Original Research Article

A Comparative Study of Effect of Short-term Sedation of Post-operative Mechanically Ventilated Patients with Dexmedetomedine and Propofol

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Abstract

Background and Objectives: Post-operative mechanically ventilated patient in the intensive care unit (ICU) frequently need sedation and analgesia to facilitate care. Inadequate Sedation in patients admitted to the ICU after surgery leads to patient discomfort, ventilator asynchrony, accidental device removal, and increase metabolic demands during respiration. Careful drug selection for sedation by the ICU team is essential so that patients can be easily weaned from mechanical ventilation after stopping sedation to achieve lesser duration of mechanical ventilation and to decrease ICU stay. Dexmedetomidine, a short-acting alpha-2-agonist, has anxiolytic, anesthetic, hypnotic, and analgesic properties.Propofol is recommended for the short-term (<24 h) treatment of anxiety in post-operative mechanically ventilated patients. The objective of this study was to compare the efficacy and safety of dexmedetomidine versus propofol for post-operative mechanically ventilated patients in ICU before weaning from mechanical ventilation. *Methodology:* Thirty patients aged above 20 years after major abdominal or pelvic surgeries requiring at least 6 hrs artificial ventilation admitted to ICU were included as subjects and they were randomly divided into two groups of fifteen each. Group D received Dexmedetomidine, a loading dose of 2.5 µg/kg and a maintenance dose of 0.5 µg/kg/hr and Group P received Propofol, a loading dose of 1 mg/kg and a maintenance dose of 0.5 mg/kg/hr. Both the groups were compared for level of sedation using Ramsay sedation score, hemodynamic variables, safety profile and fentanyl requirement to achieve adequate analgesia. *Results:* Ramsay sedation score was within the desired level (2-4) in both Dexmedetomidine and Propofol groups (p>0.05). Patients who received Dexmedetomidine infusion had significantly decreased heart rates when compared to patients who received Propofol infusion (p<0.00). Total Fentanyl dose requirement was significant in Propofol group (66.3 ± 10.1 µg) when compared to Dexmedetomidine group. (31.0 ± 9.5 µg; p=0.001). *Conclusion:* Dexmedetomidine and Propofol are safe sedative drugs for post-operative mechanically ventilated patients.To compare with Propofol, Dexmetomidine induces less sedation level with the same duration of mechanical ventilation and has its own analgesic effect and shortens the length of patient's stay in ICU. Bradycardia was noted more frequently in Dexmedetomidine while arterial hypotension, general malaise and delirium in Propofol group.Fentanyl requirement was more with Propofol group.

Keywords: Dexmedetomidine; Propofol; Short-Term Sedation; Postoperative Sedation.

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Introduction

The Intensive Care Unit is an environment of high level stress and discomfort for patients. The use of adequate sedation and analgesia are important in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in the ICU [2]. Post-operative patients requiring mechanical ventilation in an intensive care unit are exposed to different noxious stimuli including postoperative pain, multiple venipuncture, invasive monitoring, and endotracheal intubation; therefore they are usually managed using a continuous-infusion of sedative [1]. The sedation of the patients reduces the stress response, provides anxiolysis, improves the tolerance of ventilator support and facilitates nursing care. whereas, inadequate sedative techniques may adversely affect such patients resulting in unstable hemodynamics and increased morbidity and mortality.

The ideal agent should satisfy the physician's desire for an effective, safe, titratable, cheap and rapidly acting drug that has both sedative and analgesic properties, and should also prevent anxieties and unpleasant memories for the patient [3]. The consequences of inadequate sedation and analgesia can be substantial, including self-removal of important intraluminal tubes and vascular catheters, aggressive behaviour by patients against care providers and poor patient–ventilator synchrony [4]. Oversedation can lead to prolonged duration of mechanical ventilation, longer ICU stay.

For decades, Gama aminobutyric acid receptor agonists like propofol and benzodiazepines such as midazolam have been most commonly administered sedative drugs for ICU patients Worldwide [5]. As pain is often the culprit in agitation, an opioid analgesic is recommended, in addition to the previously mentioned agents, to provide adequate analgesia [7]. Benzodiazepines are anxiolytic and amnestic agents, but they can also cause paradoxical agitation in the elderly. Propofol (2,6, di-isopropylphenol) is a short acting and rapidly metabolized intravenous anaesthetic agent and the rapid metabolism of the drug and virtual lack of cumulation would make it suitable for continuous infusion in the ICU. But it can cause dose dependent respiratory depression, hypotension and hyperlipidaemia. It lacks analgesic properties and prolonged use of high dose propofol causes prolonged infusion syndrome [6].

