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A Comparison of Dexmedetomidine with Midazolam for Sedation in Elderly Patients Undergoing Regional Anaesthesia

Shaikh Mohd Mudassir[1], Jitendra R. Waghmare[2], Sudhir Bhope[3]

[1,2] Assistant Professor [3]Professor, Department of Anaesthesiology, IIMSR Medical College, Badnapur, Jalna, Maharashtra 431202, India.

Abstract

Introduction: Chemically induced tranquillity improves acceptance of Regional Anaesthetic techniques. Intravenous sedative medications are useful for the same as positioning for surgery can be uncomfortable and spontaneous movements by an inadequately sedated patient can cause interference with the surgical procedure. To allay this problem, sedation remains as inevitable modality. *Objectives:* Comparison of the sedation properties and efficacy of Dexmedetomidine with Midazolam when used for intraoperative sedation during Regional Anaesthesia. *Methods:* Prospective, randomized study was carried out in 100 patients of ASA grade 2 & 3, above 60 years of age, weighing 40 to 90 Kg, of both genders, scheduled for elective procedures. In our study, patients were divided into 2 groups of 50 each with the help of a computer generated table of random numbers. They received either Dexmedetomidine or Midazolam intravenously during Sedation for Regional Anesthesia. Accordingly patients receiving dexmedetomidine were classified as group X1 and those receiving Midazolam as group X0. HR, MAP recorded in all patients and compared. *Result:* HR and MAP in Dexmeditomidine group is significantly low than Midazolam group. *Conclusion:* Dexmedetomidine can be considered superior than Midazolam as a sedative agent for sedation under Regional Anaesthesia in Elderly patients.

Keywords: Sedation; Midazolam; Dexmeditomidine; Regional Anaesthesia; Elderly Patients.

Introduction

The operating room is an anxiety provoking environment. The use of regional anaesthesia is often limited by the unwillingness of patients to remain awake during surgery. Though surgeries like Total Knee Replacement, Bipolar Hemiarthroplasty, Total Hip Replacement etc are done under Regional Anaesthesia; patient's anxiety, pain and mobility, and consequent sympathetic responses with hemodynamic instability remain as major problem for surgeon and anaesthetist. Patients usually have three major concerns prior to surgery/procedure - the outcome of the procedure (will I be able to walk again?), complications of the procedure, and most importantly the question "Doctor, how much of the procedure will I feel?" or "Will it hurt?" With modern sedation and careful monitoring the great majority of patients will feel comfortable during the procedure.

Chemically induced tranquillity improves acceptance of Regional Anaesthetic techniques. Intravenous sedative medications are useful for the same as positioning for surgery can be uncomfortable and spontaneous movements by an inadequately sedated patient can cause interference with the surgical procedure. To allay this problem, sedation remains as inevitable modality [1].

An optimal perioperative experience also encompasses effective pain control with minimal side effects from anaesthetic and analgesic drugs. The International Association For The Study of Pain

Corresponding Author: Jitendra R. Waghmare, Assistant Professor, Department of Anaesthesiology, IIMSR Medical College, Badnapur, Jalna, Maharashtra- 431202, India.
E-mail: drjitendragurav77@gmail.com

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(IASP) has aptly defined pain as "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*" [1]. As per above definition, anxiety and apprehension of procedure can also affect degree of pain perceived by patient. So it becomes necessary to achieve good anxiety relief, possibly by good sedation.

Sedation *is the reduction of irritability or agitation by administration of drugs, generally to facilitate medical or diagnostic procedure.*

The goal of conscious sedation for surgery is to enhance patient comfort, to include preservation of protective airway reflexes, to avoid painful stimuli and to help maintain hemodynamic stability during the whole surgical procedure[2]. Sedation methods include inhalation sedation (using nitrous oxide), oral sedation, and intravenous (IV) sedation. Oral sedation is generally used in paediatric cases. Inhalation sedation is also sometimes referred to as *Relative Analgesia*. And only inhalational agent used is nitrous oxide, which has its own side effects. Sedation is also used extensively in the intensive care unit so that patients who are being ventilated tolerate presence of an endotracheal tube.

