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Original Research Article

Dexmedetomidine versus propofol as a sedative agent in the intensive care unit: a randomized single blinded prospective study

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ABSTRACT

Background: Sedation is an essential prerequisite for every ICU patient. It promotes patient comfort, helps in alleviation of anxiety, stabilizes vitals and reduces the time to extubation and ICU discharge. This study aims at comparing dexmedetomidine versus propofol in ICU sedation with respect to maintenance of vitals, time to extubation, incidence of adverse effects and cost effectiveness.
Methods: 60 intubated and mechanically ventilated post-surgical ICU patients were randomly allocated to two groups of 30 each. Group D received dexmedetomidine infusion as a loading dose of 0.1mcg/kg/min IV over 10 minutes followed by maintenance infusion of 0.2-0.7mcg/kg/h IV. Group P received propofol infusion as a loading dose of 5mcg/kg/min IV over 5 minutes followed by a maintenance infusion of 0.3-3mg/kg/h IV. Patients in both groups were maintained at Richmond agitation sedation score of -1 to -2. Measurements of HR, NIBP, SpO_2 were taken at regular intervals till cessation of sedation and extubation. Data thus collected was subjected to statistical analysis.
Results: Dexmedetomidine was seen to be comparable to propofol as far as maintaining vitals was concerned. Group D (dexmedetomidine) had a statistically significant shorter mean duration to sedation cessation and extubation than group P (propofol). Dexmedetomidine also had the added advantages of minimal respiratory depression, decreased opioid requirements as well as greater cost effectiveness.
Conclusions: Dexmedetomidine was found to be a better choice for sedation in the ICU compared to propofol.

Keywords: ICU sedation, Mean arterial pressure, Richmond agitation sedation score

INTRODUCTION

Considerable pain and suffering is experienced by all patients admitted in an ICU. This, along with inadequate means of relief from such pain and suffering, explains why patients discharged from an ICU remember discomfort and unrelieved pain as a dominant experience during their ICU stay.[1] Anxiety, agitation and delirium are seen in as much as 85% of the patients in the ICU.[2]

Several factors have been put forward as being the reasons of stress in the ICU, the major ones being unrelieved pain, inadequate sedation, inability to communicate in intubated patients, difficulty in sleeping as well as hallucinations and nightmares. Painful procedures like frequent venipuncture have been cited as the most frequent source of stress.[3] Such stressful experiences can have prolonged neuropsychiatric effects, with a study reporting a 25% incidence of post-traumatic stress disorder 4 years post discharge from the ICU among patients who have had stressful experiences during their ICU stay.[4]

Sedation is the process of relieving anxiety and establishing a state of calm. This is frequently required as a component of compassionate care in ICU patients. Adequate sedation promotes healing and obviates the effects of sleep deprivation that are so commonly seen in

ICU patients. It also optimizes safety for the attendants and caregivers besides facilitating mechanical ventilation.

However, care must be taken not to oversedate or undersedate the patient. Oversedation can worsen patient outcome by prolonging duration of ventilation and thereby ICU stay which in turn increases the risk of complications like ventilator dependence and ventilator associated pneumonia. Undersedation can lead to anxiety, hyperactivity and increased patient-ventilator dysynchrony.

Many drugs have been used as sedatives in the ICU so far. For decades, the most commonly used drugs for ICU sedation have been the benzodiazepines and propofol. In spite of their well-known drawbacks, they continue to be widely used worldwide. Recent advances in the field of ICU sedation have favoured the use of nurse-implemented algorithms and drug interruption protocols using these drugs to optimize their delivery. But, these guidelines have not yet been seen as uniformly beneficial and their adoption has therefore been slow.[5] Hence, adoption of newer drug classes and comparing them to conventionally used drugs is the need of the hour.