Now newer drugs are being used for sedation in critically ill patients which have benefits over the conventional drugs. Alpha 2 agonist dexmedetomidine has sedative and analgesic effects and has been proved for ICU sedation for up to 24 h [1], with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus ceruleus, a small nucleus present in the pons, analgesia via receptors in the spinal cord and attenuation of the stress response with no significant respiratory depression. In addition to sedation, dexmedetomidine provides analgesic effects, sympatholytic blunting of the stress response, preservation of neutrophil function and may establish a more natural sleep-like state [5]. It produces mild cognitive impairment allowing easy communication between the healthcare provider and the patient. It also has the advantages of reducing the costs of ICU stay and more natural liberation from mechanical ventilation [9,10].

The present randomized prospective study was undertaken in a manner to evaluate sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics with dexmedetomidine compared to propofol, in order to provide alternative or better sedation in post-operative mechanically ventilated patients.

Objectives of the Study

To evaluate

1) Onset, duration and level of sedation

2) Hemodynamic parameters (HR, BP, SpO_2)

3) Requirement of Fentanyl analgesia

Materials and Methods

A randomized prospective study was undertaken in the Intensive Care Unit of Bapuji Hospital attached to JJM Medical College, Davanagere during the academic year from July 2013 to July 2014.

A total of 30 patients aged above 20 years after major abdominal or pelvic surgeries requiring at least 6 hrs artificial ventilation admitted to Intensive care units of the above hospital were included as subjects. The permission from Institutional ethical review committee was obtained before the study was started. An informed bilingual written consent was obtained either from patient if they were conscious and co-operative or immediate Kith and Kins of the patients. The inclusion and exclusion criteria were as follows-

Inclusion Criteria

➢ Patients aged 20 years and above

➢ Post operative mechanically ventilated patients who require atleast 6 hrs artificial ventilation after major abdominal or pelvic surgery.

Exclusion Criteria

➢ Neurological procedures

➢ Known allergy to propofol or dexmedetomidine

➢ Known or suspected pregnancy

➢ Gross obesity (over 50% above ideal body weight)

➢ Severe hepatic or renal disease

➢ Spinal or epidural anaesthesia

➢ History of corticosteroid therapy within the last 3 months

➢ Uncontrolled diabetes

About 30 patients who satisfied the inclusion and exclusion criteria were allocated randomly in to two groups by using random numbers table.

Group D - Dexmedetomidine group received a loading dose- 2.5 µg/kg and a maintenance dose- 0.5 µg/kg/hr.

Group P - Propofol group received a loading dose- 1 mg/kg and a maintenance dose- 0.5 mg/kg/hr.

Anaesthetic technique prior to entry into the ICU was carried out with, 5 mg/kg thiopental sodium, 2-3 µg/kg fentanyl and vecuronium 0.05 mg/kg.

After admission to ICU, patients were randomized into either of one group, an IV line was secured and patients were connected to multipara mointor which records heart rate, non-invasive measurements of SBP, DBP, MAP, and continuous ECG monitoring and oxygen saturation. Patients were immediately artificially ventilated with synchronized intermittent mandatory ventilation (SIMV) with pressure support mode. Sedatives used before study enrollment was discontinued prior to the initiation of the study drug.

Each patient received study drug after randomization. Optional loading doses (upto 2.5 µg/kg dexmedetomidine or 1 mg/kg propofol) was administered at the investigator's discretion. The starting maintenance infusion dose of study drug was 0.5 µg/kg/hr for dexmedetomidine and 0.5 mg/kg/hr for propofol corresponding to the midpoint of the allowable infusion dose range.

Dosing of study dose was adjusted by managing clinical team based on sedation assessment performed with the Ramsay Sedation Score (RSS), a minimum of every 1 hour for first 6 hours, thereafter every 2 hours. Analgesia with fentanyl bolus doses (0.5-1 µg/kg) was administered as needed. No other sedatives or analgesics or muscle relaxants were allowed during the study period. Study drug infusion was stopped at the time of extubation in both the groups or after a maximum of 24 hours.