An Ideal supplemental sedative should provide, effective anxiolysis, an easily controllable level of sedation, predictable depth of amnesia, a rapid and clear headed recovery, minimal intraoperative side effects, no evidence of cumulation and minimal postoperative side effects [3]. Numerous agents ranging from Ketamine to Propofol and Midazolam to Dexmedetomidine have been used as sedative adjuvants to regional anaesthesia, with their very own advantages and disadvantages over one another.

Objectives

1. Comparison of the sedation properties of Dexmedetomidine with Midazolam when used for intraoperative sedation during Regional Anaesthesia.
2. Comparison of the efficacy of Midazolam and Dexmedetomidine with respect to the cardio-respiratory parameters as following:-

a. Heart rate
b. Mean arterial pressure
c. Oxygen saturation
d. Respiratory rate

Material and Methods

This prospective, randomized study was carried out following approval from the Institutional ethics committee. Patients included in this study were informed about the procedure in their own language, and a written informed consent was taken from all of them.

100, ASA grade 2&3 patients, above 60 years of age, weighing 40 to 90 Kg, of both genders, scheduled for elective procedures, were included. They were initially assessed in the preoperative check-up room, where along with general and systemic examinations, baseline measurements of heart rate, mean arterial pressure by non-invasive sphygmomanometer, pulse oximetry, respiratory rate was made by a single observer.

Following Patients were Excluded from the Study

- Patients with history of Allergic reaction to the study drugs
- Those with significant cardiac, pulmonary, hepatic or renal dysfunction.
- Patients on Beta Blockers.
- Obese patients (>130% ideal body weight)
- Those with history of chronic use of sedative drugs
- Full stomach patients
- Epileptic patients were excluded from the study.

Sedative premedication was not given to any patient to avoid interference with results.

To facilitate blinding, two syringes of "study drug" were prepared for each patient by an anesthesiologist not associated with the study and labeled "Infusion" and "Bolus top-up." One syringe of each pair contained active sedative drug(s), the other contained placebo (saline).

Patients in the X0 Group received a 1mL "Bolus" from 10cc syringe containing 1mg/ml Midazolam and a 50 mL "Infusion" syringe containing placebo that was run via infusion pump.

Patients in the X1 Group received a 50 mL "Infusion" syringe containing Dexmedetomidine 4 μg/mL as well as a 1 mL placebo "Bolus" syringe. Sedation was initiated as follows:

X1 Group

-Initial loading dose of Dexmedetomidine (0.5 μg/kg) over 10 min followed by infusion at 0.2

$\mu gkg^{d1} \cdot h^{d1}$ from the 50-mL "Infusion" syringe. d1 mL Placebo bolus from the 10-mL "Bolus" syringe followed by 0.5 mL boluses every 30 min after 1st hour of surgery.

X0 Group: d1 mL bolus from the 10 mL "Bolus" syringe (1 mg Midazolam or 0.02mg/kg) followed by 0.5 mL boluses every 30 min after 1st hour of surgery.

–Initial loading dose plus Infusion of Placebo from 50 mL "Infusion" syringe at a corresponding rate to the X1 group.

Result and Statistics

In our study, patients were divided into 2 groups of 50 each with the help of a computer generated table of random numbers. They received either Dexmedetomidine or Midazolam intravenously during Sedation for Regional Anesthesia. Accordingly patients receiving dexmedetomidine were classified as group X1 and those receiving Midazolam as group X0.

During study, 4 patients from X0 group and 2 patients from X1 group required general anesthesia, due to prolonged duration of surgery/ intraoperative surgical complications. These cases are excluded from study, but Sample size in both groups is kept constant.

The data obtained was subjected to statistical analysis using Students Unpaired t- Test and Chi-square test to find out significant difference between the groups and Mann and Whitney non parametric test was used for qualitative data. For statistical comparison, difference was considered significant when the p- value was found to be less than 0.05.

5.82E-05= 0.0000582 (where E stands for 10 raised to)

Where quantitative data failed 'Normality test', non-parametric test has been applied

In group X1 there were 26 female and 24 male patients and in group X0 there were 29 females and 21 male patients. On statistical analysis, the association found was not significant (p value= 0.546) implying that a random distribution of patients was done as concerns the sex of the patient.

