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COMPARISON BETWEEN DEXMEDETOMIDINE AND PROPOFOL FOR SHORT TERM SEDATION IN POSTOPERATIVE MECHANICALLY VENTILATED PATIENTS

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ABSTRACT

Background and Aim: Sedation in the ICU allows for a comfortable and cooperative patient, decreases the level of anxiety and stress, reduces insomnia and the risk of awareness during stressful interventions. The present study was undertaken to evaluate sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics with dexmedetomidine compared to propofol in postoperative mechanically ventilated patients. **Setting and design**: 40 postoperative patients admitted in the ICU were selected randomly after taking informed written consent from the relatives.Patients were randomly allocated into 2 groups **Group D**-Dexmedetomidine group **Group P**-Propofol Group and prospectively studied using single blinded design. **Methods:** All patients were randomly allocated to receive intravenous infusions of either dexmedetomidine or propofol whilst being mechanically ventilated, together with the short acting opioid fentanyl for analgesia if required An initial loading dose infusion of dexmedetomidine or propofol was given to rapidly achieve a steady state plasma concentration. The loading dose infusion of dexmedetomidine was 1.0μg/kg^{-1} over 10 minutes followed by a maintenance infusion of 0.5μg/kg/hr into a peripheral or central vein. Propofol was given undiluted as an infusion of 1-3mg/kg/hr, after a loading dose infusion of 1mg/kg over 10 minutes. Fentanyl was used in IV bolus if required, at 1μg/kg if the patient indicated he or she was in pain. The degree of sedation was measured and recorded hourly using the Ramsay Sedation Score (RSS). The aim with both drugs was to keep patients at RSS > 3 by adjustments to the sedative regimen., safety profile, cardiovascular responses, ventilation and extubation characteristics with dexmedetomidine compared to propofol in postoperative mechanically ventilated patients. **Result:** In our study we found that dexmedetomidine is an effective and safe agent for postoperative sedation in ICU. The sedative profile of dexmedetomidine was comparable to propofol which is a well established IV sedative agent regularly used in ICU. With the advantage that the opioid requirement was reduced in patients who received dexmedetomidine which could be attributed to central analgesic properties of dexmedetomidine. In this study equipotent sedative doses of these agents infused in patients with similar haemodynamics resulted in equivalent mild reductions in arterial pressures. However the significantly lower heart rate seen with dexmedetomidine in comparison with patients receiving propofol may lower the risk of ischemic events during the stressful ICU episode, in particular over the extubation period. **Conclusion:** Patients sedated with dexmedetomidine were easily arousable and cooperate well with the ICU staff.

KEYWORDS: Dexmetomidine, Propofol, Sedation, ICU, Mechanical ventilation.

INTRODUCTION

Sedation has been an integral part of critical care management in minimizing patient discomfort. Many different techniques have been tried, all have potential side effects and some have been associated with serious side effects and the potential to prolong mechanical ventilation which may increase health cost. Sedation in critically ill patients is essential to ensure maximal quality of life in the high stress environment of the ICU. The main goals of sedation include augmentation of pain control, management of agitation and psychological distress, improvement of patient tolerance and acceptance of endotracheal tube and ventilator support. Dexmedetomidine is an alpha 2 adrenoceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the Locus Ceruleus,

analgesia via receptors in the spinal cord and attenuation of the stress response with no significant respiratory depression, sympatholytic blunting of the stress response, preservation of neutrophil function (compared with the neutrophil suppressing effect of GABA agonist medications) and may establish more natural sleep like state.[1]

Propofol is selected as the comparator medication owing to its frequent use for short term sedation and is often identified as the sedative most commonly used in ICU.The present study was aimed to compare the sedative effects of dexmedetomidine and propofol in mechanically ventilated patients and also to compare the recovery profile of these drugs after their stoppage.