Among the newer drugs, the alpha$_2$ agonist dexmedetomidine has been seen to show good promise in this regard. It is the dextro-rotatory and pharmacologically active isomer of medetomidine that was used as a popular veterinary sedative and is 8 times more alpha$_2$ selective than clonidine.[6] It was approved by the US-FDA in 1999 as an agent for sedation in the ICU and for short procedures in adults.[7]

On intravenous administration, dexmedetomidine gets metabolized in the liver and excreted by the kidney. It causes stimulation of alpha$_2$ receptors in the pontine locus ceruleus that causes sedation quite unlike that produced by benzodiazepines or propofol. Also known as 'conscious sedation', it closely mimics natural sleep. The patient maintains spontaneous respiration and can follow commands. However, hypotension and bradycardia are important side effects that need to be kept in mind.

This study was aimed at evaluation of the newer drug dexmedetomidine and its comparison with the conventionally used drug propofol with regard to ICU sedation. The two drugs were compared with respect to maintenance of vitals, incidence of adverse effects especially respiratory depression and also cost effectiveness.

METHODS

The study was conducted in the ICU of the Department of Anaesthesiology and Critical Care in a tertiary care Government-run teaching hospital during June to December, 2017. A sample size of 60 was decided, based on previous similar studies that obtained statistically significant results using the same sample size.

Institutional human ethical committee clearance was taken prior to commencement of the study. Written and informed consent was taken from each patient party prior to inclusion in the study.

Inclusion criteria

- Post-surgical patients
- 18-65 years of age
- Haemodynamically stable
- Requiring post-operative mechanical ventilation
- Requiring sedation for tolerance of mechanical ventilation.

Exclusion criteria

- Refusal of consent
- Head injury
- Pregnancy and lactation
- Abnormal higher mental functions
- Contra-indication to drugs used in this study
- Abnormal organ function tests (Renal/liver/thyroid).

The 60 patients were randomly divided into two groups (D and P) of 30 each. Randomization was done by means of a box containing 60 pieces of paper each containing the letters A (30 pieces) or B (30 pieces). Upon receiving consent, each patient party was asked to draw a paper piece from the box at random and the group allocation was done as per the letter on the paper (A to Group D, B to Group P). The patient party was thus blinded as to what study drugs were used.

Group D received dexmedetomidine as a loading dose of 0.1 mcg/kg/min IV over 10 minutes followed by a maintenance dose of 0.2-0.7mcg/kg/hour IV. On the other hand, group P received propofol as a loading dose of 5mcg/kg/min IV over 5 minutes followed by a maintenance dose of 0.3-3mg/kg/h IV.

For analgesia, a multimodal approach was adopted using fentanyl 0.7-10mcg/kg/h IV and ketorolac 30mg IV 6 hourly for all patients.

For assessment and maintenance of sedation, the Richmond agitation sedation scale as devised by Sessler CN, Gosnell MS et al was used which is described as follows[8]

To determine RASS, a three step approach was used:

- Observation of the patient without interaction. If patient is alert, an appropriate score (0 to +4) is given. If not, we go to the next step.
- The patient is addressed by name in a loud voice and instructed to look toward the observer. If patient responds, an appropriate score (-1 to -3) is given. If no response even after repeating this once, we go to the final step.

- The patient's shoulder is shaken vigourously. If no response, the sternum is rubbed vigourously. The appropriate score (-4 to -5) is given.

In this study, the sedative infusions in both groups D and P were adjusted hourly in such a way so as to maintain a target RASS score of -1 to -2. During the period of sedation, patients were connected to monitors for ECG, NIBP and SpO_2. Heart rate (HR) and mean arterial pressure (MAP) were monitored at baseline, after loading dose administration, then at intervals of 15 min, 30 min, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours and lastly when drug infusion was stopped.

Table 1: Richmond agitation sedation scale (RASS).

Score	Term	Description
+4	Combative	Overly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tubes/catheters, or aggressive behaviour
+2	Agitated	Frequent non-purposeful movement or patient-ventilator asynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but awakens for >10 sec, with eye contact, to voice
-2	Light sedation	Briefly awakens (<10 sec), with eye contact, to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Ventilator settings were as follows for all patients:

- Mode- synchronous intermittent mandatory ventilation
- Tidal volume- 7mL/kg ideal body weight
- Frequency- 12 per minute
- FiO_2- 50%
- PEEP- 5cm H_2O
- Pressure support- 10cm H_2O.

