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Original Research Article

A Randomised Double Blind Prospective Study of Comparison of Midazolam, Propofol and Dexmeditomidine Infusion for Sedation in Mechanically Ventilated Patients in ICU

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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. 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: Fentanyl, dexmedetomidine, mechanical ventilation.

Introduction

In the context of postoperative care for patients requiring mechanical ventilation after major surgical procedures, sedation plays a crucial role in managing pain, anxiety, and discomfort associated with the ventilator and tracheal tube. Such patients often face significant challenges, including intense anxiety and pain, which necessitate effective sedation strategies to ensure their comfort and facilitate recovery. The ideal sedative agent for this purpose should possess several key attributes: it should allow for precise control over the sedation level through dose titration, avoid adverse effects on cardiovascular and respiratory systems, be cost-effective, have a short duration of action without cumulative effects, and enable rapid recovery of spontaneous respiration once the infusion is halted. Traditionally, sedatives such as benzodiazepines, propofol, short-acting opioids like remifentanil, and dexmedetomidine are employed to manage these patients. While opioids are effective for managing postoperative pain, they are not sufficient on their own for comprehensive sedation, especially in patients who are mechanically ventilated. Dexmedetomidine, an α2-adrenergic agonist, stands out due to its unique properties. It provides sedation, anxiolysis, and analgesia without causing respiratory depression, which is particularly beneficial in short-term postoperative ventilation scenarios. This study aims to evaluate and compare the effects of dexmedetomidine-based sedation with traditional agents such as midazolam and propofol in postoperative neurosurgical patients who require short-term mechanical ventilation. By focusing on the efficacy and safety profiles of these

sedatives, the study seeks to determine the optimal sedative strategy that balances effective sedation with minimal respiratory and cardiovascular complications. The comparison will provide insights into how dexmedetomidine performs relative to other commonly used agents, potentially offering a more effective and safer alternative for managing the sedation of mechanically ventilated patients in a postoperative setting.

Need of the study

Sedation in mechanically ventilated patients in the Intensive Care Unit (ICU) is a critical aspect of care, impacting patient comfort, respiratory stability, and overall recovery. Traditionally, sedative agents like midazolam, propofol, and dexmedetomidine are utilized to manage sedation, each with its own set of advantages and limitations. The choice of sedative is pivotal, as it affects patient outcomes, including the duration of mechanical ventilation, the incidence of complications, and the speed of recovery. Midazolam, a benzodiazepine, is widely used for its anxiolytic and amnesic properties but may be associated with respiratory depression and prolonged sedation, which can complicate the weaning process from mechanical ventilation. Propofol, a fast-acting sedative-hypnotic, offers rapid onset and recovery but may cause cardiovascular instability and does not provide adequate analgesia on its own. Dexmedetomidine, an α2-adrenergic agonist, provides sedation and analgesia with minimal respiratory depression, making it an attractive option for short-term ventilation. Despite their common use, there is limited comparative data evaluating the efficacy, safety, and overall impact of these sedatives on patient outcomes in the ICU setting. Existing studies often lack rigorous design features such as randomization and blinding, which can introduce biases and affect the reliability of results. Furthermore, while each agent has distinct properties, there is no clear consensus on the optimal choice for sedation in mechanically ventilated patients.

Aim and Objectives

To evaluate and compare the efficacy, safety, and overall impact of midazolam, propofol, and dexmedetomidine infusion for sedation in mechanically ventilated patients in the Intensive Care Unit (ICU).

Materials and Methods

This prospective, randomized controlled, patient-blinded study was conducted in the Intensive Care Unit (ICU) of Mamata Medical College, Khammam, Telangana, from March 2023 to March 2024, following approval from the local institutional ethics committee and obtaining written informed consent from patients and their relatives. The study included 100 adult patients, aged 20 to 65 years, classified as ASA grade I to III, who were undergoing elective neurosurgical procedures and were anticipated to need postoperative ventilator support. Patients with significant hepatic, renal, or neurological impairments, second or third-degree heart block, a history of long-term use of benzodiazepines or opioids, known allergies to any study drug, gross obesity (more than 50% above ideal body weight), or known or suspected pregnancy were excluded from the study.

The standard anesthetic technique for the perioperative period included the administration of midazolam (0.04 mg/kg), fentanyl (2 mcg/kg), and thiopental sodium (5 mg/kg) for induction, followed by vecuronium (0.15 mg/kg) to facilitate tracheal intubation. Anesthesia maintenance involved a combination of oxygen and nitrous oxide (O2:N2O; 33:66), isoflurane, intermittent boluses of vecuronium, and fentanyl. At the end of the surgical procedure, neuromuscular blockade was not reversed, and patients were transferred to the neurological ICU for elective ventilation, initiated with synchronized intermittent mechanical ventilation (SIMV) with pressure support mode.

Upon arrival in the ICU, patients were randomly assigned into three groups of 30 each using a computer-generated randomization table. Each group received intravenous infusions of either dexmedetomidine, propofol, or midazolam, prepared by personnel not involved in the study or patient care. All patients also received short-acting fentanyl infusions (5 mcg/ml), with infusion rates adjusted by the ICU doctor based on the patient's pain relief needs. No muscle relaxants were administered during the study period.

