

Comparison of Dexmedetomidine, Propofol and Midazolam for Short-Term Sedation in Postoperatively Mechanically Ventilated Neurosurgical Patients

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ABSTRACT

Background: Effective management of analgesia and sedation in the intensive care unit depends on the needs of the patient, subjective and/or objective measurement and drug titration to achieve specific endpoints.

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

Materials and Methods: Ninety patients aged 20-65 years, ASA physical status I to III, undergoing neurosurgery and requiring postoperative ventilation were included. The patients were randomly divided into three groups of 30 each. Group D received dexmedetomidine 1 mcg/kg over 15 minutes as a loading dose, followed by 0.4-0.7 mcg/kg/h. Group P received propofol 1 mg/kg over 15 minutes as a loading dose, followed by 1-3 mg/kg/h. Group M received midazolam 0.04 mg/kg over 15 minutes as a loading dose, followed by 0.08 mg/kg/h.

Measurements: Heart rate, mean arterial pressure, sedation level, fentanyl requirement, ventilation and extubation time were recorded.

Results: Adequate sedation level was achieved with all three agents. Dexmedetomidine group required less fentanyl for postoperative analgesia. In group D there was a decrease in HR after dexmedetomidine infusion ($p < 0.05$), but there was no significant difference in HR between group P and group M. After administration of study drug there was a significant decrease in MAP comparison to baseline value in all groups at all time intervals ($p < 0.05$), except postextubation period ($p > 0.05$). Extubation time was lowest in group P ($p < 0.05$).

Conclusion: Dexmedetomidine is safer and equally effective agent compared to propofol and midazolam for sedation of neurosurgical mechanically ventilated patients with good hemodynamic stability and extubation time as rapid as propofol. Dexmedetomidine also reduced postoperative fentanyl requirements.

Keywords: Hemodynamic changes, Neuroprotection, Opioids

INTRODUCTION

Patients requiring postoperative mechanical ventilation after a major surgical procedure typically have significant anxiety and pain [1]. These patients require sedation to tolerate the tracheal tube and the ventilator, to suppress coughs, to prevent respiratory fighting during intensive care procedures and to prevent psychological complications associated with pain and anxiety. An ideal sedative agent should allow for rapid modification of the sedation level by titration of doses, no depressant effects on the cardiovascular or respiratory systems, cheap, have short duration without cumulative effects, and allow rapid recovery of effective spontaneous respiration after stopping the infusion [2].

Commonly used agents include benzodiazepines, propofol, short acting opioids like remifentanyl and dexmedetomidine. Although opioids are useful for treatment of postoperative pain, they alone cannot be appropriate for sedation for postoperative mechanically ventilated patients [3].

Dexmedetomidine a α_2 adrenoceptors agonist are capable of producing sedation, anxiolysis and analgesia without respiratory depression [4]. These properties make them potentially useful for short duration postoperative ventilation like; neurosurgical patients requiring delayed extubation.

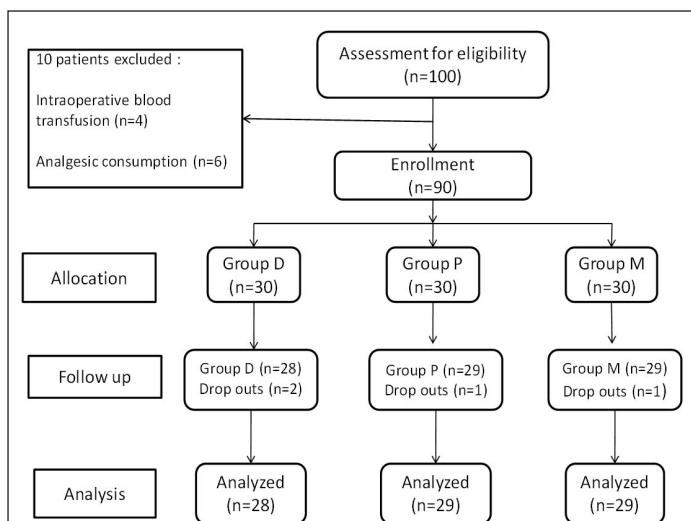
With the aim to evaluate and compare the effects of dexmedetomidine-based sedation with midazolam and propofol, this study was conducted in the postoperative neurosurgical patients requiring short term postoperative ventilation.