The ventilators were set to spontaneous mode for 5 minutes every 4 hours to check the ability of the patient for spontaneous respiration. Time to start apnoea ventilation was set to 20 seconds after which ventilator would start controlled ventilation if no respiratory efforts were seen. Every morning at 8am, the sedative infusions were stopped in each patient and assessment was done as to whether the patient could be extubated that day. If found fit, patients were extubated and then discharged from the ICU. The time taken from cessation of sedation till extubation as well as incidence of any adverse effects (hypotension, bradycardia and apnoea) were also noted.

Statistical analysis

The data thus collected was compiled using Microsoft Excel 2013 and analyzed using IBM SPSS 20 software. The main outcome variable for this study was the mean duration from cessation of sedation to extubation between the two groups D and P which was analyzed using the one way ANOVA test.

Other variables such as patient age, weight, haemoglobin concentration, baseline mean arterial pressure, heart rate, SpO_2 were also analyzed using the one way ANOVA test. A p value of <0.05 was taken as statistically significant. The incidence of adverse events like hypotension, bradycardia and apnoea were also compared between the two groups.

RESULTS

The two groups were comparable with respect to age, sex, weight, and baseline parameters (HR, NIBP, and SpO2) as outlined in Table 2.

Table 2: Comparison of essential parameters between the two groups.

Mean parameter	Group D	Group P	p value
Age (years)	41.7+/-12.1	42.4+/-11.9	0.68
Sex ratio	18:12	13:17	-
Weight (kg)	63.5+/-11.1	62.8+/-9.7	0.89
Baseline HR (/min)	87.4+/-10.2	87.4+/-9.5	0.41
Baseline MAP (mmHg)	84.2+/-7.4	86.0+/-8.0	0.24
Baseline SpO2 (%)	93.8+/-2.5	94.8+/-2.66	0.90

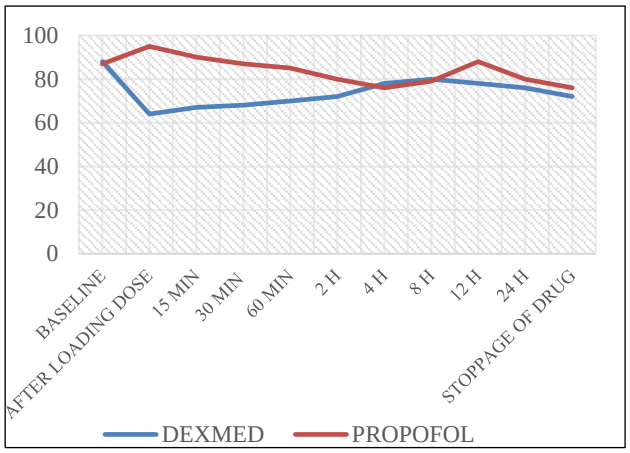

Figure 1: Heart rates before, during and after sedation.

Heart rates and mean arterial blood pressures were maintained between both groups as is shown in Figure 1 (for heart rate) and Figure 2 (for mean arterial pressure).

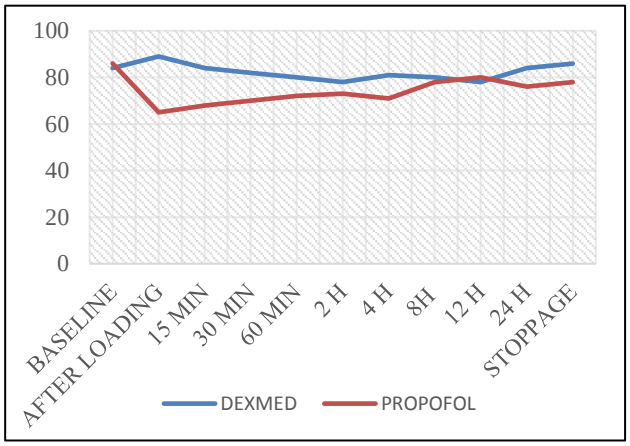

Figure 2: Mean arterial pressures before, during and after sedation.