Group D received dexmedetomidine with a loading dose of 1 mcg/kg over 15 minutes, followed by a maintenance infusion rate of 0.4-0.7 mcg/kg/h. Group P was administered propofol with a loading dose of 1 mg/kg over 15 minutes, followed by a maintenance infusion rate of 1-3 mg/kg/h. Group M received midazolam with a loading dose of 0.04 mg/kg over 15 minutes, followed by a maintenance infusion rate of 0.08 mg/kg/h. Dosages were adjusted to maintain desired sedation levels, assessed hourly using the Ramsay Sedation Score (RSS) and continuously monitored with the Bispectral Index (BIS). RSS levels of 2, 3, or 4 were considered adequate, while levels of 1 and 5 or 6 were deemed insufficient and excessive, respectively. BIS levels were maintained in the range of 60-80, and pain was assessed using the Critical Care Pain Observation Tool (CPOT).

The infusion rates were adjusted by varying the dose by 10% to keep sedation within the adequate range. Parameters recorded included total fentanyl

consumption, quality of sedation, total time on mechanical ventilation, and extubation time. Sedative infusion was discontinued in preparation for extubation, which occurred when patients met specific criteria, including responsiveness to commands, cardiovascular stability, normothermia, adequate arterial oxygen tension (PaO2) on minimal FiO2, acceptable positive end-expiratory pressure (PEEP), and spontaneous respiration. The extubation time was defined as the interval from discontinuation of sedative infusion to extubation.

Recorded parameters included heart rate (HR), mean arterial pressure (MAP), sedation levels (RSS and BIS), total fentanyl requirement, total time on mechanical ventilation, extubation time, and any complications. The sample size was determined to detect a 30% reduction in mean heart rate with a significance level of 0.05 and a power of 80%, requiring 25 patients per group. To account for potential dropouts or protocol violations, 30 patients were enrolled in each group.

Results

Out of 100 patients initially assessed for eligibility, 90 were randomized into the study, and 86 patients (95.5%) successfully completed the study. The ten patients who were excluded from the study did so for various reasons. Four patients were excluded due to perioperative blood transfusions, while six patients were excluded because of a history of chronic analgesic consumption. Additionally, four patients were excluded during the study: one from Group M due to reoperation within 24 hours of surgery to address postoperative hemorrhage, two from Group D who experienced hypotension requiring vasopressors, and one from Group P who was extubated after 24 hours because of a poor neurological status. Although the data from these excluded patients were included in the comparison of demographic profiles, they were not subjected to further statistical analysis.

Table 1: Basic characteristics of the study subjects

	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

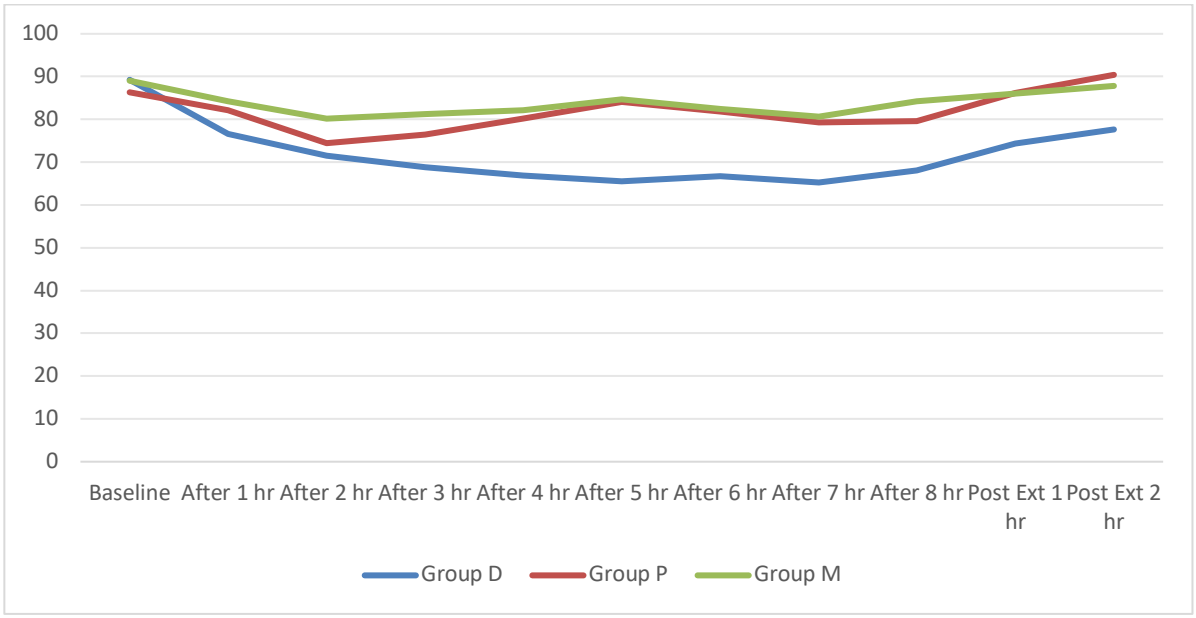

Figure 1: Mean Heart rate at different time interval in all 3 group

The three groups were comparable in terms of their demographic profiles, duration of postoperative ventilation, and sedation scores as measured by the Ramsay Sedation Score (RSS) and Bispectral Index (BIS) (p>0.05). The details of the various surgical procedures are presented in [Table/Fig-3]. The mean dose of fentanyl required in the propofol (Group P) and midazolam (Group M) groups was