MATERIAL AND METHODS

The study was conducted on 40 patients of either sex between 18 years to 60 years who needed postoperative mechanical ventilation. This study was conducted in ICU of Government S.M.H.S. Hospital, an associated hospital of Government Medical College, Srinagar. 40 postoperative patients admitted in the ICU were selected randomly after taking informed written consent from the relatives.

Patients were randomly allocated into 2 groups:
Group D-Dexmedetomidine group received a Loading dose-1.0mcg/kg.
And a maintenance dose-0.5mcg/kg/hr.
Group P-Propofol Group received a Loading dose-1mg/kg.
And a Maintenance dose-0.5mg/kg/hr.

Intraoperatively, all patients received the same anaesthetic technique by using propofol in a dose of 2.5mg/kg for induction, Atracurium in a dose of 0.5mg/kg for endotracheal intubation and isoflurane in oxygen-nitrous oxide mixture 40:60% for maintenance. Intraoperative analgesia was provided by fentanyl alone. At the end of the surgical procedure, neuromuscular blockade was not reversed and artificial ventilation was continued. Immediately, all patients were transferred to ICU by portable oxygen driven ventilator. On arrival in ICU, all patients were connected to monitor to record pulse, NIBP, ECG and SPO2. All patients were randomly allocated to receive intravenous infusions of either dexmedetomidine or propofol whilst being mechanically ventilated, together with the short acting opioid fentanyl for analgesia if required. Fentanyl was used in preference to morphine because recovery after infusion is generally rapid and excretion of active metabolites is not a problem with fentanyl. An initial loading dose infusion of dexmedetomidine or propofol was given to rapidly achieve a steady state plasma concentration. The loading dose infusion of dexmedetomidine was $1.0\mu g/kg^{-1}$ over 10 minutes followed by a maintenance infusion of 0.5μg/kg/hr into a peripheral or central vein. Propofol was given undiluted as an infusion of 1-3mg/kg/hr, after a loading dose infusion of 1mg/kg over 10 minutes. Fentanyl was used in IV bolus if required, at 1μg/kg if the patient indicated he or she was in pain. The degree of sedation was measured and recorded hourly using the Ramsay Sedation Score (RSS). The aim with both drugs was to keep patients at RSS > 3 by adjustments to the sedative regimen. No other sedative or analgesic agents were given, and no patient received spinal o or epidural analgesia in the perioperative period.

Ramsay Sedation Scale

- **Level 1:** Patient anxious and agitated or restless or both.
- **Level 2:** Patient cooperative, oriented and tranquit.
- **Level 3:** Patient responds to commands only.
- **Level 4:** Asleep but with a brisk response to a light glabellar tap or loud auditory stimulis.
- **Level 5:** Asleep but sluggish response to light glabellar tap or loud auditory stimulus.
- **Level 6:** Asleep, no response.

Patients were ventilated mechanically with oxygen enriched air to attain acceptable blood gases. The sedative infusion was discontinued, in preparation for extubation, when there was no evidence of bleeding and the patient was alert, cardiovascularly stable, normothermic and with an arterial oxygen tension > 10 kpa an inspired oxygen concentration < 40% and had positive end expiratory pressure (PEEP) < 5 cmH_2O. Once spontaneous respiration had been established with pressure support < 10cmH_2O, a tidal volume >6ml/kg and respiratory rate > 10 breaths/minute but < 20 min^{-1}, extubation was undertaken. Extubation time was defined as the time from cessation of sedation infusion to extubation. Heart rate, blood pressure, central venous pressure and oxygen saturation were monitored continuously. Venous samples were taken for routine hematological (full blood count, coagulation profile) and biochemical (electrolytes, urea, creatinine, blood sugar, liver function, phosphate and calcium) profiles immediately on arrival in ICU and then at 24 hours and 48 hours. Cardiovascular and respiratory adverse events were defined as a change in arterial pressure of > 40% from baseline, bradycardia < 50 beats / min, tachyarrhythmia, and a respiratory rate < 8 or > 25 breaths / minute after extubation.