Table 1: Association among study group for SEX

St Group		SEX		Total
		Male	Female	
X1 Group	Count	24	26	50
	Percent	48.0%	52.0%	100.0%
X0 Group	Count	21	29	50
	Percent	42.0%	58.0%	100.0%
Total	Count	45	55	100
	Percent	45.0%	55.0%	100.0%
Chi-Square Tests	Value	df	P value	Association is
Pearson Chi-Square	0.364	1	0.546	Not significant
Fisher's Exact Test			0.688	Not significant

Table 2: Comparison among study group for AGE

Age	X1 Group				X0 Group				Mann Whitney Test	P Value
	Mean	Std. Dev.	Median	IQR	Mean	Std. Dev.	Median	IQR		
AGE	70.46	9.29	69.00	16.00	72.04	8.22	72.00	12.00	1.196	0.232

Note: Normality Test (Shapiro-Wilk) Failed (P < 0.050), thus P value calculated for Mann-Whitney Rank Sum Test

Table 3: Comparison among study group for Pulse rate (pre min)

Pulse rate (pre min)	X1 Group				X0 Group				Unpaired T test	P value
	Mean	Std. Dev.	Median	IQR	Mean	Std. Dev.	Median	IQR		
0 min *	86.92	13.39	83.00	24.00	87.08	13.30	89.00	20.00	0.203	0.839
30 min *	66.20	9.99	67.00	17.00	78.94	11.68	80.50	21.00	4.974	0.000
60 min *	63.52	9.34	63.00	15.00	77.26	12.15	79.50	20.00	5.315	0.000
90 min *	62.36	10.35	61.00	17.00	76.54	11.10	76.50	19.00	5.508	0.000
120 min	63.26	9.42	61.00	17.00	78.58	10.36	79.00	15.00	7.734	0.000
150 min	63.48	8.97	63.50	10.00	78.36	10.25	77.50	18.00	7.727	0.000
180 min	80.76	9.76	82.00	16.00	85.34	9.89	84.50	13.00	2.331	0.022

Note: P value calculated for Unpaired T test except at "*". Note:"*" Normality Test (Shapiro-Wilk) Failed (P < 0.050), thus P value calculated for Mann-Whitney Rank Sum Test.

Table 4: Comparison among study group for Mean Arterial Pressure (MAP in mmHg)

MAP (mmHg)	X1 Group				X0 Group				Unpaired T test	P value
	Mean	Std. Dev.	Median	IQR	Mean	Std.Dev.	Median	IQR		
0 min	93.54	7.53	92.50	11.00	92.40	6.50	92.50	9.00	0.810	0.420
30 min	75.64	6.36	74.00	11.00	84.84	8.89	84.50	11.00	5.953	0.000
60 min *	74.38	6.16	73.00	10.00	82.34	9.36	80.50	13.00	4.278	0.000
90 min *	74.56	5.90	73.00	9.00	81.70	9.46	82.00	14.00	3.840	0.000
120 min *	73.78	5.22	73.00	8.00	82.60	13.13	82.50	17.00	4.850	0.000
150 min *	74.26	10.08	76.00	9.00	84.04	9.90	85.00	13.00	4.774	0.000
180 min	89.98	8.01	90.00	11.00	91.42	6.37	91.50	6.00	0.995	0.322

Note: P value calculated for Unpaired T test except at "*". Note: "*" Normality Test (Shapiro-Wilk) Failed (P < 0.050), thus P value calculated for Mann-Whitney Rank Sum Test.