As can be observed in the above with regard to heart rate, dexmedetomidine group showed the characteristic fall in heart rate during loading dose but the fall was maintained within acceptable limits and did not worsen patient outcome. With regard to mean arterial blood pressure, propofol group showed the characteristic hypotension and dexmedetomidine group showed the characteristic biphasic response (hypertension followed by hypotension) but again the MAP was maintained within acceptable limits. Thus, the two drugs were found to be comparable with respect to maintenance of heart rate as well as mean arterial pressure.

The main outcome variable of this study was the mean duration from cessation of sedation till extubation. This was found to be 3.2+/-1.3 hours for the dexmedetomidine group as compared to 9.5+/-2.2 hours for the propofol group, which was statistically significant with a p value of 0.023. Thus, dexmedetomidine sedation was found to result in a significantly shorter duration to extubation compared to that using propofol which decreased ICU length of stay, thereby improving patient outcome. Comparison of adverse effects between the two groups can be summarized in the form of Table 3 below

Table 3: Comparison of incidence of adverse effects between the two groups.

Adverse effect	Group D	Group P
Bradycardia (HR<65/min, requiring Atropine 0.6 mg IV)	20%	5%
Hypotension (MAP<70 mm Hg, requiring Ephedrine 6mg IV)	10%	40%
Apnoea (checked every 4 hours)	3%	60%

Thus, it was seen that barring bradycardia, incidence of other adverse effects was much higher in propofol group than in dexmedetomidine group. It was observed that dexmedetomidine sedation at maximum maintenance dose (0.7mcg/kg/h) cost around 125 rupees per hour, as per the price list of drugs approved by the concerned authorities. This was more cost effective than propofol infusion at maximum maintenance dose (50mcg/kg/h) which cost 180 rupees per hour according to the same list. Besides, dexmedetomidine group was also associated with lesser opioid requirements for pain management compared to propofol group.

DISCUSSION

Adequate sedation and analgesia in the ICU is the basic right of every patient. Anger et al, published an important study in this regard which suggested sedation therapy and pain management as vital components of improved ICU outcomes.[9] This has propelled development of newer sedatives and sedation protocols for use in the ICU. However, the ideal ICU sedative still eludes mankind despite significant efforts in this direction.

In this study, we have evaluated dexmedetomidine infusion as a sedative agent in the ICU and compared it to propofol infusion. Since its approval as a sedative agent in the ICU, dexmedetomidine has been used by a number of workers in research pertaining to ICU sedation with promising results. Dexmedetomidine, thus, has indeed opened up a new frontier in ICU sedation. The ‘conscious sedation’ with spontaneous respiration and minimal cognitive impairment seen with dexmedetomidine is unique from the GABA mediated sedative effects characteristic of benzodiazepines and propofol. This circumvents many of the adverse effects of the latter drugs, chiefly respiratory depression and is one of the most important reasons for earlier extubation and discharge of dexmedetomidine sedated ICU patients.

Studies using propofol and benzodiazepines done over the years found them to be effective but also saw significant adverse effects that could prolong ICU stay and worsen outcome. A number of studies in recent years have therefore evaluated dexmedetomidine for use in ICU sedation. Earlier studies by Venn et al, as well as Arain and Ebert, demonstrated the safety of dexmedetomidine as a sedative as regards hemodynamic stability and avoidance of respiratory depression.[10,11]

A number of other studies post FDA approval in 2008 have since favoured dexmedetomidine to other agents in ICU sedation. Reichert et al, compared dexmedetomidine to propofol in post CABG ICU patients where dexmedetomidine showed good results.[12] Hoy and Keating, in their study also used dexmedetomidine for ICU patients and observed that IV dexmedetomidine is generally well tolerated when used in mechanically ventilated ICU patients.[13] Eren and Cukurova, concluded that dexmedetomidine was as effective as high doses of benzodiazepines as far as ICU sedation was concerned with minimal haemodynamic and respiratory effects.[14]

A landmark study in this regard was the PRODEX trial (2012). An important observation in this multicenter large randomized controlled trial was that dexmedetomidine sedation resulted in reduced duration to tracheal extubation compared to propofol sedation.[15] These and other ongoing studies have led to dexmedetomidine gradually becoming the ICU sedative of choice and its rapid implementation in current ICU protocols used globally.

