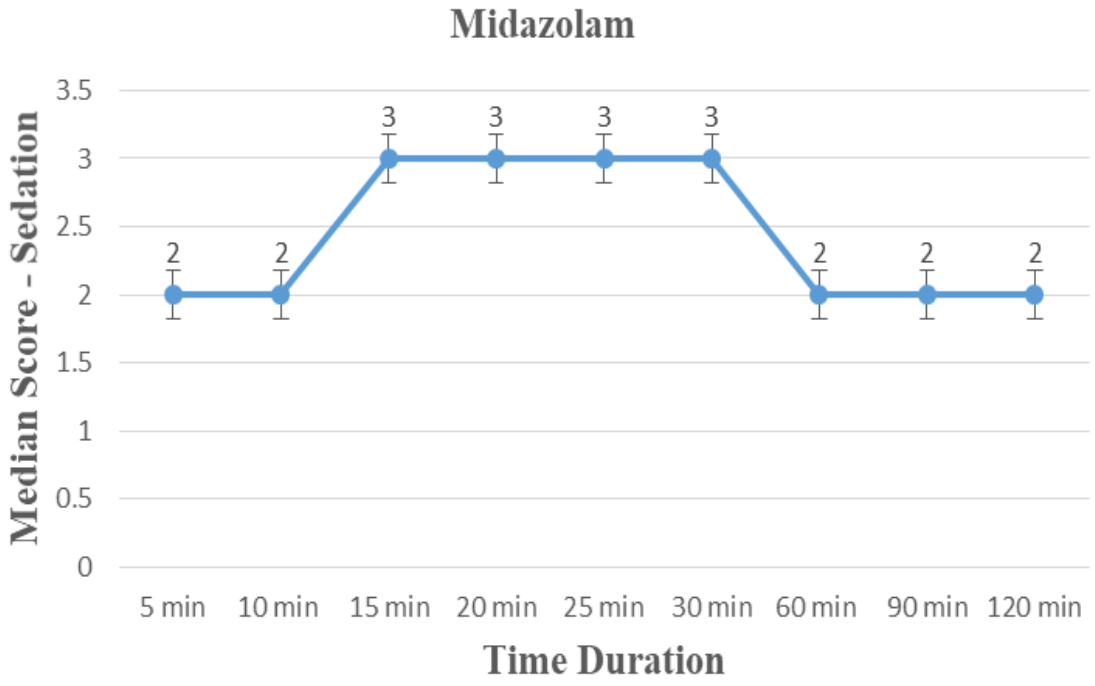

Figure 2: Line Diagram Showing Sedation Score with The Midazolam Group at Various Time Interval

Similar kind of analysis was also made for the study subjects representing Dexmedetomidine group. In this case, the median score for sedation levels remained same at 3 from 5 to 15 minutes time interval. Then the median score was increased and remained same at 4 between 20 to 30 minutes duration. Later on, the score was reduced to 3 at 60 minutes and further reduced to 2 at 90 minutes as well as 120 minutes duration (Table 7). The respective Z and *P*

values obtained at each interval have also been given in the table. As explained for the Midazolam group, similar representation of line diagram for the study subjects administered with Dexmedetomidine are given in Figure 3.