Table 5: Comparison among study group for Ramsay Sedation Score

RSS	X1 Group				X0 Group				Mann Whitney Test	P Value
	Mean	Std. Dev.	Median	IQR	Mean	Std. Dev.	Median	IQR		
0 min	1.68	0.47	2.00	1.00	1.66	0.48	2.00	1.00	0.172	0.863
30 min	3.58	0.88	4.00	1.00	3.42	0.88	4.00	1.00	1.013	0.311
60 min	3.74	0.69	4.00	1.00	3.58	0.73	4.00	1.00	0.841	0.400
90 min	3.58	0.54	4.00	1.00	3.20	1.03	3.00	1.00	1.910	0.056
120 min	3.62	0.57	4.00	1.00	3.44	0.84	4.00	1.00	0.831	0.406
150 min	3.32	0.74	3.00	1.00	3.20	0.86	3.00	1.00	1.006	0.314
180 min	2.28	0.64	2.00	1.00	2.06	1.02	2.00	2.00	1.741	0.082

As depicted in the table, the mean age in Group X1 was 70.46 and the mean age in Group X0 was 72.04 with a p value of 0.232 indicating statistically not significant.

In our study the mean baseline Pulse rate in group X1 was (86.92±13.39) bpm and in group X0 was (87.08±13.30) bpm respectively. Difference between them is not statistically significant as per the p value (0.839). At 30 min Intraoperatively, the mean Pulse rate was decreased to (66.20±9.99) bpm in group X1 and (78.94±11.68) bpm in group X0 respectively. After that the difference in the Pulse rates at all points was analyzed by the unpaired T-Test and P value was less than 0.05 throughout, indicating that there was significant difference in both groups.

The mean baseline mean arterial pressure in group X1 was (93.54±7.53) mmhg and in group X0 was (92.40±6.5) mmhg respectively. Difference between them is not statistically significant as per the p value (0.420). At 30 min intraoperatively, the MAP was (75.64±6.36) mm hg in group X1 and (84.84±8.89) mm hg in group X0 respectively. Both group has shown decrease in MAP than preop MAP, but significantly greater in X1 group than in X0 group.

The difference in the heart rates at all points was analyzed by the unpaired T-Test and P value was less than 0.05 throughout in further study, indicating that there was significant difference in both groups except last reading which shows p value around 0.322.

As sedation score is a qualitative data, we can't apply routine unpaired T test to such data. We have to apply 'Mann- Whitney' test in such case. We don't extract mean but deduce mean rank for such data. In above table we can see there is no significant difference between mean ranks of both groups though value of mean ranks is fluctuating.

As we can see, p value at all readings remained more than 0.05 which denotes that there is no significant difference between sedation achieved in Group X1and Group X0.

Discussion

Sedative-hypnotic drugs are also commonly used to make procedures more tolerable for patients by reducing anxiety and providing an appropriate degree of intraoperative sedation and amnesia. During longer surgical procedures, patients may become restless, bored, or uncomfortable when forced to remain immobile.

Therefore, sedative-hypnotic drugs, as well as non-pharmacologic approaches (e.g., music), may prove beneficial because they allow patients to rest during the operation. Patients' anxiety can be reduced by using benzodiazepines, as well as by good preoperative communication, keeping the patient warm and covered, and allowing the patient to listen to relaxing music during the procedure.

Since the approval of Midazolam by FDA in 1985, practitioners embraced the versatility provided by Midazolam. Opioids also remained as good option/ or supportive drug. The risk of losing airway control, hypoxia and hypotension with higher doses of Midazolam has also been recognized. With the recent development of highly specific $\alpha 2$ agonists clonidine and dexmedetomidine, there has been a renewed interest in this class of drugs for use in perioperative period. as they offer both sedation, analgesia and can provide induced hypotension with a bloodless surgical field [4].

As an ideal sedative agent, it should provide advantages of general anesthesia, viz ; immobility, and controlled hypotension. But simultaneously patient should be cooperative and arousable so that surgeon can interact with patient during surgery. Adequate sedation level must be achieved without losing airway reflexes. In our study we compared two agents for above given parameters. One of them which is classically used, Midazolam, and another is newer drug from alpha 2 agonist group, dexmedetomidine. 100 patients are divided randomly in two groups, each of 50, which received one of the above mentioned drugs and comparison done for parameters such as sedation, analgesia, and cardio respiratory parameters.

In our study the mean age of the patients was comparable between the two groups with mean age in group X1 being (70.46) and that in group X0 being (72.04). The difference was statistically not significant. The proportion of males and females was comparable between the two groups and statistically not significant (p= 0.232).