In the present study, dexmedetomidine has been evaluated in comparison to propofol with special emphasis on time taken from sedation cessation to extubation. The p value obtained in this regard was 0.023 which was statistically significant. Dexmedetomidine group showed comparable haemodynamics with respect to propofol and also had the added advantages of minimal respiratory depression as well as decreased opioid requirements and better cost effectiveness.

CONCLUSION

It is thus concluded that dexmedetomidine is a good choice as far as ICU sedation is concerned. It is a drug worthy of supplementing or even replacing conventional drugs like propofol and benzodiazepines. The main advantage of dexmedetomidine is its propensity to induce a ‘conscious sedation’ devoid of significant respiratory depression that leads to decreased duration from sedation cessation to extubation as well as earlier discharge. The other advantages of dexmedetomidine include haemodynamic stability, decreased analgesic requirements as well as greater cost effectiveness. The only thing to be kept in mind while using dexmedetomidine safely is that continuous monitoring of HR, NIBP and SpO2 is mandatory. Bradycardia, though a significant adverse effect especially during loading dose administration, was not found to be life threatening and atropine was easily able to restore normal heart rate.

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REFERENCES

1. Rotondi AJ, Chelluri L, Sirio C, Mendelsohn A, Schulz R, Belle S, et al. Patients’ recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. Critical care medicine. 2002 Apr 1;30(4):746-52.
2. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001 Dec 5;286(21):2703-10.
3. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, et al. Current practices in sedation and analgesia for mechanically ventilated critically Ill patientsA prospective multicenter patient-based study. Anesthesiology: J American Society of Anesthesiologists. 2007 Apr 1;106(4):687-95.
4. Stoll C, Schelling G, Goetz AE, Kilger E, Bayer A, Kapfhammer HP, et al. Health-related quality of life and post-traumatic stress disorder in patients after cardiac surgery and intensive care treatment. J thoracic and cardiovascular surgery. 2000 Sep 1;120(3):505-12.
5. Singh G, Srinivas K. Comparison of Intensive Care Unit Sedation using Dexmedetomidine, Propofol and Midazolam. Int J Sci Stud. 2017;4(10):115-24.
6. Gerlach AT, Dasta JF. Dexmedetomidine- an updated review. Ann Pharmacother. 2007;41:245-52.
7. Pollock M. Precedex (dexmedetomidine) Safety and Drug utilization Review- FDA, 2016. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM494470.pdf.
8. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'neal PV, Keane KA, et al. The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. American J respiratory critical care medicine. 2002 Nov 15;166(10):1338-44.

9. Anger KE, Szumita PM, Baroletti SA, Labrethe MJ, Fanikos J. Evaluation of dexmedetomidine versus propofol based sedation therapy in mechanically ventilated cardiac surgery patients at a tertiary academic medical center. Crit Pathw Cardiol. 2010;9:221-6
10. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001;86:650-6.
11. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. Anesth Analg. 2002;95:461-6.
12. Reichert MG, Jones WA, Royster RL, Slaughter TF, Kon ND, Kincaid EH. Effect of a dexmedetomidine substitution during a nationwide propofol shortage in patients undergoing coronary artery bypass surgery. Pharmacotherapy. 2011;31:673-7.
13. Hoy SM, Keating GM. Dexmedetomidine: A review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs. 2011;71:1481-501.
14. Eren G, Cukurova Z, Demir G, Hergunsel O, Kozanhan B, Emir NS. Comparison of dexmedetomidine and three different doses of midazolam in preoperative sedation. J Anaesthesiol Clin Pharmacol. 2011;27:367-72.
15. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine for long-term sedation investigators: dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151-60.

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