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GAVIN PUBLISHERS

Journal of Anesthesia and Surgical Reports

Gani TT, et al. J Anesth Surg Rep: JASR-101.

DOI: 10.29011/JASR-101.100001

Research Article

A Comparative Study to Evaluate the Efficacy and Safety of Dexmedetomidine and Midazolam for Sedation in Neurosurgical Patients Requiring Short Term Postoperative Mechanical Ventilation

Tantry Tariq Gani[1*], Shahid Ahmad Mir[1], Tanveer A. Sofi[2]

[1]Department of Anesthesiology and Critical Care, Sheri Kashmir Institute of Medical Sciences, India

[2]Department of Zoology, University of Kashmir, Srinagar, India

[*]**Corresponding author:** Tantry Tariq Gani, Department of Anesthesiology and Critical Care, Sheri Kashmir Institute of Medical Sciences, India. Email: tantarytariq2@gmail.com

Citation: Gani TT, Mir SA, Sofi TA (2018) A Comparative Study to Evaluate the Efficacy and Safety of Dexmedetomidine and Midazolam for Sedation in Neurosurgical Patients Requiring Short Term Postoperative Mechanical Ventilatio. J AnesthSurg Rep: JASR- 101. DOI: 10.29011/JASR-101.100001

Received Date: 05 March, 2018; **Accepted Date:** 16 April, 2018; **Published Date:** 24 April, 2018

Abstract

Background: Neurosurgical patients requiring short term postoperative mechanical ventilation need sedatives and analgesics to facilitate their care. Dexmedetomidine possesses anxiolytic, hypnotic and analgesic properties.

Aim: The present study compared the efficacy of dexmedetomidine and midazolam for sedation in neurosurgical patients for postoperative mechanical ventilation.

Design: Prospective randomised study.

Materials and Methods: 60 patients of either sex, aged 18 to 60 years, ASA physical status I or II, preoperative GCS 15, undergoing neurosurgery and requiring short term postoperative ventilation were included. The patients were randomly divided into two groups of 30 each. Group I received dexmedetomidine 1 μgkg-1 over 10 minutes followed by maintenance infusion at a rate of 0.2-0.5 μgkg-1hr-1. Group II received midazolam as a bolus of 0.1 mgkg-1 initially, followed by an infusion of 0.05-0.1 mgkg-1hr-1. Additional analgesia, if required, was provided by fentanyl infusion. Heart rate, mean arterial pressure, central venous pressure, oxygen saturation, sedation level, fentanyl requirement, ventilation and extubation time were recorded.

Results: Adequate sedation level was achieved with both drugs. Ramsay sedation score was 3.76 ± 0.42 and 4.14 ± 0.37 for dexmedetomidine and midazolam, respectively, ($p=0.136$). Total fentanyl dose in the dexmedetomidine group was 28.5 ± 8.50 μg compared to 80.5 ± 25.50 μg in the midazolam group, ($p<0.05$). There was 62.7% of reduction of fentanyl consumption in the patients who received dexmedetomidine. Patients who received dexmedetomidine infusion had significantly lower heart rates compared to patients who received midazolam infusion, ($p<0.05$). No difference was found in mean arterial pressures of two groups. Extubation times were rapid with the use of dexmeditomedine (25.7 ± 8.33 minutes for Group I and 38.42 ± 12.54 minutes for Group II, $p<0.05$). No adverse events related to sedative infusions occurred in either group.

Conclusion: Dexmedetomidine is safe and effective agent compared to midazolam.

Keywords: Dexmedetomidine; Midazolam; Neurosurgical Patients

Introduction

Sedation is an essential component of the management of intensive care patients. Sedation has become integral part of critical care to minimise patient discomfort and stress response, provide anxiolysis, facilitate nursing care, improve tolerance of ventilatory support, facilitate procedures like endotracheal tube suctioning and physiotherapy [1,2]. Patient agitation may result from a specific

cause such as hypoxia, under ventilation, metabolic derangement and other correctable entities that should be addressed, but it may be the result of sleep deprivation, or pharmacological interactions, and require sedation to control [1,3]. Proper sedation reduces long term psychological sequelae of ICU admission, time on mechanical ventilation and length of hospital stay [4].