The following parameters were assessed

1. Onset of sedation in both groups
2. Level of sedation was assessed by Ramsay sedation score initially every 1 hr for 6 hours, there after every 2 hours till extubation or up to 24 hours
3. Hemodynamic parameters (HR, BP, SpO_2)
4. Pain assessment using visual analog score
5. Total fentanyl requirement and duration of ICU stay.

Statistical Methods

➢ Results are presented as Mean, Standard deviation and Number and percentages.

➢ Unpaired 't' test was used to compare the mean levels between 2 groups.

➢ Categorical data was analysed by chi square test.

➢ A p value of 0.05 or less was considered to be statistically significant.

➢ SPSS Ver 17 was used for analysis.

➢ Microsoft word and Excel have been used to generate graphs, tables etc.

Results

1. Age Distribution

Table 1: Age Distribution

Age (years)	dexmed	propofol
Mean Age ± SD	38.2 ±12.9	39.1 ± 13.7
T value	0.24	
P value	0.81, NS	

The mean age of patients of Dexmedetomidine group was 38.2 ± 12.9 years and that of Propofol group was 39.1 ± 13.7 years. There was no statistically significant difference in the age of patients between Dexmedetomidine and Propofol groups. Both groups were similar with respect to age distribution (p=0.81) (Table 1).

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2. Sex Distribution

Table 2: Sex Distribution

Sex	Dexmed		Propofol	
	Number	%	Number	%
Male	7	46.6	8	53.3
Female	8	53.3	7	46.6
Total	15	100	15	100

About 46% of patients in Dexmedetomidine group and 53% of patients in Propofol group were males (Table 2).

3. Weight Distribution

The mean weight of patients of Dexmedetomidine group was 60.93 ± 11.45 kg and that of Propofol group was 66.47 ± 10.98 kg.

4. Sedation Score Comparison

The mean Ramsay sedation scores in both groups at different intervals. The mean Ramsay sedation score ranged from 2.3 to 3.5 in Group D and 2.6 to 3.7 in Group P. The sedation scores were not statistically significant between Group D and Group P (Graph 1).
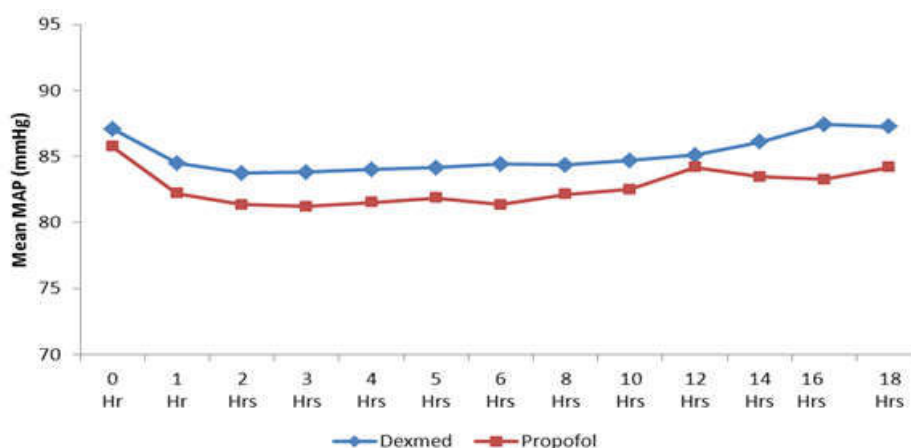
5. Heart Rate Comparison

