

ORIGINAL RESEARCH ARTICLE

COMPARISON OF DEXMEDETOMIDINE WITH PROPOFOL FOR SEDATION IN CRITICALLY ILL ADULT PATIENTS

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ABSTRACT

Background: Patients in intensive care unit setting require invasive monitoring and treatments that often lead to anxiety and pain. To reduce anxiety, increase tolerance and improve outcome of such interventions, sedation is common practice. Propofol and Dexmedetomidine both are frequently used for sedation in ICU.

Methods: In a randomized, prospective, open label study, seventy critically ill adult patients requiring mechanical ventilation were assigned to receive either propofol infusion with 1.2 mg/kg/hr or dexmedetomidine infusion with 0.2 mcg/kg/hr starting dose within twelve hours of intubation and titration of study drug to achieve Richmond agitation sedation score (RASS) of -2 to 0 until extubation or for seven days whichever was longer. Primary end point was percentage of time within target sedation range and secondary end points were prevalence of delirium, duration of mechanical ventilation and use of fentanyl and haloperidol.

Results: The percentage of time within target sedation range (Richmond agitation sedation score -2 to 0) was similar ($p=0.947$). Consumption of median dose of fentanyl ($p=0.043$) and haloperidol ($p=0.025$) were less in dexmedetomidine group. Ability to communicate pain via visual analogue scale was significantly higher in dexmedetomidine group 28 (80%) as compared to propofol group 14 (40%); $p=0.001$. Adverse events like hypotension, bradycardia was not significantly different.

Conclusions: Sedation with dexmedetomidine was similar as compared to propofol in mechanically ventilated critically ill adult patients. Dexmedetomidine reduced duration of delirium consumption of fentanyl and improved patients' ability to communicate pain compared to propofol.

INTRODUCTION

Patients in the intensive care unit (ICU) setting require invasive monitoring and treatments that often lead to anxiety and pain.¹ In particular, use of mechanical ventilation may create a variety of physical and psychological stresses.² To reduce anxiety, increase tolerance, and improve outcomes of such interventions, sedation is a common practice.³

Dexmedetomidine has been shown to be non-inferior to both midazolam and propofol in maintaining light to moderate sedation.^{4,5} It appears to shorten time to extubation and enhance arousability and patients' ability to communicate with caregivers.⁵

Recent guideline of Society of Critical Care Medicine recommend using non-benzodiazepine agent, such as propofol or dexmedetomidine over benzodiazepines as a first line sedative.⁶ Despite few years of use, no study compared these drugs in our population. This study was conducted to compare the efficacy and safety of dexmedetomidine and propofol for sedation in mechanically ventilated critically ill adult patients.

METHODS

In this prospective randomized study, after ethical approval from institutional review board and consent from patients legal guardian, total of 70 patients were randomly assigned 1:1 to receive propofol [$n=35$] or dexmedetomidine [$n=35$] in mechanically ventilated critically ill adult patients admitted in intensive care unit (ICU) of Tribhuvan University Teaching Hospital (TUTH) over 6 months. Randomization was done using computer generated schedule and allocation concealment was done with closed envelop.

Adults older than 16 years, intubated and mechanically ventilated for less than 12hr prior to start of study drugs with anticipated ventilation and sedation duration of at least 24hr were included in the study. Patients under dialysis of all types, pregnant or lactating mother, neuromuscular blockade other than for intubation, serious mental illness, delirium and dementia, Left ventricular ejection fraction less than 30%, heart rate less than 50 per minute, second or third degree heart block and systolic BP less than 90mmHg despite continuous infusions of two vasopressors before the start of study drug infusion were excluded from the study.

Each patient received study drug within 12 hours after intubation. Sedatives used before study enrolment was discontinued prior to the initiation of study drug. Starting maintenance infusion dose of study drug was 0.2 mcg/kg/hr for dexmedetomidine and 1.2mg/kg/hr for propofol. Titration of drug was done by multiple of initial dose, maximum dose used was five times the initial dose. For dexmedetomidine, dose was increased from 0.2 to 0.4, 0.4 to 0.6, 0.6 to 0.8 then 0.8 to 1mcg/kg/hr. For propofol, dose was increased from 1.2 to 2.4, 2.4 to 3.6, 3.6 to 4.8 then 4.8 to 6 mg/kg/hr. Drug titration was done every 10- 15 min until target Richmond agitation sedation score (RASS) range was achieved. Dosing of study drug was adjusted by the managing clinical team based on sedation assessment performed with the RASS a minimum of every 2 hr. When over sedation (RASS range -3 to -5) did not respond to decreasing study drug infusion rate, the infusion was stopped until patient returned to the acceptable sedation range. Fentanyl bolus doses (1mcg/kg) were administered every 15 min, when sedation was not adequate (RASS >0) with maximum dose of study drug. Intravenous bolus doses of fentanyl were given prior to an anticipated noxious stimulation such as chest physiotherapy or suctioning. No other sedative or analgesics were allowed during study period. Intravenous haloperidol was given for treatment of agitation or delirium in increments of 1 to 5 mg, repeated every 20 min as needed. Study drug infusion was stopped at the time of extubation or after a maximum of 4 days. Delirium was assessed daily in patients with the RASS range of -2 to 0 using Confusion Assessment Method for the ICU (CAM-ICU). Patient's ability to communicate pain was assessed using visual analogue scale. Vitals were recorded in minimum of every 2 hr. Adverse events were assessed by principal investigator and were recorded from 1st dose of study drug until 48hr after discontinuation.