RESULTS

Table 1: Distribution of Sex in Study Groups.

Group	Total No. of Patients	Males	Females	P value
I	20	8 (40%)	12 (60%)	> 0.401
II	20	9 (45%)	11 (55%)	

Of the 40 patients studied (20 in each group) there were about 60% and 55% female in group I and group II respectively. Statistically there was no significant relationship in sex ratio with p value > 0.401.Similarily

there was no significant relationship in Age distribution as shown in table 2.

Table 2: Distribution of Age (Years) in Study Groups.

Group	Total No. of Patients	Age Range (Years)	Mean+SD	P value
I	20	26-55	40.2+8.087	> 0.790
II	20	25-60	41.5+10.400	

Table 3: Comparison of Time (min) Since Arrival in ICU to the Beginning of Sedation in Study Groups.

Group	Total No. of Patients	Time (min)	Mean+SD	P value
I	20	57-79	67.10+6.38	> 0.7
II	20	58-78	68.20+6.88	

The mean interval between the time (min) of arrival of patient to intensive care unit to the beginning of sedation in Group I and Group II was 67.10+6.38 (range 57-79 minutes) and 68.20+6.88 (range 58-78 minutes) respectively. On comparison there was statistically not significant difference in this time interval between the two groups (p value > 0.7) as shown in table 3.

Table 4: Comparison of Heart Rate (min) Since Arrival in ICU to the Beginning of Sedation in Study Groups.

Time in Hrs.	Group I Mean + SD	Group II Mean + SD	P value
On Arrival	78.90+5.28	79.30+6.24	> 0.80
1 Hour	76.45+5.16	75.90+5.38	> 0.75
2 Hours	74.85+6.83	78.14+5.20	> 0.60
3 Hours	76.43+5.81	75.10+5.45	> 0.45
4 Hours	74.25+7.34	75.24+6.55	> 0.65
5 Hours	78.10+6.45	77.90+5.15	> 0.90
6 Hours	76.75+4.38	77.90+4.10	> 0.40
7 Hours	76.38+5.10	77.24+5.25	> 0.60

The mean heart rate per minute in Group I and Group II was observed at 0, 1, 2, 3, 4, 5, 6 and 7 hours and was compared between them, also the mean heart rate was compared among each group itself at different intervals of time. No significant difference in heart rate was found between Group I and Group II. Also a non significant difference was observed within Group I and Group II at different intervals of time when compared as shown in table 4.

Table 5: Comparison of SBP (mmHg) Between Group I and Group II at Different Intervals of Time.

Time in Hrs.	Group I Mean + SD	Group II Mean + SD	P value
On Arrival	125.95+7.00	127.80+7.80	> 0.40
1 Hour	123.55+9.10	122.10+8.40	> 0.45
2 Hours	124.10+8.10	120.80+7.50	> 0.20
3 Hours	123.90+9.60	121.60+7.30	> 0.40
4 Hours	121.10+7.48	120.10+8.75	> 0.60
5 Hours	121.60+8.10	121.00+8.27	> 0.90
6 Hours	122.10+7.10	120.50+8.00	> 0.70
7 Hours	122.10+7.10	120.80+6.75	> 0.60

The mean systolic blood pressure (mmHg) in Group I and Group II was observed at 0, 1, 2, 3, 4, 5, 6 and 7 hours and was compared between them, also the mean SBP was compared among each group itself at different intervals of time. No significant difference in SBP was found between Group I and Group II. Also a non significant difference was observed within Group I and Group II at different intervals of time when compared as shown in table 5.

Table 6: Comparison of DBP (mmHg) Between Group I and Group II at Different Intervals of Time.