MATERIALS AND METHODS

This prospective, randomized control, patient-blinded study was conducted in neurological intensive care unit, after local institutional ethics committee approval and written informed consent from the patients and relatives. A total of 100 adult patients, 20 to 65 years of age, ASA grade I to III, undergoing elective neurosurgical procedure and expected to require postoperative ventilator support were included. Exclusion criteria included significant hepatic, renal, or neurologic impairment, second or third degree heart block, history of use of long-term benzodiazepine, opioids, and a known allergy to any of the study drug, gross obesity (over 50% above ideal body weight) and known or suspected pregnancy

A Standard anaesthetic technique for the perioperative period included midazolam 0.04 mg/kg, fentanyl 2 mcg/kg and thiopental sodium 5 mg/kg body weight for induction followed by vecuronium 0.15 mg/kg body weight for facilitation of tracheal intubation. Maintenance of anaesthesia was done with oxygen: nitrous oxide ($O_2:N_2O$; 33:66), isoflurane, intermittent boluses of vecuronium and fentanyl. At the end of the surgical procedure, neuromuscular blockade was not reversed and patients shifted to the neurological ICU for elective ventilation. Ventilation was commenced with synchronized intermittent mechanical ventilation (SIMV) with pressure support mode.

On arrival in the ICU, patients were allocated randomly into three groups of 30 with the help of a computer generated table of random numbers to receive i.v. infusions of dexmedetomidine, propofol or midazolam whilst being mechanically ventilated. Drug infusions were prepared by personnel not involved in the study or the patient's



[Table/Fig-1]: Study design

	Group D	Group P	Group M	p-value
Age (Yrs)	50.53±7.44	52.1±8.48	51.27±8.04	0.749
Male/Female	25/5	23/7	22/8	0.638
Weight (Kg)	61.87±6.83	59.97±6.43	63.23±6.29	0.155
Duration of Ventilation (hrs)	12.03±3.13	12.86±3.52	12.72±3.20	0.6011
Extubation time (Min)	35.28±5.92	26.13±5.32	48.21±7.23	<0.001
RSS	3.42±0.74	3.75±0.99	3.62±0.94	0.384
BIS	68.85±5.80	69.65±6.50	66.48±6.98	0.1571
Fentanyl Requirement (mcg/kg/hr)	0.26±0.13	0.50±0.14	0.42±0.14	<0.001

[Table/Fig-2]: Demographic profile

care. All patients received short acting fentanyl infusions (5mcg/ml). The infusion rate was adjusted by the ICU doctor as required by the patient to relieve pain. No muscle relaxants were given during the study period.

Group D - Dexmedetomidine loading dose 1 mcg/kg over 15 minutes, followed by maintenance infusion at a rate of 0.4-0.7 mcg/kg/h

Group P - Propofol loading dose 1mg/kg over 15 minutes, followed by maintenance infusion at a rate of 1-3 mg/kg/h

Group M – Midazolam loading dose 0.04 mg/kg over 15 minutes, followed by maintenance infusion at a rate of 0.08 mg/kg/h

The dosages were adjusted to achieve the desired level of sedation as assessed by Ramsay sedation score (RSS) hourly and bispectral index (BIS) continuously by ICU residents [5]. Three levels of RSS were considered: adequate (sedation level was grade 2, 3, or 4), insufficient (sedation level was 1) and excessive (sedation level was grade 5 or 6). BIS levels in the range 60-80 were maintained. Pain assessment is done by critical-care pain observation tool (CPOT) [6].

The dose of drugs was adjusted by varying the dose by 10% increase or decrease in infusion rate in order to maintain the level of sedation within the range previously considered adequate. The total amount of fentanyl consumption and the quality of sedation were recorded. Registration of total time on mechanical ventilation (hours) were recorded.

The sedative infusion was discontinued, in preparation for extubation. Patients were extubated when they were responding to simple commands, cardiovascularly stable, normothermic and with an arterial oxygen tension (PaO_2) $\geq 75\text{mmHg}$ on an inspired

Variables	Group D (n=30)	Group P (n=30)	Group M (n=30)
Craniotomy			
Hematoma	6	8	9
Contusion	4	4	5
Tumor	7	4	3
Spine Surgery			
(A) Cervical			
Atlantoaxial dislocation	2	1	2
Anterior plate fusion	8	9	7
(B) Thoracic			
Tumor decompression	1	1	0
Decompression and fusion	2	3	4

[Table/Fig-3]: Pathology and surgical procedures

oxygen concentration (FiO_2) $\leq 33\%$ and had positive end-expiratory pressure (PEEP) $< 5\text{ cm H}_2\text{O}$, spontaneous respiration had been established with pressure support $< 10\text{ cm H}_2\text{O}$, a tidal volume of $> 6\text{ ml/kg}$ and respiratory rate $\geq 10\text{ breaths/min}$ but $< 20\text{ breaths/min}$. The extubation time was the time of discontinuation of sedative infusion to extubation.

The following parameters were recorded –

- (1) Heart rate (HR) and Mean arterial pressure (MAP)
- (2) Sedation level as assessed by RSS and BIS
- (3) Total fentanyl requirement
- (4) Total time on mechanical ventilation
- (5) Extubation time
- (6) Complications if any

The sample size was calculated based on the assumption that there would be a 30% reduction in the mean heart rate following therapy; this required 25 patients in each group for results to be significant (with $\alpha = 0.05$ and power of 80%). We enrolled 30 patients in each group to account for potential dropouts or protocol violations.