significantly higher compared to the dexmedetomidine group (Group D) ($p<0.001$). Baseline hemodynamic parameters, including heart rate (HR) and mean arterial pressure (MAP), were similar across the groups ($p>0.05$). However, one hour after administering the study drug, patients in Group D exhibited a significantly lower heart rate compared to those in Groups P and M ($p<0.01$).

No significant differences in HR were noted between Groups P and M at most time intervals, except at 2 and 3 hours. Following extubation, Group D also showed a significantly lower heart rate compared to Groups P and M ($p<0.001$) [Table/Fig-4]. All groups experienced a significant decrease in MAP compared to baseline values at all time intervals after drug administration ($p<0.05$), with no significant differences during the post-extubation period ($p>0.05$). Two patients (6.66%) in Group D required vasopressors (dopamine 5 mcg/kg/min) to maintain blood pressure. No other adverse effects were observed in Groups P and M.

The extubation time was shortest in Group P (26.13±5.32 minutes) compared to Groups D and M ($p<0.001$). One patient in Group P was extubated after 24 hours due to poor neurological status, while one patient in Group M required reoperation to control postoperative hemorrhage. Despite these instances, no respiratory adverse events occurred after extubation in any of the groups, and no patients required re-intubation.

Table 2: Mean Heart rate at different time interval in all 3 group

Time inter-val	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*	98.276±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

Discussion

Inadequate sedation techniques in the ICU can negatively impact morbidity and mortality, as the choice of sedative can influence neuroendocrine stress and the inflammatory response to surgery, which are crucial for recovery. Recent research indicates that long-term use of sedatives may pose significant risks and adverse effects [2]. Our study utilized Bispectral Index (BIS) monitoring alongside the Ramsay Sedation Scale (RSS) to provide objective assessments of sedation levels, minimizing observer bias. Previous studies have shown good correlation between responsiveness and BIS levels with sedatives like isoflurane, midazolam, propofol, and dexmedetomidine [7,8].

We found that dexmedetomidine, propofol, and midazolam achieved comparable sedation depths, with the added benefit that dexmedetomidine required less fentanyl. The interaction between α2-adrenoceptors and opioids leads to reduced fentanyl dosage requirements. Specifically, α2-adrenoceptors in the spinal cord and descending noradrenergic pathways can decrease opioid needs by 30% to 50%. Our findings align with other studies in this regard [9,10]. Dexmedetomidine is known to reduce heart rate due to its sympatholytic and vagal mimetic effects. While some studies, like the MIDEX trial, reported higher bradycardia rates with dexmedetomidine, the PRODEX trial found similar bradycardia incidences across study groups [11]. Our study also demonstrated similar heart rate effects when compared to propofol and midazolam. Dexmedetomidine's effects on heart rate and mean arterial pressure (MAP) are consistent with its known properties and previous research [12,13].

Despite predictions of longer extubation times with dexmedetomidine based on pharmacokinetic data [14], our study found similar extubation times with dexmedetomidine and propofol, both of which were faster compared to midazolam. This might be attributed to the lower fentanyl dose used in the dexmedetomidine group. Riker et al. [16] also noted significantly shorter extubation times with dexmedetomidine compared to midazolam. Patients sedated with dexmedetomidine could be easily aroused and cooperated without irritation.

In neuroanesthesia, goals such as maintaining intracranial homeostasis, hemodynamic stability, reducing cerebral blood flow [17], and providing neuroprotection [18] are often achieved with dexmedetomidine. It offers a unique sedation experience similar to natural sleep, allowing patients to remain tranquil yet responsive to verbal stimuli [19]. This feature facilitates better

neurological assessments in mechanically ventilated patients compared to other ICU sedatives. However, our study has limitations: (1) the sample size is relatively small, limiting broader generalizability, (2) the study is not fully drug-blinded due to the distinct appearance of propofol, (3) we did not assess plasma catecholamine levels to evaluate neurohumoral pathway suppression, and (4) patient satisfaction scores and biochemical and hematological variables were not measured during the study period.

Conclusion

Dexmedetomidine proves to be a safer and equally effective agent compared to propofol and midazolam for the sedation of neurosurgical patients on mechanical ventilation. It maintains good hemodynamic stability and achieves extubation times comparable to propofol. Additionally, dexmedetomidine reduces the need for postoperative fentanyl, contributing to its overall efficacy and safety profile.

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