The primary end point was the proportion of time within the target sedation range (RASS score -2 to 0): calculated as total hr patient within target sedation range/total study hr x 100. Secondary outcomes were prevalence and duration of delirium, use of haloperidol and fentanyl, duration of mechanical ventilation, ability to communicate pain using VAS and adverse events. Heart rate and blood pressure were considered adverse events if mean arterial pressure was less than 65 mmHg or greater than 130 mmHg and heart rate less than 40/min or greater than 120/min or any change greater than 30% from baseline heart rate or blood pressure. Bradycardia was managed by administration of intravenous atropine. Hypotension was managed by titration of study drug or intravenous phenylephrine.

RESULTS

Planned enrollment was seventy five patients in the study. Assuming effect size of 0.7 in determining differences in average time in target sedation, sample size of 35 in each group gives 80% power and 95% confidence level. The intention to treat populations included thirty five patients in both dexmedetomidine and propofol groups. The intention to treat population, including all randomized patients, was used for all other efficacy variables to analyze difference. Safety was analyzed in patients who received any study drug. Data were collected

as per the proforma. All data were entered in Microsoft office Excel worksheet 2007. Continuous variables were presented as mean +/- SD and median [interquartile range (IQR)]. Categorical variables were presented as number (percentage). A 2-sided significance level of 0.05 was used in all treatment comparisons. For statistical analysis, unpaired t test and Mann Whitney U test were used for continuous variables and chi square test for categorical variables. For the analysis of data Statistical package for the social Sciences (SPSS) 17 was used.

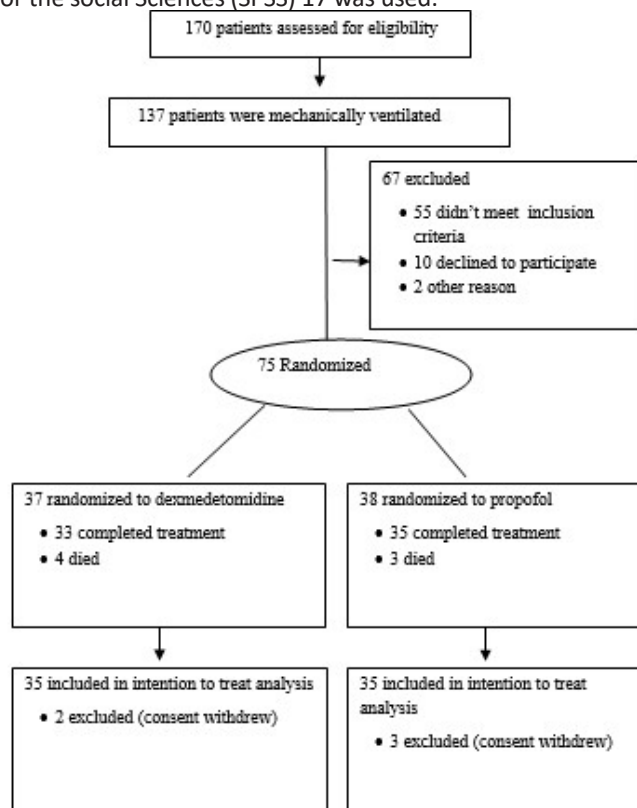


Figure1: Flow diagram of the study

Patient's characteristics, demographic and severity of organ failure between the two groups were similar. Equal number of male and female was included in the study (table1).

Table 1: Demographic and severity of organ failure at baseline

Variables	Dexmedetomidine (n=35)	Propofol (n=35)	p-value ^b
Age (year)	49 ± 16	47 ± 18	0.601
BMI (kg/m ²)	25.81 ± 4.04	24.59 ± 3.20	0.167
Gender			
Female	17(48.6%)	17(48.6%)	1
Male	18(51.4%)	18(51.4%)	
SOFA II ^a ± SD	5.71 ± 2.65	4.83 ± 2.56	0.159
Disease Pattern			
Surgical	26	19	0.212
Medical	9	16	

Abbreviations: BMI-bodymassindex; SOFA-sequential organ function assessment.

^aSum of SOFA score excluding the central nervous system score (range of possible values: 0 – 20; higher score indicate greater illness).

^bFor categorical variables, analysis used the chi square test, and for continuous variables independent t- test. Data are presented as mean±SD and gender as number (percentage).