Dexmedetomidine, a selective α_2 adrenergic agonist, has a role as a sedative agent in patients requiring intensive care. Hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons in the locus ceruleus [5]. Midazolam is a widely used benzodiazepine sedative with rapid onset time in adults (0.5-5 min), and its effects after a single dose disappear quickly. It acts through gamma-aminobutyric acid-benzodiazepine receptor complex and undergoes extensive oxidation in the liver through the cytochrome P450 to form water-soluble hydroxylated metabolites, which are excreted in urine [6]. However, infusion for more than 1hr increases its deposition in peripheral tissues, and effects of midazolam thus continue after the infusion has been stopped, owing to release from peripheral tissues to blood. Moreover, paradoxical reactions to benzodiazepines and hemodynamic changes may be experienced [7].

Aims and Objectives

To compare sedation, analgesia and hemodynamic effects between dexmeditomidine and midazolam in neurosurgical patients requiring short term post-operative mechanical ventilation.

Material and Methods

This prospective randomised study was conducted in the department of Anesthesiology and Critical Care at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir from May 2016 to June 2017. After taking the Institutional Review Board approval, 60 patients of either sex, belonging to ASA physical status I or II, in the age range of 18 to 60 years undergoing elective craniotomy for resection of supratentorial intracranial tumours and expected to require a minimum of 6 hours' postoperative mechanical ventilation were included in this study. Patients with GCS < 15, Head injury, history of ischemic heart disease or second or third degree heart block, comorbidities like uncontrolled hypertension and diabetes, Pregnant patients, severe hepatic and renal dysfunction, allergic to trial drugs and any untoward effect during surgery which was likely to effect the duration of stay in ICU were excluded from the study.

During the preoperative visit, all patients were clinically evaluated, assessed and investigated. The study protocol was explained to all patients and written informed consent was taken from them. No sedative premedication was administered. In the Operating room, the anesthesia technique was same in all the patients. Appropriate size venous cannulae were inserted and peripheral lines were secured for administration of drugs and fluids. Anesthesia was induced with fentanyl 2 μgkg^{-1}, propofol 2 $mgkg^{-1}$ and vecuronium bromide 0.1 $mgkg^{-1}$ body weight. After endotracheal intubation anesthesia was maintained with isoflurane and nitrous oxide in oxygen and analgesia was provided by fentanyl 1 μgkg^{-1} every hour. Patients were mechanically ventilated to maintain partial pressure of carbon dioxide between 30 and 35 mmHg. At the end of the surgical procedure patients were transferred to ICU and artificial ventilation was continued.

Patients were randomly allocated (using sealed envelopes) to two groups of 30 patients each to receive intravenous infusion either dexmedetomidine hydrochloride (Group I) or midazolam (Group II). Dexmedetomidine was diluted with normal saline to a concentration of $4\mu gml^{-1}$. Patients received a loading dose of dexmedetomidine 1 μgkg^{-1} over 10 minutes followed by maintenance infusion at a rate of 0.2-0.5 $\mu gkg^{-1}hr^{-1}$, with the dosage adjusted to achieve the desired level of sedation. On the other hand, midazolam was given undiluted as a bolus of 0.1 $mgkg^{-1}$ initially, followed by an infusion of 0.05-0.1 $mgkg^{-1}hr^{-1}$, with the dosage adjusted to achieve the desired level of sedation. All patients received fentanyl infusion at the rate of 0.5 $\mu gkg^{-1}hr^{-1}$. The infusion rate was adjusted as required by the patient to relieve pain. No muscle relaxants were given during the study period. No other sedative and analgesic agents were used. The degree of sedation was measured and recorded hourly using six grade Ramsay Sedation Score (RSS) as Grade 1: Anxious, Grade 2: Cooperative and tranquil, Grade 3: Responding to commands only, Grade 4: Brisk response to light glabellar tap, Grade 5: Sluggish response to light glabellar tap and Grade 6: No response to light glabellar tap. Grades 2, 3, 4 and 5 were considered adequate sedation (desired level), Grade 1 insufficient sedation and Grade 6 excessive sedation.

The total amount of fentanyl consumption and the quality of sedation was recorded. The total time on mechanical ventilation was recorded. Heart Rate (HR), Mean Arterial Pressure (MAP) and Central Venous Pressure (CVP) were monitored continuously and recorded hourly. The sedative infusion was discontinued, in preparation for extubation, when there was no evidence of bleeding and the patient was alert, hemodynamically stable, normothermic and an arterial oxygen tension $\geq$75 mmHg on an inspired oxygen concentration <40% and had positive end expiratory pressure $\leq$ 5 cm H_2O. Once spontaneous respiration was established with pressure support <10 cm H_2O, a tidal volume of >6 ml kg^{-1}, and respiratory rate $\geq$10 breaths min^{-1} but <20 breaths min^{-1}, extubation was undertaken. Extubation time defined as the time from cessation of sedation infusion to extubation was recorded. Cardiovascular and respiratory adverse events defined as a change in arterial pressure of $\geq$40% from baseline, bradycardia <50 beats min^{-1}, tachyarrhythmia, and a respiratory rate <8 or >25 breaths min^{-1} after extubation, were noted and treated accordingly.