Time in Hrs.	Group I Mean + SD	Group II Mean + SD	P value
On Arrival	79.90+5.10	82.40+5.20	> 0.10
1 Hour	78.60+7.15	81.20+5.70	> 0.30
2 Hours	80.15+6.25	81.45+5.85	> 0.50
3 Hours	78.25+6.40	80.15+7.50	> 0.40
4 Hours	79.80+5.85	82.05+7.30	> 0.30
5 Hours	78.75+5.75	80.10+6.40	> 0.50
6 Hours	78.90+5.37	79.90+6.30	> 0.60
7 Hours	78.80+6.15	80.85+5.25	> 0.40

The mean diastolic blood pressure (mmHg) in Group I and Group II was observed at 0, 1, 2, 3, 4, 5, 6 and 7 hours and was compared between them, also the mean DBP was compared among each group itself at different intervals of time. No significant difference in DBP was found between Group I and Group II. Also a non significant difference was observed within Group I and Group II at different intervals of time when compared as shown in table 6.

Table 7: Comparison of Time (min) Since Stopping Sedation to Tracheal Extubation in Study Groups.

Group	Total No. of Patients	Time (min)	Mean+SD	P value
I	20	15-50	29.00+5.14	> 0.63
II	20	20-50	28.10+6.20	

The mean interval between the time (min) of stoppage of sedation to tracheal extubation was 29.00+5.14 (range 15-50 minutes) and 28.10+6.20 (range 20-50 minutes) in Group I and Group II respectively. On comparison there was statistically not significant difference in this time

interval between the two groups (p value > 0.63) as shown in table 7.

DISCUSSION

Sedation has been an integral part of critical care management in minimizing patient discomfort. Many different techniques have been tried, all have potential side effects and some have been associated with serious side effects and the potential to prolong mechanical ventilation which may increase health cost. Sedation in critically ill patients in essential to ensure maximal quality of life in the high stress environment of the ICU. The main goals of sedation include augmentation of pain control, management of agitation and psychological distress, improvement of patient tolerance and acceptance of endotracheal tube and ventilator support.

The present study was aimed to compare the sedative effects of dexmedetomidine and propofol in mechanically ventilated patients and also to compare the recovery profile of these drugs after their stoppage. This study included 40 patients who underwent abdominal surgeries and were electively put on mechanical ventilation in postoperative period. The patients were allocated randomly to receive either dexmedetomidine or propofol for sedation. Dexmedetomidine was given as IV loading dose of 1ug/kg over 10 minutes followed by infusion of 0.5ug/kg/hr and propofol was given as IV loading dose of 1mg/kg over 10 minutes followed by infusion of 0.5mg/kg/hr to achieve the Ramsay Sedation Score (RSS) of 3 to 4.

In our study we found that dexmedetomidine is an effective and safe agent for postoperative sedation in ICU. The sedative profile of dexmedetomidine was comparable to propofol which is a well established IV sedative agent regularly used in ICU. An equivalent depth of sedation between dexmedetomidine and propofol in the ICU was achieved, with the advantage that the opioid requirement was reduced in patients who received dexmedetomidine which could be attributed to central analgesic properties of dexmedetomidine. It is difficult to quantify the cooperation and ease of management seen with patients sedated with dexmedetomidine in the ICU which presumably reflects only mild cognitive impairment. This may explain the ease and speed of extubation after dexmedetomidine infusion. Although extubation times were similar in the groups, a longer extubation time would have been predicted with dexmedetomidine from volunteer pharmacokinetic data as the elimination half life of propofol is approximately 3 times shorter (30-60 minutes for propofol versus 100-150 minutes for dexmedetomidine).

Great interest exists in the comparative difference in cardiovascular responses between dexmedetomidine and propofol. Vasodilation which manifests itself as a reduction in arterial blood pressure is a feature of sedation with both propofol and dexmedetomidine.