The comparison of outcome measures of the groups is shown in Table 2

Table 2: Outcome measures in both the groups

Outcome measures	Dexmedetomidine (n=35)	Propofol (n=35)	p-value
Proportion of time in target sedation range(RASS-2 to 0)	73.01 ± 17.89	74.09 ± 13.17	0.947
Prevalence rate of delirium	22.90%	37.10%	0.192
Duration of delirium (days)	0.2±0.47	0.74± 1.15	0.013
Consumption of haloperidol (mg)	0 [0 - 5]	5 [0 - 20]	0.025
Consumption of fentanyl (mcg)	360	500	0.043
Duration of mechanical ventilation (hrs)	57.37 ± 15.96	60.6 ± 16.8	0.413
Communicate via VAS scale	28 (80%)	14 (40%)	0.001
Adverse event	10 (28.5%)	9 (26.9%)	0.788
Hypotension	24.90%	17.13%	
Bradycardia	8.60%	8.60%	

Data are presented as Mean ± SD, or Median [Range] or Number of patients (Percentage)

DISCUSSION

In this prospective study, we compared efficacy of dexmedetomidine with propofol for sedation in mechanically ventilated patients. Our target sedation was RASS -2 to 0. In this study light sedation with dexmedetomidine was found to be comparable with propofol. Both the drugs having different mode of action, have been in use for sedation in ICU. Alpha-2 receptor activation by dexmedetomidine reduces locus ceruleus activities resulting into sedation, analgesia, hypnosis and sympatholysis⁷ while propofol exerts its hypnotic actions by activation of the central inhibitory neurotransmitter - gamma-aminobutyric acid (GABA).⁸ Similar results were also found in other studies.^{5, 9, 10} Our secondary objective was to evaluate the prevalence and duration of delirium between the two groups. We assessed delirium every study day using CAM-ICU method.¹¹ We continued study drug infusion for maximum over 4 days. Most of the cases were extubated on second and third day and those cases that required mechanical ventilation longer than 4 days were discontinued from study drug infusion based on decision of clinical management team. Prevalence of delirium was significantly lower in dexmedetomidine group on second day and no case of delirium on further days. Duration of delirium was less with dexmedetomidine as compared to propofol. This reduction of delirium could be due to some specific properties of dexmedetomidine as it improves the quality of sleep in critically ill patients, has opioid-sparing effect, is lacking anticholinergic activity, and attenuates the inflammatory response.¹²

Though distribution of medical and surgical cases were similar between two study drug groups, consumption of fentanyl was significantly lesser with dexmedetomidine as compared to propofol. In contrast to propofol which has no known analgesic property, alpha-2 receptor mediated analgesic property of dexmedetomidine may have reduced the requirement of fentanyl in our study. Consumption of haloperidol for treatment of delirium was significantly lower in dexmedetomidine group. In our study minimum duration of mechanical ventilation was 28 hours and maximum duration was 407 hours. Most of the patients were ventilated for

24 – 48 hours and they received study drug as per protocol however 5 patients in propofol group and 3 patients in dexmedetomidine group remained in mechanical ventilation for longer period but received study drug for only up to 96 hours as the clinical management team decided to discontinue the sedative drug beyond that period. Decision of clinical management team was based on ICU protocol of our institute.

Total duration of mechanical ventilation was not different between the two groups because besides sedative, there were many factors that may prolong the duration of mechanical ventilation e.g. severity of disease, diagnosis, age, ventilator associated pneumonia, etc. Since the study drug was limited to 4 days but mechanical ventilation was considered up to 15 days, we couldn't continue study drug beyond 4 days.

Patients who had Richmond agitation sedation scale value -2 to 0 were assessed for ability to communicate pain using visual analogue scale. Dexmedetomidine group had significantly higher ability to communicate pain via visual analogue scale as compared to propofol group. Those who answered by showing the scale were considered to be able to communicate whereas those who didn't answered at all were considered to be not able to communicate. Those who were not within Richmond agitation sedation scale -2 to 0 also considered not able to communicate. The better arousability and ability to communicate pain allows more appropriate use of opioids and facilitate earlier mobilization and functional recovery.

Though there were adverse effects such as hypotension and bradycardia in both the group, the effects were mild and in most patients they were managed with titration of study drug. Few patient who didn't respond even after discontinuation of study drug, were managed with fluid. Drug intervention was not needed in any case.

It was a randomized controlled study with adequate concealment of allocation. We considered washout time for the standard sedation preceding randomization so the possibility of impact of those sedatives on study drugs was avoided. We used daily sedation stop and frequent

sedation assessment at every two hours which was standard method to reduce over sedation or under sedation. We used CAM-ICU to assess delirium every study day whereas most of the studies assessed delirium only after extubation.

This study was not blinded to patients and health care provider. To evaluate sedation in prolong mechanical ventilation, only study up to 96 hours couldn't be sufficient to explore the outcome appropriately. As there

is growing evidence of beneficial effects of continuous light sedation in prolonged mechanical ventilation,¹³⁻¹⁵ future studies should continue infusion for longer duration.

CONFLICT OF INTEREST: None

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