The basal heart rate were comparable in both the groups. Statistical evaluation between the groups showed a significant fall in heart rate in Group D after drug administration and the fall in heart rate was maintained throughout the study period. A fall of 17 beats per min was observed immediately after administration of Dexmedetomidine. The mean
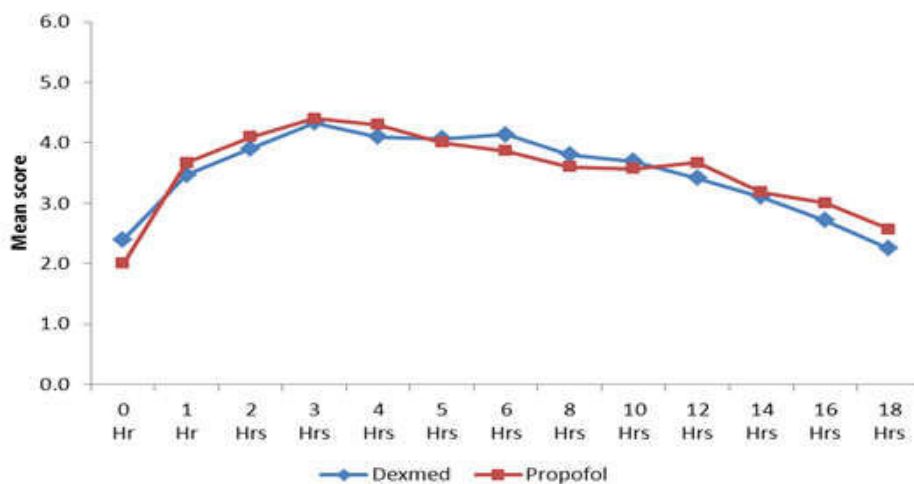
Graph 1: Sedation Score Comparison
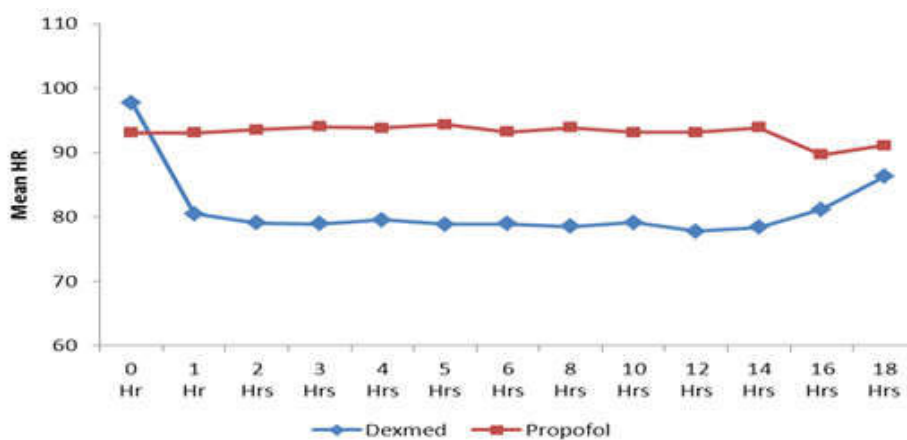
Graph 2: Heart Rate Comparison

Graph 3: Map Comparison

heart rate ranged between 77 – 97 bpm in Group D and 89 – 93 bpm in Group P. There was statistically highly significant fall in heart rate in Group D compared to Group P (p=0.00) (Graph 2).

6. SBP Comparison

The mean SBP were ranged from 113.0 to 117.7 mmHg in Group D, while that in Group P were ranged from 110.0 to 119.6 mmHg. There was no statistically significant difference in SBP between Group D and Group P.

7. DBP Comparison

The mean basal DBP were comparable in both groups (P=0.16). The mean DBP were ranged from 69.0 to 72.0 mmHg in Group D and that in Group P were ranged from 65.5 to 70.8 mmHg. There was no statistically significant difference in DBP among the two groups.

8. MAP Comparison

The basal MAP in group D was comparable to Group P (p=0.49). The mean MAP during study period were ranged from 83.7 to 87.4 mmHg in Group D whereas the mean MAP in Group P were ranged from 80.7 to 85.7 mmHg. There was no statistically significant differences in MAP among the two groups (Graph 3).

9. SpO$_2$ Comparison

The oxygen saturation level was ranged from 98.0 to 99.0% in Group D and that in Group P was ranged from 98.1 to 99.1%. There was no statistically significant difference in oxygen saturation between Group D and Group P.

10. VAS Score Comparison

The mean VAS in Group D were ranged from 2.2 to 3.1 after the infusion of Dexmedetomidine while that of mean VAS in Group P were ranged from 2.0 to 4.0 after the infusion of Propofol. There was no statistically significant difference in VAS between Group D and Group P.

11. Total Dose of Fentanyl Requirement

The mean dose of Fentanyl requirement to achieve adequate analgesia was 31.0 ± 9.5µg in Group D and that of mean Fentanyl requirement in Group P was 66.3 ± 10.1µg. Statistical evaluation between the groups showed a statistically highly significant reduction in the dose of Fentanyl requirement in Group D compared to group P (p=0.001).

12. Number of Days of ICU Stay

Table 3: Number of Days of ICU Stay

No of icu stay(days)	Dexmed		Propofol	
	Mean	SD	Mean	SD
	2.4	0.6	2.6	0.6
Mean difference		0.2		
T value		1.25		
P value		0.22, NS		

The mean ICU stay in Group D was 2.4 days and that of Group P was 2.6 days. There was no statistically significant difference in ICU stay between Group D and Group P. (p=0.22) (Table 3).

