



A COMPARATIVE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DEXMEDETOMIDINE AND PROPOFOL FOR SEDATION IN NEUROSURGICAL PATIENTS REQUIRING SHORT TERM POSTOPERATIVE MECHANICAL VENTILATION

Anaesthesiology

Sheikh Irshad Ahmad

Additional Professor, Sheri Kashmir Institute of Medical Sciences, Kashmir, India

Aayushi Mahajan

Senior Resident, Sheri Kashmir Institute of Medical Sciences, Kashmir, India

Tantry Tariq Gani*

Senior Resident, Sheri Kashmir Institute of Medical Sciences, Kashmir, India
*Corresponding Author

Imtiaz Naqash

Professor and HOD Anesthesiology, Sheri Kashmir Institute of Medical Sciences, Kashmir, India

Tanveera Gani

Senior Resident, Sheri Kashmir Institute of Medical Sciences, Kashmir, India

ABSTRACT

Background: Neurosurgical patients requiring short term postoperative mechanical ventilation frequently need sedatives and analgesics to facilitate their care. **Aim:** The present study compared the efficacy of dexmedetomidine and propofol 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 propofol as a bolus of 1 mgkg⁻¹ initially, followed by an infusion of 0.5-1 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 3.88 ± 0.39 and 4.04 ± 0.47 for dexmedetomidine and propofol, respectively, ($p=0.152$). Total fentanyl dose in the dexmedetomidine group was 33.5 ± 7.51 µg compared to 72.2 ± 18.15 µg in the propofol group, ($p<0.05$). Patients who received dexmedetomidine infusion had significantly lower heart rates compared to patients who received propofol infusion, ($p<0.05$). No difference was found in mean arterial pressures of two groups. Extubation times were similar and rapid with the use of both sedative agents (27.4 ± 9.53 minutes for Group I and 30.36 ± 10.66 minutes for Group II, $p>0.05$). No adverse events related to sedative infusions occurred in either group. **Conclusion:** Dexmedetomidine is safe and equally effective agent compared to propofol for sedation of neurosurgical mechanically ventilated patients with good hemodynamic stability and extubation time as rapid as propofol.

KEYWORDS

Dexmedetomidine, propofol, sedation

INTRODUCTION

Sedation has become integral part of critical care to minimise patient discomfort and stress response, provide anxiolysis, facilitate procedures like endotracheal tube suctioning and physiotherapy.^{1,2} Patient agitation may result from 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 agonist, has a role as a sedative agent in patients requiring intensive care and its hypnotic effect is mediated by the hyperpolarization of noradrenergic neurons in locus ceruleus.⁵

Propofol, an intravenous general anesthetic agent having sedative and hypnotic properties results in widespread inhibition of NMDA subtype of glutamate receptor through modulation of sodium channel gating, an action that may also contribute to drug's CNS effects.⁶

AIMS AND OBJECTIVES

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

MATERIAL AND METHODS: This prospective randomised study was conducted in a tertiary care from December 2012 to November 2014. 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 tumors 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. The study protocol was explained to all patients and written informed consent

was taken from them. In the Operating room, the anesthesia technique was same in all the patient. Anesthesia was induced with fentanyl 2 µgkg⁻¹, propofol 2 mgkg⁻¹ and vecuronium bromide 0.1 mgkg⁻¹ body weight. Anesthesia was maintained with isoflurane and nitrous oxide and oxygen and analgesia was provided by fentanyl 1 µgkg⁻¹ every hour. 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 propofol (Group II). Dexmedetomidine was diluted with normal saline to a concentration of 4 µgml⁻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 µgkg⁻¹hr⁻¹, with the dosage adjusted to achieve the desired level of sedation. On the other hand, propofol was given undiluted as a bolus of 1 mgkg⁻¹ initially, followed by an infusion of 0.5-1 mgkg⁻¹hr⁻¹, with the dosage adjusted to achieve the desired level of sedation. All patients received fentanyl infusion at the rate of 0.5 µgkg⁻¹hr⁻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). 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 ≥ 75 mmHg on an inspired oxygen concentration <40% and had positive end-expiratory pressure ≤ 5 cm H₂O. Once spontaneous respiration was established with pressure support <10 cm H₂O, a tidal volume of >6 ml kg⁻¹, and respiratory rate ≥ 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 ≥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].