In this study equipotent sedative doses of these agents infused in patients with similar hemodynamics resulted in equivalent mild reductions in arterial pressures. However the significantly lower heart rate seen with dexmedetomidine in comparison with patients receiving propofol may lower the risk of ischemic events during the stressful ICU episode, in particular over the extubation period. **RM Venn and RM Grounds (2001)** In a prospective randomized clinical study conducted on 20 patients expected to require a minimum of 8 hours artificial ventilation after surgery were randomized to receive sedation with either dexmedetomidine or propofol infusion, they concluded that patients sedated with dexmedetomidine could be easily aroused to cooperate with procedures.[2]

The sedative and analgesic profile in the study done by Hall et al.[3] stated that small dose of dexmedetomidine infusion over 12 hours postoperatively was the best sedative and analgesic technique they ever used. Gertler et al.[4] studied sedative and analgesic properties of dexmedetomidine in mechanically ventilated patients in ICU and they used also the bispectral index to measure depth of sedation and found out that most patients had good level of sedation with cardiovascular stability and better extubation criteria.

Martin et al.[5] confirmed the importance of the analgesic sparing effect of dexmedetomidine with an “easier to manage” judgment of nursing staff when describing dexmedetomidine sedated patients.

Samia Elbaradie, et al In a randomized clinical study conducted on 60 adult patients who were expected to require a minimum of 6 hours postoperative short term ventilation and sedation, were allocated randomly, to receive IV infusion of either dexmedetomidine 0.2-0.5mcg/kg/hr or propofol 0.5-1mg/kg/hr and all patients received short acting fentanyl infusion 0.25-0.5mcg/kg/hr to achieve desired sedation and analgesia. They concluded that dexmedetomidine and propofol are safe sedative drugs for postoperative mechanically ventilated patients and patients were easily aroused to co-operate for procedures with less fentanyl analgesia in dexmedetomidine group.[6]

Azrina MD Ralib, et al in a prospective, randomized single-blinded trial with postoperative open heart surgery patients in the ICU, it was concluded that Dexmedetomidine is comparable to propofol in the provision of sedation, and its effect on hemodynamic and respiratory parameters.[7]

Anger KE, et al In a single center, descriptive study of clinical practice at a 20-bed cardiac surgery ICU in a tertiary academic medical center, adult mechanically ventilated postcardiac surgery patients were received either dexmedetomidine or propofol for sedation therapy. The study concluded that no differences in the ICU

length of stay and duration of mechanical ventilation in both the groups.[8]

Ahmed El Shaer and Amal H Rabie conducted a study to evaluate and compare the use of propofol with dexmedetomidine in two different dose regimins for prolonged sedation for the mechanically ventilated patients. The present study shows that sedation with dexmedetomidine in doses from 0.7-1.0 µg/kg/h can be as effective as, besides being safer than, propofol. Dexmedetomidine in doses less than 0.7µg/kg/hour may be less effective and probably needs supplementation with other sedative.[9]

Zhi-Qiu Xia et al assessed the influence of dexmedetomidine and propofol for adult intensive care unit (ICU) sedation, with respect to patient outcomes and adverse events. For ICU patient sedation, dexmedetomidine may offer advantages over propofol in terms of decrease in the length of ICU stay and the risk of delirium. However, transient hypertension may occur when dexmedetomidine is administered with a loading dose or at high infusion rates.[10] There was statistically no significant difference between both the study groups with regard to age (years), weight (kg) and sex. As for the hemodynamic variables the mean arterial blood pressure showed no statistically significant difference between both the groups. No adverse effects recorded in both the study groups. No patient required addition of ionotropic support. With respect to mean heart rate, the dexmedetomidine group exhibited a lower heart rate compared with propofol group but the difference was statistically non significant. Mean extubation times were comparable between dexmedetomidine and propofol with statistically non significant difference. There were no respiratory adverse events after extubation in either group and no patient required reintubation.

In conclusion Patients sedated with dexmedetomidine were easily arousable and cooperate well with the ICU staff.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding publication of this paper.

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