Discussion

Demographic Criteria

The mean age of the subjects in this study was 38.2 ± 12.9 years in Dexmedetomidine group and

39.1 ± 13.7 years in Propofol group. About 53% in Group D and 56% in Group P were males. The mean weight of patients were 60.93 Kgs and 66.47 Kgs in Group D and Group P, respectively. There was no statistically significant difference with regards to mean age, weight and sex. Hence the two groups were comparable.

Sedation Score

The level of sedation was assessed by Ramsay sedation score. The mean sedation scores were ranged from 2.3 to 3.5 in Group D and 2.6 to 3.7 in Group P. There was no significant difference in Ramsay sedation score between Group D and Group P during the study period. In a study conducted by R.M. Venn et al. [15]., there were no overall differences in the distribution of Ramsay sedation scores between the dexmedetomidine and placebo groups while intubated. However intubated patients receiving dexmedetomidine required significantly less midazolam than those receiving placebo. In a similar study by Samia Elbaradie et al., [19] dexmedetomidine produced equivalent sedation as propofol and the patients who were received Dexmedetomidine, despite artificial ventilation and intubation, were easily aroused to co-operate without showing irritation.

Hemodynamic Parameters

In the present study, there was a significant bradycardia in Dexmedetomidine group compared to Propofol group. There was fall of 15 bpm after dexmedetomidine infusion and the fall in heart rate was sustained throughout the study period and did not require any treatment. In a similar study by Hussein M Agameya et al., [20] heart rate showed significant reduction in dexmedetomidine group than in propofol group (p= 0.026).

In a study by Samia Elbaradie et al., [19] also noted Patients who received dexmedetomidine infusion had significantly lower heart rates compared to patients who received Propofol infusion, (p=0.041), but did not need any intervention.

The mean systolic blood pressure in Propofol group were decreased about 6 mmHg from baseline value where as the fall in Dexmedetomidine group were 5 mmHg from baseline value, immediately after transfusion of study drugs, which was non-significant. The mean diastolic blood pressure were decreased by 4 mmHg and 3 mmHg in Dexmedetomidine and Propofol groups, respectively and it was not significant.

The mean arterial pressure was reduced by 3 mmHg and 4 mmHg in Dexmedetomidine and Propofol groups, respectively. The fall in MAP in patients received Propofol did not need any intervention and it was not significant. In a similar study by Samia Elbaradie et al., [19] noted there was no significant difference in MAP between Dexmedetomidine and Propofol group. No patients in the 2 groups required inotropic support.

The mean oxygen saturation levels were within the optimal range in both groups during the study period of 24 hours. In a similar study by R.M. Venn and R.M. Grounds [3] noted that there was no significant difference between oxygen saturation and arterial blood gases in both Dexmedetomidine and Propofol groups.Similarly study done by R.M. Venn et al., [15] showed no significant difference in respiratory rate and oxygen saturation between dexmedetomidine and placebo groups.

Analgesia

In the present study, visual analog scores were within the optimal range. VAS of 2-3 was achieved in both groups using Fentanyl analgesia. The total Fentanyl requirement was significant in Propofol group when compared with Dexmedetomidine group (p<0.00). In a similar study by Prerana N Shah et al., [8] noted patients who received propofol infusions required significantly more analgesics than patients who received Dexmedetomidine infusions.

In a study by Herr D L et al. [16] noted requirement of morphine was significantly more in Propofol group compared to Dexmedetomidine group. Similarly study done by R.M. Venn et al.,[15] the requirement for morphine was reduced by half in the dexmedetomidine group while intubated.

ICU Stay

In the present study, there was no significant difference in length of ICU stay in both groups. In a similar study by R.M. Venn and R.M. Grounds [14] noted the recovery time and length of ICU stay were similar in both Dexmedetomidine and Propofol groups.

Conclusion

Dexmedetomidine and Propofol are safe sedative drugs for post-operative mechanically ventilated patients. To compare with Propofol, Dexmetomidine induces less sedation level with

the same duration of mechanical ventilation and awakening rate. Dexmetomidine provides its own analgesic effect and shortens the length of patient's stay in ICU. Bradycardia was noted more frequently in Dexmedetomidine while arterial hypotension, general malaise and delirium-in Propofol group.

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