Results and Observations

Demographic patterns and pre-operative vital parameters were similar when the two groups were compared (Table 1).

Parameters	Group I (n=30) Mean ± SD	Group II (n=30) Mean ± SD	P value
Age (years)	41.32 ± 4.23	43.30 ± 6.27	0.47
Gender(M/F)	20/10	19/11	0.48
Weight (kg)	65.64 ± 6.46	63.47 ± 7.08	0.28
Mean Duration of Surgery(hours)	5.72 ±1.54	5.88 ± 1.59	0.345
Preoperative heart rate (bpm)	94 ± 6.10	96 ± 4.95	0.325
Preoperative MAP (mmHg)	106.2 ± 5.08	103.3 ± 4.76	0.142
Preoperative CVP (mmHg)	9.56 ± 1.76	9.65 ± 1.45	0.195
Preoperative SpO_2 (%)	98.87 ± 0.64	98.70 ± 0.82	0.391
Data are given as mean ± SD, Test done: Independent sample t-test, $Pearson Chi square. n: Number of patient; M/F :Male/Female; Kg: Kilograms; bpm: Beats per minute; MAP: Mean arterial pressure; CVP: Central Venous Pressure; SpO_2: oxygen saturation by pulse oximetry			

Table 1: Two groups were compared.

There was a statistically significant difference between the heart rates of two groups, patients receiving dexmedetomidine for sedation had lower mean heart rate (74.6 ± 6.12 bpm under sedation and 84.13 ± 4.64 after discontinuation of sedation) as compared to midazolam group (88.45 ± 5.07 bpm under sedation and 90.76 ± 2.87bpm after discontinuation of sedation)). A fall in MAP was seen in both the groups after sedative infusion was started. The difference in mean MAP was significant at 2nd and 3rd hour after starting the drug infusion but the overall difference in mean MAP over the study period of 6 hours was statistically insignificant. Patients receiving dexmedetomidine for sedation had MAP (98.2 ± 4.532 mmHg under sedation and 102.31 ± 3.80after discontinuation of sedation) as compared to midazolam group (96.81 ± 3.431mmHgunder sedation and 100.12 ± 3.19 mmHg after discontinuation of sedation). The overall mean CVP for 6 hours was comparable between the two groups. Patients receiving dexmedetomidine for sedation had CVP (8.25 ± 0.90mmHg under sedation and 9.87 ± 0.89 mmHg after discontinuation of sedation) as compared to midazolam group (8.66 ± 0.74 mm Hgunder sedation and 10.07 ± 0.26 mmHg after discontinuation of sedation). The mean oxygen saturations remained above 95% at all-time intervals between the two groups. The overall oxygen saturations between the two groups remained similar ($p > 0.05$). Overall mean sedation score (RSS) was comparable between the two groups (Table 2).

Parameter	Group I (n=30) Mean ± SD	Group II (n=30) Mean ± SD	P value
Heart rate under sedation(bpm)	74.6 ± 6.12	88.45 ± 5.07	<0.001
Heart rate after discontinuation of sedation(bpm)	84.13 ± 4.64	90.76 ± 2.87	<0.001
MAP under sedation(mmHg)	98.2 ± 4.532	96.81 ± 3.431	0.125

MAP after discontinuation of sedation(mmHg)	102.31 ± 3.80	100.12 ± 3.19	0.867
CVP under sedation(mmHg)	8.25 ± 0.90	8.66 ± 0.74	0.108
CVP after discontinuation of sedation(mmHg)	9.87 ± 0.89	10.07 ± 0.26	0..675
SPO_2 under sedation(%)	99.01 ± 1.20	98.99 ± 1.31	0.564
SPO_2 after discontinuation of sedation (%)	98.34 ± 0.62	98.65 ± 0.67	0.675
Ramsay Sedation Score under sedation	3.76 ± 0.42	4.14 ± 0.37	0.136
Data are given as mean ± SD, Test done: Independent sample t-test, $Pearson Chi square. n: Number of patient; bpm: Beats per minute; MAP: Mean arterial pressure; CVP: Central Venous Pressure; SpO_2: oxygen saturation by pulse oximetry.			