TABLE 1

Parameters	Group I (n=30) Mean ± SD	Group II(n=30) Mean ± SD	P value
Age (years)	42.96 ± 4.18	44.3 ± 7.67	0.4
Gender(M/F)	22/8	19/11	0.578
Weight (kg)	62.36 ± 6.46	64.93 ± 8.09	0.18
Mean Duration Of Surgery(hours)	5.43±1.89	5.78±1.79	0.465
Preoperative heart rate (bpm)	95 ± 5.32	96.1±5.38	0.443
Preoperative MAP (mmHg)	104.2±4.99	102.3±4.4	0.123
Preoperative CVP (mmHg)	8.9±1.34	9.27±1.33	0.295
Preoperative SpO2 (%)	99.57±0.81	99.60±0.72	0.868

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; SpO2: oxygen saturation by pulse oximetry

There was a statistically significant difference between the heart rates of two groups, patients receiving dexmedetomidine for sedation had lower mean heart rate (72.6±4.08 bpm under sedation and 81.6±2.72 after discontinuation of sedation) as compared to propofol group(87.7±4.07 bpm under sedation and 89.8±1.47bpm 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 (97.2±4.552 mmHg under sedation and 101.31±2.80after discontinuation of sedation) as compared to propofol group(95.7±3.431mmHgunder sedation and 101.22±2.39 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 (9.25±0.60mmHg under sedation and 10.44±0.554 mmHg after discontinuation of sedation) as compared to propofol group(9.57±0.84 mmHgunder sedation and 10.50±0.63 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).

TABLE 2

Parameter	Group I (n=30) Mean ± SD	Group II(n=30) Mean ± SD	P value
Heart rate under sedation(bpm)	72.6±4.08	87.7±4.07	<0.001
Heart rate after discontinuation of sedation(bpm)	81.6±2.72	89.8±1.47	<0.001
MAP under sedation(mmHg)	97.2±4.552	95.7±3.431	0.169
MAP after discontinuation of sedation(mmHg)	101.31±2.80	101.22±2.39	0.894
CVP under sedation(mmHg)	9.25±0.60	9.57±0.84	0.101
CVP after discontinuation of sedation(mmHg)	10.44±0.554	10.50±0.63	0.713
SPO2 under sedation(%)	99.01±1.20	98.99±1.31	0.943
SPO2 after discontinuation of sedation(%)	98.78±0.22	98.86±0.37	0.302
Ramsay Sedation Score under sedation	3.88±0.39	4.04±0.47	0.152

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; SpO2: oxygen saturation by pulse oximetry.

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).

Table 3

Cumulative Hours Under Different Levels Of Sedation			
Sedation	Group I (n=30) Mean ± SD	Group II(n=30) Mean ± SD	P Value
Inadequate level (RSS Grade 1)	2%	3.6%	0.329
Adequate level (RSS Grade 2,3,4,5)	93.2%	90.8%	
Excessive level (RSS Grade 6)	4.80%	5.6%	

Mean fentanyl consumption was significantly lower in Group I(33.5±7.51 mcg) compared to Group II(72.2±18.15 mcg). There was a reduction of 53.6% 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 (8.3±1.86 hours in Group I and 8.36±2.05 hours in Group II). Mean extubation times were rapid and similar in both groups(27.4±9.53hours in Group I and 30.36±10.66 hours in Group II)(TABLE 4).

TABLE 4

Parameters	Group I (n=30) Mean ± SD	Group II(n=30) Mean ± SD	P Value
Postoperative Fentanyl Requirement(mcg)	33.5±7.51	72.2±18.15	<0.001
Duration Of Mechanical Ventillation(hours)	8.3±1.86	8.36±2.05	0.895
Duration Of Extubation Time(hours)	27.4±9.53	30.36±10.66	0.26

Data are given as mean±SD, Test done: Independent sample t-test, \$Pearson Chi square. n: Number of patient; mcg: micrograms.