STATISTICAL ANALYSIS

Performed using the Graph pad prism 6.0 statistical software. All data are presented as Mean±SD (standard deviation). The demographic data were analysed by one way analysis of variance (ANOVA). Male and female data were analysed with Chi-square test. Intergroup comparison of heart rate and mean arterial pressure were done with one way analysis of variance (ANOVA), followed by an unpaired t-test. Repeated measure analysis of variance (ANOVA) with the *post hoc* Tukey test was used to compare means for hemodynamic variables in intra group comparison to baseline parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 patients were assessed for eligibility, out of which 90 patients were included in the study after randomization and 86 patients (95.5%) completed the study [Table/Fig-1]. Ten patients were not included in this study on account of perioperative blood transfusion (4 patients) and history of chronic analgesic consumption (6 patients). Four patients were not included in this study on account of reoperation within 24 hours of surgery to stop postoperative haemorrhage in group M (one patient), history of hypotension in group D (two patients) which require vasopressors and one patient in group P was extubated after 24hr because of poor neurological status. Their data has been included in the comparison of demographic profile; however, they were not subjected to further statistical analysis.

Time interval	Group D	Group P	Group M	p value D vs P	p value D vs M	p value D vs M
Baseline	89.25±7.28	86.31±6.69	89.03±6.38	0.118	0.905	0.118
After 1 hr	76.67±6.64*	82.10±6.31	84.20±5.23	<0.01	<0.001	0.172
After 2 hr	71.46±5.28*	74.44±5.75*	80.17±4.67*	0.046	<0.001	<0.001
After 3 hr	68.89±4.58*	76.51±4.84*	81.20±5.52*	<.001	<0.001	<0.01
After 4 hr	66.89±4.01*	80.24±6.59*	82.13±7.60*	<0.001	<0.001	0.314
After 5 hr	65.46±3.90*	84.06±5.35	84.62±8.64	<0.001	<0.001	0.771
After 6 hr	66.71±3.11*	81.79±6.27	82.45±6.28	<0.001	<0.001	0.692
After 7 hr	65.25±3.67*	79.34±5.54*	80.62±6.84*	<0.001	<0.001	0.438
After 8 hr	68.03±3.48*	79.65±7.04*	84.27±6.40*	<0.001	<0.001	0.011
Post Ext 1 hr	74.36±4.27*	86.17±5.38	86.07±4.61	<0.001	<0.001	0.937
Post Ext 2 hr	77.71±5.20*	90.41±6.13	87.86±5.38	<0.001	<0.001	0.097

[Table/Fig-4]: Heart rate, Mean value±SD, *p<0.05 within group (vs baseline value)

The three groups were similar in their demographic profile, duration of postoperative ventilation and sedation scores as assessed by RSS and BIS ($p>0.05$) [Table/Fig-2]. Different surgical procedures are shown in [Table/Fig-3].

The mean fentanyl dose requirement in groups P and M were significantly more compared to group D ($p<0.001$) [Table/Fig-2]. Baseline hemodynamic parameters such as HR and MAP were similar among the groups ($p>0.05$). After administration of the study drug patients in group D had a significantly lower heart rate comparison to Groups P and M ($p<0.01$) at 1h. There was no significant difference of HR between group P and group M at all time intervals except 2 and 3 hours. After extubation, the HR in group D was significantly lower than that of the propofol and midazolam group ($p<0.001$) [Table/Fig-4]. After administration of study drug there was a significant decrease in MAP compared to baseline value in all groups at all time intervals ($p<0.05$), except postextubation period ($p>0.05$) [Table/Fig-5]. Two patients (6.66%) in group D required vasopressors (dopamine 5mcg/kg/min) to maintain blood pressure. No other side effect was observed in group P and group M.

Extubation time was least in group P (26.13±5.32 minutes) comparison to group D and group M ($p<0.001$) [Table/Fig-2]. One patient in group P was extubated after 24hr because of poor neurological status. One patient in group M needed a reoperation for control of postoperative hemorrhage. There were no respiratory adverse events after extubation in either group, and no patients require re-intubation.

DISCUSSION

The inadequate sedative technique may adversely affect morbidity and even mortality in the ICU. In addition, the sedative drug used can modulate the neuroendocrine stress and the inflammatory response to surgery, which is more important in improving recovery. Recent studies suggest that long term administration of those drugs might be associated with significant risks and adverse effects [2].