Thus with respect to demographic variables both the groups were comparable. The importance of the variation being non-significant for age, sex, weight and ASA grading is that a random distribution of patients was confirmed to and there were no confounding factors which would later interfere with the perioperative assessment.

Baseline heart rate at o min, in both X1 & X0 group were 86.92 & 87.08 respectively; the difference between them is not statistically significant (p=0.839). After 30 mins, pulse rate decreased in both groups (X1 group- 66.20 & X0 group-78.94.) It was significantly less in X1 group than X0 group with p=0.000. This trend remained constant according to graph at 60, 90, 120, 150 & 180 minutes. Pulse rate in X1 group was persistently and significantly remained lower than X0 group with p value as respectively. But at end of surgery, at 180 minutes, again there is rise in pulse rate, with (80.76 & 85.34) in group X1 & X0 respectively, approaching to pre op pulse rate.

Dr Indira kumar et al, 2012 [4] observed sixty patients undergoing ENT surgery under MAC. They were divided into two groups of 30 patients each. The patients in Group C received clonidine 2 mcg/kg IV and in Group M received Midazolam 20 mcg/kg IV over 10min. RSS, requirement of intraoperative rescue sedation and analgesic, postoperative VAS & analgesic requirement, adverse effects, recovery profile and satisfaction scores of patients and surgeon were recorded. No significant change was observed in respiratory rate and SpO2 in both the groups (p>0.05).

Results are concordant with study conducted by A. Abdellatif et al, 2012 [5] who compared dexmedetomidine and Midazolam as sedative agents in middle ear surgeries. In group D the HR values started to be lower from the baseline at 10 min from the start of sedation. This significant reduction in heart rate continued till the end of surgery and showed significant difference from those values recorded in group M that showed more stable Hemodynamics. The surgical field bleeding score was superior in group D compared to group M (p <0.001). The surgeon observed grade I surgical field in 18 patients of group D vs only in four cases in group M.

Kenan kaygusuz et al, 2008 [6] studied 40 patients, posted for shockwave lithotripsy which is randomly divided in two groups, one received dexmedetomidine and other got propofol as sedating agent which are compared for Hemodynamics, SpO2, RR and sedation level. In the dexmedetomidine and propofol groups, HR significantly decreased during sedation and recovery, compared with baseline. The Heart rate values during sedation were significantly lower than those in dexmedetomidine group.

Another important haemodynamic parameter we monitored is mean arterial pressure. Mean arterial pressure is directly related to surgical field quality and surgeons satisfaction. Baseline MAP at o min, in both X1 & X0 group were 93.54 & 92.40 respectively; the difference between them is not statistically significant. (p=0.420). After 30 mins, MAP decreased in both groups (X1 group- 75.64 & X0 group- 84.84). When compared to each other, it was significantly less in X1 group than X0 group with p=0.000. This trend remained constant according to graph at 60, 90, 120,150 & 180 mins. MAP in X1 group was persistently and significantly remained lower than X0 group with p value as low as 0.000. But at end of surgery, at 120 mins, again there is rise in MAP, with (89 & 91) in group X1 & X0 respectively, approaching to pre op MAP, though not exactly same as before.

Kamer dere et al, 2010 [7] studied 60 patient with ASA II, to compare the effects of dexmedetomidine versus Midazolam on perioperative Hemodynamics, sedation, pain, satisfaction and recovery scores. In Group D, a significant statistical decrease was found with regard to mean arterial pressure values at the onset of the study and at the 5th minute ($P<0.05$). Changes in MAP were similar between the groups throughout further study.

It can be stated from our result that Dexmedetomidine, showed much better haemodynamic control over Midazolam throughout the procedure. The lower HR and MAP observed in Dexmedetomidine group could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine [8,9].

One of the aims of our study is the comparison of effect on respiration by both study drugs. We have monitored Respiratory rate & oxygen saturation. Baseline respiratory rate in both groups are 15.40±0.86& 15.3±1.05 (in group X1 & group X0 respectively). There is no significant difference between both groups according to p value (0.858). After giving drugs, in X0 group, rate decreases and remains lower than X1 group throughout the study. When compared, significant difference is found between two groups according to p values.