DISCUSSION

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.7 Dexmedetomidine 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.⁸

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. At 1st hour and 2nd hour after starting the drug infusions the mean heart rates (beats min⁻¹) of two groups showed no significant change. 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 propofol 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. 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 α₂ adrenoceptor agonists, and has been confirmed from previous studies in volunteers by B C Bloor et al, J B Dyck et al, P Talke et al.9,10,11. 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.¹²

Mean extubation times were rapid and similar in both groups. There were no adverse respiratory effects after extubation. No patient in either of the two groups required reintubation. Although, longer extubation times would have been predicted with dexmedetomidine from volunteer pharmacokinetic data as the elimination half life of propofol is approximately three times shorter (30 to 60 minute for propofol v/s 100 to 150 minutes for dexmedetomidine).^{13,14} But our study and many studies done before this have shown that dexmedetomidine does not cause any adverse effect on respiration and the extubation times of dexmedetomidine and propofol are similar. Infact, dexmedetomidine can be used safely over the extubation period. In our study similar extubation time may be due to the less dose of fentanyl used in dexmedetomidine group. Our results were similar to the results seen by Vinit K Srivastava,^{2014,15}

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. So an equivalent depth of sedation between dexmedetomidine and propofol in ICU was achieved. Our results are consistent with the studies like Prerana N Shah et al.¹⁶

CONCLUSION

Both dexmedetomidine and propofol are safe sedative drugs for postoperative mechanically ventilated neurosurgical patients. Dexmedetomidine decreases both heart rate and MAP. However, with careful patient selection, by proper fluid administration and by decreasing the loading dose of dexmedetomidine these effects can be minimised. Also dexmedetomidine significantly lessens consumption of opioids compared to propofol.

REFERENCES

1. Marlies E Ostermann, Sean P Keenan, Roxanne A Seiferling et al – Sedation in Intensive Care Unit: a Systematic Review; JAMA 2000; 283: 1451-1459
2. Gavin Werret- Sedation in intensive care patients; Practical Procedures 2003; 16; article 5
3. Judith Jacobi, Gilles L Fraser, Douglas B Coursin et al - Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult; Critical Care Medicine 2002; 30: 1
4. Annamaria Iakovou, Kim Moi Wong Lama, Adey Tsegaye – Update on Sedation in Critical Care Unit; The Open Critical Care Medicine Journal 2013; 6: 1: M5: 66-79
5. Judith E Hall, Toni D Uhrich, Jill A Barney et al – Sedative, Amnestic, and Analgesic properties of small dose dexmedetomidine infusions; Anesthesia Analgesia 2000; 90: 699-705
6. Miller's Anesthesia; Ronald D Miller; Publisher Elsevier 2010; Edition 7: 721-726; 756; 800-801
7. Juliana Barr, Gilles L Fraser, Kathleen Puntillo et al - Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit; Critical Care Medicine 2013
8. J C Hunter, D J Fontana, L R Hedley et al - Assessment of the role of α_2 -adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice; British Journal of Pharmacology 1997; 122: 1339-1344
9. B C Bloor, Denham S Ward, Jon P Belleville et al- Effects of Intravenous Dexmedetomidine in Humans II Hemodynamic Changes; Anesthesiology 1992; 77: 1134-1142
10. J B Dyck, M Maze, C Haack et al, 1993- The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride on adult human volunteers; Anesthesiology 1993; 78: 813-820
11. P Talke, J Li, U Jain et al- Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group; Anesthesiology 1995; 82: 620-633
12. R M Venn, John Hell, R M Grounds – Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care; Critical Care 2000; 4: 302-308
13. ZP Khan, I T Munday, R M Jones et al – Effects of dexmedetomidine on isoflurane requirements in healthy volunteers: 1. Pharmacodynamic and pharmacokinetic interactions; British Journal of Anesthesia 1999; 83: 3: 372-380.
14. J P Beller, T Pottecher, A Lugnier et al – Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion; British Journal of Anesthesia 1988; 61: 583-588.
15. Vinit K. Srivastava, Sanjay Agrawal, Sanjay Kumar et al- Comparison of Dexmedetomidine, Propofol and Midazolam for Short-Term Sedation in Postoperatively Mechanically Ventilated Neurosurgical Patients; Journal of Clinical and Diagnostic Research 2014; 8: 9: GC04-GC07
16. Prerana N Shah, Vaibhao Dongre, Vijay Patil et al - Comparison of post-operative ICU sedation between dexmedetomidine and propofol in Indian population; Indian Journal of Critical Care Medicine 2014; 18: 5