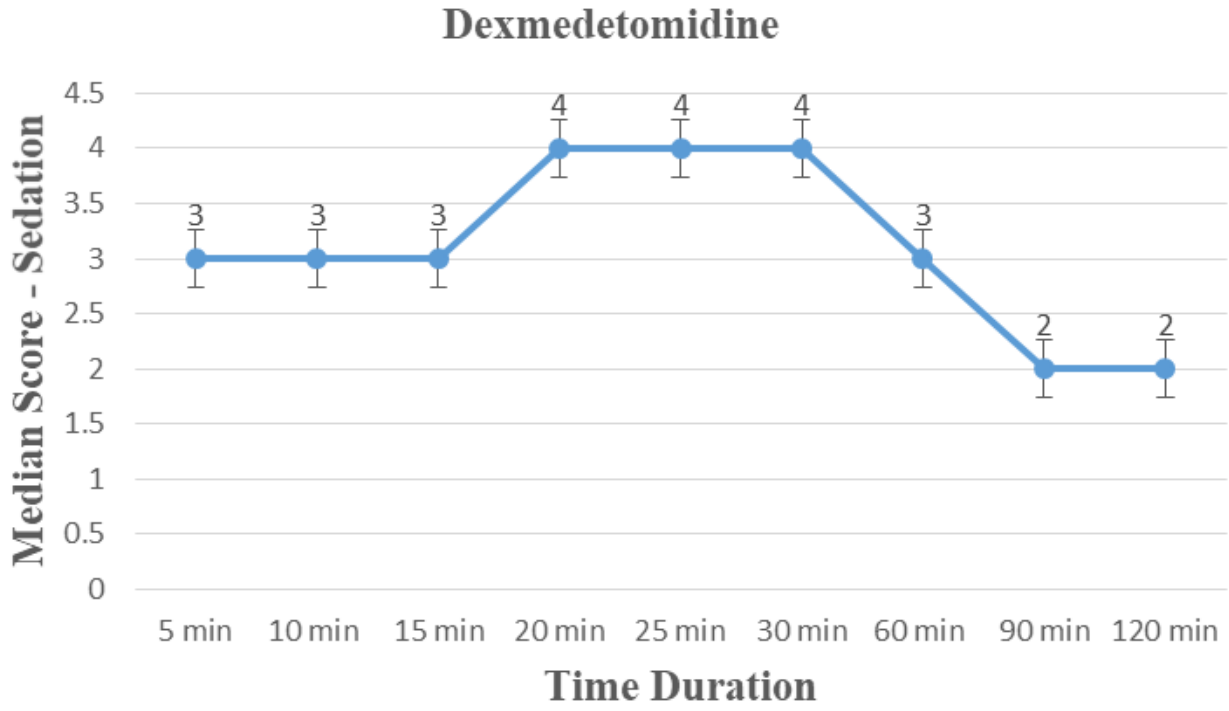

Figure 3: Line Diagram Showing Sedation Score with The Dexmedetomidine Group at Various Time Interval

In their work, Ronald et al have described that 0.07 mg/kg midazolam, 1.0 mg/kg hydroxyzine and placebo midazolam diluent were given intramuscularly to 100 patients of ASA type I and II[12]. From the results they concluded that Midazolam exhibited an efficacious and safe premedication in healthy patients. Minimal tissue irritation was observed and onset of action of intramuscular Midazolam was found to be prompt[12]. Riku et al conducted a study in 20 healthy ASA I patients by single blind method. When the subjects underwent uterine dilatation and curettage, using four different doses (0.167, 0.33, 0.67 and 1.0 microgram/kg) the effects of Dexmedetomidine intravenous infusion on anaesthetic requirements, hemodynamics and catecholamine levels in plasma were monitored[13]. They observed that tolerance to Dexmedetomidine was good and drug-related subjective side effects or adverse events were not serious. Reductions in blood pressure, heart rate and plasma norepinephrine levels were reduced after administration of the drug. The optimal dose for single-dose intravenous premedication in minor surgery was found to be 0.334 to 0.67 mic/kg[13]. Several reports of using Dexmedetomidine and Midazolam for inducing sedation in the preoperative medication are available[14-17]. All the investigations have unanimously concluded that both the drugs have produced comparable preoperative sedation and anxiolysis. As observed in the earlier studies hemodynamic and respiratory effects were found minimal. Dexmedetomidine was effective in

attenuating pressor response to intubation and possessed significant anaesthetic as well as opioid sparring effect.

CONCLUSION

In the present study, 50 patients belonging to ASA grade I & II were randomly divided into 2 groups with each group comprised of 25 patients. Two different class of drugs Midazolam and Dexmedetomidine were administered for the respective groups. After shifting the patients to OT, patients belong to Group I were supplied with Midazolam in 100 ml saline infused over 20 minutes. Similarly Group II subjects were supplied with Intravenous Dexmedetomidine 5 µg per Kg in 100 ml normal saline infused over 20 minutes. Several parameters such as mean age, weight and gender distribution prevailed among both the groups were determined. From the comparative analysis, Dexmedetomidine was found to be superior in all aspects. But it produced biphasic response as far as blood pressure (systole, MAP, diastole) was concerned. Addition to this, it has produced bradycardia also and hence may not be suitable for those on beta blockers. In select cases Dexmedetomidine was found effective in producing arousable sleep and patent airway apart from reducing the need for analgesics. It has also acted as powerful antiemetic. Midazolam has known to produce some severe cough following mild aspiration of saliva. It can produce deep sleep involving tongue falling back and producing respiratory obstruction. This may need insertion of airway or during triple manoeuvre to make airway patent apart from adequate bag and mask oxygenation. The observations found in Midazolam was never present in Dexmedetomidine. To conclude, Dexmedetomidine was found to be an effective agent for preoperative sedation. However, comparative studies focusing on the effects of drugs like Midazolam and Dexmedetomidine on more debilitated older patients are much more needed in future.

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