Oxygen saturations at baseline in our study are 98.32±1.45 & 98.32±1.74 in group X1 & group X0 respectively. There was no significant difference found in them. ($p = 0.866$.) Values in both groups didn't show clinically significant difference at 30 min, 60 min, 150 min and at 180 min interval in further intraoperative period. P values remained consistently higher than 0.05. But at 90 min & 120 min interval oxygen saturation values in M group were significantly low than those of D group. But it is clear that those values were never low to be called as clinically significant. Active interventions were not required.

The observed lower value of SpO2 in Group X0, at 90 & 120 mins would suggest that breathing was likely low tidal volume at that time. We have seen that Ventilatory frequency found to be consistently lower in X0 group than X1 group. From above results we can conclude that, as compared to Dexmedetomidine; Midazolam shows greater depression in respiratory drive.

Hsu, Yung-Wei; Cortinez, Luis et al, 2004 [10] measured and compared respiratory responses of six healthy male volunteers during (1) a stepwise target-controlled infusion of remifentanil, (2) a stepwise target-controlled infusion of dexmedetomidine, and (3) a pseudo natural sleep session in mechanical controlled ventilation. The respiratory effects of dexmedetomidine markedly contrasted with those of remifentanil. When compared with baseline, during dexmedetomidine infusions, the respiratory rate significantly increased, and the overall apnea/ hypopnea index significantly decreased. The distribution of inspiratory time/ Ventilatory cycle time showed an increased peak. In addition, dexmedetomidine seemed to mimic some aspect of natural sleep.

Main purpose of our study drugs is optimal sedation so as to provide calm & comfortable patient with no intra-op movements. We have used Ramsay sedation scale to assess sedation level. In both groups, after giving sedative RSS score increased from baseline but when compared with each other, according to p value (0.863, 0.311, 0.400, 0.056, 0.406, 0.314 & 0.082) no statistical difference is found at any point in study. Result suggest both drugs achieve same degree of sedation with given doses

Yavuz Demiraran et al [11] investigated and compared the safety and efficacy of dexmedetomidine versus Midazolam in providing sedation for gastroscopy in total of 50 adult patients (25 patients receiving dexmedetomidine and 25 patients receiving Midazolam). Dexmedetomidine performed as effectively and safely as Midazolam when used as a sedative in upper gastroscopy; it was superior to Midazolam with regard to retching, rate of side effects and endoscopist satisfaction.

One of the highest densities of α_2 receptors has been detected in the Locus ceruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The hypnotic and sedative effects of α_2-adrenoceptor activation have been attributed to this site in the CNS. The locus ceruleus is also the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. In this region of the brain α_2-adrenergic and opioid systems have common effector mechanisms, indicating that dexmedetomidine has a supraspinal site of action [12,13].

We also studied sedation using Bispectral Index Monitoring. We used BIS scale to assess sedation and used Mann Whitney test to compare mean ranks. In both groups, after giving sedative RSS score decreased from baseline but when compared with each other, according to p value (0.255, 0.341, 0.361, 1.629, 1.771, 1.436, 0.342) no statistical difference is found at any point in study. Result suggest both drugs achieve same degree of sedation with given doses.

Jalowiecki, Przemyslaw et al, 2005 [14] evaluated the ability of dexmedetomidine to provide analgesia and sedation for outpatient colonoscopy. Sixty-four patients were randomly assigned to one of three treatment regimens. In group D, patients received dexmedetomidine, Group P received meperidine with Midazolam, and group F received fentanyl on demand. Supplemental fentanyl was required in 47% of patients receiving dexmedetomidine to achieve a satisfactory level of analgesia (*vs.* 42.8% of patients in group P and 79.2% of patients in group F). That means rescue analgesic requirement was not much reduced by dexmedetomidine.

We didn't find any complication like hypotension, apnea or bradycardia which required active intervention and discontinuation of study drug, throughout the study in any group.

Conclusion

Study shows that Intravenous Dexmedetomidine and Intravenous Midazolam provided similar sedation during Regional Anesthesia.

But considering effect of both drugs on haemodynamic and respiratory parameters, Dexmedetomidine can be considered superior than Midazolam as a sedative agent for sedation under Regional Anaesthesia in Elderly.

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