Use of BIS monitoring in addition to Ramsay sedation scale (RSS) in our study provided objectivity in monitoring without producing observer bias. Good correlation between responsiveness and BIS levels in healthy volunteers has been described during sedation with isoflurane, midazolam, propofol and dexmedetomidine [7,8]. An equivalent depth of sedation between dexmedetomidine, propofol and midazolam was achieved, with the advantage that the total amount of fentanyl required by the dexmedetomidine group was less.

Time interval	Group D	Group P	Group M	p value D vs P	p value D vs M	p value D vs M
Baseline	104.89±7.51	103.17±7.41	105.10±7.88	0.388	0.918	0.340
After 1 hr	95.93±6.21*	90.10±8.26*	98.27±6.68*	<0.01	0.175	<0.001
After 2 hr	94.68±6.91*	91.07±6.55*	95.62±5.74*	0.050	0.577	<0.05
After 3 hr	92.89±7.35*	92.59±6.09*	95.07±5.03*	0.864	0.196	0.096
After 4 hr	95.86±9.14*	92.62±5.26*	98.38±5.80*	0.105	0.217	<0.01
After 5 hr	96.82±7.24*	93.21±4.30*	98.76±6.36*	0.025	0.287	<0.01
After 6 hr	95.86±5.72*	94.31±4.67*	94.51±6.32*	0.267	0.406	0.888
After 7 hr	98.36±5.86*	95.59±5.83*	96.86±5.79*	0.079	0.337	0.406
After 8 hr	98.14±6.55*	92.21±4.19*	98.28±6.19*	<0.001	0.937	<0.001
Post Ext 1 hr	103.64±5.21	99.34±5.11	107.59±5.43	<0.01	<0.05	<0.001
Post Ext 2 hr	105.00±5.21	101.00±5.13	108.41±4.82	<0.05	<0.05	<0.001

[Table/Fig-5]: Mean arterial pressure
Mean value±SD, *p<0.05 within group (vs baseline value)

The interaction of α^2 -adrenoreceptors and opioids lead to decrease in the dose of fentanyl. The α^2 adrenoceptors have an effect on the spinal cord, especially α^2 A and α^2 C as well as modulating the descending noradrenergic pathways leading to 30% to 50% reduction in the requirements of opioids. Our study is in accordance with other studies [9,10].

Use of dexmedetomidine has been associated with a decrease in heart rate, in part because of the sympatholytic effects of this drug, but also because of a vagal mimetic effect. Propofol either resets or inhibits the baroreflex, thus reducing the tachycardic response to hypotension. The MIDEX trial revealed a significantly higher incidence of bradycardia in patients receiving dexmedetomidine, whereas the PRODEX trial demonstrated that the incidence of bradycardia was comparable in the study groups [11]. This study also demonstrates similar effects on heart rate when compared with propofol and midazolam. Dexmedetomidine also is known to decrease sympathetic outflow and circulating catecholamine levels and would therefore be expected to cause a decrease of MAP similar to those of propofol. The hypotension and bradycardia that occurred in the dexmedetomidine group were predictable from the known properties of α^2 agonists, and have been confirmed from previous studies [12,13].

The extubation times were similar and rapid with the use of dexmedetomidine and propofol both compared to midazolam. Although, a longer extubation time would have predicted with dexmedetomidine from volunteer pharmacokinetic data [14], as the elimination half-life of propofol [15] is approximately three times shorter (30-60 min for propofol vs 100-150 min) for dexmedetomidine. In our study similar extubation time may be due to the less dose of fentanyl in dexmedetomidine group. Riker et al., [16] also found that extubation time was significantly shortened in patients sedated with dexmedetomidine compared with those receiving midazolam. Despite ventilation and intubation, patients sedated with dexmedetomidine could be easily aroused to co-operate without showing irritation.

Preservation of intracranial homeostasis, haemodynamic stability, reduction in cerebral blood flow [17], and neuroprotection capability [18] are common goals in neuroanaesthesiology that can be achieved using dexmedetomidine. This drug has also a unique sedation, described as similar to normal sleep, providing

a state of tranquility while at the same time the patient is able to understand and communicate upon a simple verbal stimulus from the medical team [19]. This characteristic allows a better evaluation of the neurological status of the patients in mechanical ventilation, especially when compared with other sedatives used in ICUs.

There are some limitations to our study: (1) the no of patients is too small for broad generalizations (2) this study is not completely drug blinded because the physical appearance of propofol (3) plasma catecholamines levels were not assessed by us to know the degree of suppression of neurohumoral pathway (4) we did not measure patient satisfaction score and biochemical and haematological variables during study period.

CONCLUSION

Dexmedetomidine is safer and equally effective agent compared to propofol and midazolam for sedation of neurosurgical mechanically ventilated patients with good hemodynamic stability and extubation time as rapid as propofol. Dexmedetomidine also reduced postoperative fentanyl requirements.

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