Table 2: Overall mean sedation score (RSS) was comparable between the two groups.

The percentage of cumulative hours of adequate sedation under ventilator was 93.2% for Group I and 90.8% for Group II and the difference was statistically insignificant (Table 3).

Sedation	Group I (n=30) Mean ± SD	Group II (n=30) Mean ± SD	P Value
Inadequate level (RSS Grade 1)	2.4%	3.6%	0.241
Adequate level (RSS Grade 2,3,4,5)	93%	90.6%	
Excessive level (RSS Grade 6)	4.60%	4.8%	

Table 3: Cumulative hours under different levels of sedation.

Mean fentanyl consumption was significantly lower in Group I (28.5 ± 8.50 µg) compared to Group II (80.5 ± 25.50 µg). There was a reduction of 62.7% in fentanyl consumption in Group I as compared to Group II. In our study the mean duration of mechanical ventilation was comparable between the two groups (9.70 ± 1.36 hours in Group I and 9.26 ± 1.83 hours in Group II). Mean extubation times were rapid in Group 1 (25.7 ± 8.33 minutes) than Group II (38.42 ± 12.54 minutes) (Table 4).

Parameters	Group I (n=30) Mean ± SD	Group II(n=30) Mean ± SD	P Value
Postoperative Fentanyl Requirement(mcg)	28.5 ± 8.50	80.5 ± 25.50	<0.001
Duration of Mechanical Ventilation (hours)	9.70 ± 1.36	9.26 ± 1.83	0.765
Duration of Extubation Time(hours)	25.7 ± 8.33	38.42 ± 12.54	<0.005
Data are given as mean ± SD, Test done: Independent sample t-test, $Pearson Chi square. n: Number of patient; mcg: micrograms.			

Table 4: Mean extubation times were rapid in Group I and II.

Discussion

The concept of analgesia and sedation in intensive care medicine has changed considerably over the last decade. Deep sedation is no longer the standard practice for most patients as it prolongs weaning from mechanical ventilation and length of ICU stay, and potentially increases morbidity [8]. The aim of this study was to compare dexmedetomidine, a comparatively newer drug, with midazolam, a drug which has been traditionally used in ICUs, in postoperative neurosurgical patients. Dexmedetomidine is a sedative with high affinity for α_2 adenoceptors [9]. It has a quick onset and a relatively short duration of action, it can be easily titrated, characteristics that make dexmedetomidine suitable for a critical care unit.

In this study the two groups were comparable with reference to age, gender distribution and weight, mean duration of surgery, baseline heart rate, baseline oxygen saturations and baseline mean arterial pressure. After starting the drug infusions, the mean heart rates (beats min^{-1}) of two groups showed no significant change in first 2 hours. Thereafter from 3rd to 11th hours there was a statistically significant

difference between the heart rates of two groups, patients receiving dexmedetomidine had lower heart rates as compared to midazolam group. After extubation the heart rate in Group I was still lower than Group II for a couple of hours, but after return to the baseline the heart rates became comparable again. Overall difference between the heart rates in two groups was statistically significant in extubated patients. Even after stopping the dexmedetomidine infusion its effect on heart rates stays for some time. This would be particularly helpful during extubation and peri extubational time in decreasing myocardial stress and increased oxygen demand associated with stressful extubation time. A fall in MAP was seen in both the groups after sedative infusion was started. The difference in mean MAP was significant at 2nd and 3rd hour after starting the drug infusion but the overall difference in mean MAP over the study period of 6 hours was statistically insignificant. Two patients receiving dexmedetomidine had hypotensive response at 1 hour which was corrected on administration of fluid bolus and adjusting the dose of sedative infusion. Ionotropes were not required. No other cardiovascular event in either of the two groups was seen. No patient receiving dexmedetomidine exhibited a hypertensive response to the loading dose. The overall mean CVP for 6 hours was comparable between the two groups. CVP was well maintained in all the patients throughout the study period. The hemodynamics of dexmedetomidine is predictable from the pharmacology of α_2 adenoceptor agonists, and has been confirmed from previous studies in volunteers [10-12].

The SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) trial [13] showed that in the dexmedetomidine group, there was greater tendency to develop bradycardia compared with the midazolam-treated group (42.2 vs. 18.9%; $P < 0.001$) [13]. However, in the dexmedetomidine-treated group, only 4.9% required interventions for bradycardia, such as stopping the infusion or administration of atropine. With respect to hypotension, there was no significant difference between the dexmedetomidine and the midazolam groups (56.1 vs. 55.7%; $P > 0.05$).

Oxygen saturation was comparable between the groups for the first 11 hours of intubation and mechanical ventilation. Patients were observed for another 18 hours after discontinuing the sedative infusions and extubation of the patients. There were no residual effects of drugs on the ventilation. The mean oxygen saturations remained above 95% at all-time intervals between the two groups. The overall oxygen saturations between the two groups remained similar ($p > 0.05$) after extubation of patients. No adverse respiratory event was reported. Our study correlates with study conducted by R M Venn et al, 2000 showing no significant difference between the placebo and dexmedetomidine groups for oxygen saturations measured by pulse oximetry [14].

Mean extubation times were rapid with dexmeditomidine than with midazolam group. There were no adverse respiratory effects after extubation. No patient in either of the two groups required reintubation. In our study rapid extubation time may be due to the less dose of fentanyl used in dexmedetomidine group and second reason is owing to the deposition of midazolam in peripheral tissues when infusion is continued for several hours. Our results were similar to the results seen by Riker R.R and et al. as they found that Median time to extubation was 1.9 days shorter in dexmedetomidine-treated patients (3.7 days [95% CI, 3.1 to 4.0] vs 5.6 days [95% CI, 4.6 to 5.9]; P = .01), and ICU length of stay was similar (5.9 days [95% CI, 5.7 to 7.0] vs 7.6 days [95% CI, 6.7 to 8.6]; P = .24) [13]. Shehabi et al. in 2004 also showed that mean time to extubation was shorter in dexmedetomidine group (24.21 h [22-28 h]) than midazolam group (31.35 h [26-38 h] [$P < 0.05$]) [15].

Overall mean sedation score (RSS was comparable between the two groups. Grades 2, 3, 4 and 5 of Ramsay Sedation Score were considered adequate sedation (desired level), Grade 1 insufficient sedation and Grade 6 excessive sedation. The overall sedation adequacy was determined according to the cumulative hours under each of the three sedation levels defined above. The percentage of cumulative hours of adequate sedation under ventilator was 93% for Group I and 90.6% for Group II and the difference was statistically insignificant. So an equivalent depth of sedation between dexmedetomidine and midazolam in ICU was achieved. Our results are consistent with the studies like Prerana N Shah et al. [16].

In our study it was found that patients receiving dexmedetomidine were more arousable, more cooperative, and better able to communicate their pain than patients receiving midazolam. This allows frequent neurologic assessments and communication with the patient without interruption of calming effects of sedation which can be very beneficial in neurosurgery patients.

Adequate analgesia is important as pain can cause tachycardia, immunosuppression, increased catecholamine production and increased oxygen consumption. Sedatives are often used along with analgesics to provide patient comfort and safety in ICU [3]. Analgesia in our study was provided by continuous infusion of short acting opioid fentanyl at the rate of 0.25-0.5 $\mu gkg^{-1}hr^{-1}$. The infusion rate was adjusted as required by the patient to relieve pain. Fentanyl was used in preference to morphine because recovery after fentanyl infusion is generally rapid and excretion of active metabolites is not a problem. Mean fentanyl consumption was significantly lower in Group I compared to Group II. There was a reduction of 62.7% in fentanyl consumption in Group I as compared to Group II. The interaction of α_2-adenoceptors and opioids lead to decrease in the dose of fentanyl. The α_2 adenoceptors have an effect on the spinal cord, especially α_{2A} and

α_{2C} as well as modulating the descending noradrenergic pathways leading to 30% to 50% reduction in the requirements of opioids**.** Our results are consistent with R M Venn et al who showed that patients sedated with dexmedetomidine required 50% less opioids (morphine) as compared to placebo group.

Decreasing the time on mechanical ventilation reduces the risk of complications such as pneumonia and stress ulcers, decreases the risk of patients becoming delirious, and has significant cost implications [1,3-5]. In our study the mean duration of mechanical ventilation was comparable between the two groups.

Conclusion

Dexmedetomidine is safe and effective agent compared to midazolam for sedation of neurosurgical mechanically ventilated patients with good hemodynamic stability and extubation time more rapid than midazolam.

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