Sedation for mechanically ventilated postoperative patients in the intensive care unit: comparative study between propofol and dexmedetomidine.

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ABSTRACT

Alpha 2 agonist dexmedetomidine is a new sedative and analgesic drug, which has been recently approved by FDA for use in ICU sedation. Dexmedetomidine is pharmacologically much more selective on α2 receptors than clonidine. In the present study dexmedetomidine was compared to propofol as infusion for sedating 20 patients (10 patients in each group) admitted to ICU for postoperative short-term mechanical ventilatory support (8-10hrs) after major surgical procedures. Additional analgesics were supplied using nalbuphine iv bolus doses. Depth of sedation was measured continuously by using bispectral index neurosonic 1400 monitor. Hemodynamic and ventilator variables were recorded hourly. Depth of sedation was equivalent in both groups by bispectral index scale 56(44-67) for propofol group versus 49 (42-57) for dexmedetomidine group with non-significant difference (P= 0.41) between both groups. Although dexmedetomidine group showed more alertness and cooperation during ventilator support and more rapid and easy extubation (extubation time 33minutes in propofol group versus 32minutes in dexmedetomidine group) (p= 0.7), but these changes were statistically non-significant. Also propofol group required almost three times analgesic doses than for dexmedetomidine group (240mg versus 80mg). No significant difference was found in mean arterial blood pressure or central venous pressure between both groups. However, heart rate showed significant reduction in dexmedetomidine group than in propofol group (p= 0.026).No adverse events were recorded when related to the sedative infusions used in this study.

It could be concluded that dexmedetomidine is a safe and an effective sedative agent in ICU postoperative patients as it provides safe profile and reduces analgesic requirements.

INTRODUCTION

Patients subjected to major and ultra major surgical procedures may require short periods of postoperative mechanical ventilator support, especially those operated for upper abdominal surgeries and morbidly obese patients. However, sedation of mechanically ventilated patients remains the major challenge for intensivists, as inadequate sedation may affect morbidity and even mortality in the ICU(1). The search for an ideal sedative agent continues as it should satisfy the physician’s desire for an effective, safe, titratable, cheap and rapidly acting drug that has both sedative and analgesic properties. It should also prevent anxiety and unpleasant memories for the patient. The commonly used sedative agents, midazolam and Propofol in ICU lack any analgesic properties which necessitates additional use of narcotics with their well known side effects especially on respiration(2). Propofol is commonly used as a controllable sedative drug for ICU patients for maximally 7 days .Because of the risk of contamination and the possible elevation of serum triglycerides, propofol infusion is limited to short duration use specially during the weaning phase from mechanical ventilation.(3) A dose limit (< 4 mg/Kg/hr.) is recommended to reduce the risk of development of propofolinfusion syndrome (possible symptoms: dysrrhythmias, heart failure, severe metabolic acidosis and acute renal failure).(3). A new α 2 agonist dexmedeto-midine has proven to be an effective sedative and analgesic agent and has been recently approved by FDA as an ICU sedative drug for up to 24 hours(4). It stimulates alpha 2-adrenergic recap-tors in the locus ceruleus to provide sedation. On the spinal cord
level, the drug enhances analgesia and sympatholysis via central and peripheral mechanisms\(^5\). Also it produces hemodynamic stability without any clinical effect on respiration\(^6\). Its sedative properties are unique. It produces mild cognitive impairment which allows easy communication between the medical staff and patients on ventilator. In this study we compared the sedative effect, analgesic profile, cardiovascular effects and patient comfort of dexmedetomidine with propofol for sedation in ICU.

**PATIENTS AND METHODS**

This study was conducted in Astoon-Dallah hospital-Khobar-Saudi Arabia in anesthesia and intensive care department after approval of the hospital research committee. Twenty patients were included in this study and they were all subjected to major and ultra major surgical interventions. All patients required 6-10 hours of post operative mechanical ventilator support using (Evita 2 dura Dragger ventilator). According to the type of sedation used in ICU, patients were divided into 2 groups (10 patients each), group I received propofol and group II received dexmedetomidine.

Intraoperatively, all patients received the same anesthetic technique by using Propofol in a dose of 2.5 mg/kg for induction, cistracrium in a dose of 0.2 mg/kg for endotracheal intubation and sevoflurane in oxygen- nitrous oxide mixture of 40:60\% for maintenance .Immediately after surgery, patients were all transferred to ICU by portable oxygen-driven ventilator (Samsung D-III) and ventilated using SIMV mode with 40\%oxygen enriched air with positive pressure support 7-15cm H2O (to maintain acceptable With the start of mechanical ventilation, sedation started by using propofol in group I as a bolus dose of 1mg/kg over 2 minutes and followed by continuous infusion in a dose of 2-3mg/kg/hr.In group II sedation started by a bolus dose of dexmedetomidine (precedes) 0.3 ug/kg over 10 minutes followed by continuous infusion of 0.3-0.4 ug/kg/hr. All infusions were prepared in a 50 ml syringe and infused with a syringe pump (Ohmeda-PAP\,). For both groups, hemodynamic data (heart rate, MABP, central venous pressure) were measured immediately on arrival to ICU and before start of sedation by using multi-channel monitor (Datex-Ohmeda), The degree of sedation was measured and recorded continuously using electro cephalic bispectral index BIS (7) monitor (Neurosonic 1100-Cusack -Germany) designed to monitor the depth of sedation by 2 electrodes put on the forehead and the parietal area of the scalp. Any additional need for analgesic agents was given as bolus doses of nalbuphine and was recorded. All ventilator parameters were monitored and adjusted to maintain ideal arterial O2 saturation, O2tension and CO2 tension and maintaining normal airway and lung dynamics. All hemodynamic data were recorded every 30 minutes during first two hours and then hourly until the end of the study. In absence of any evidence of surgical bleeding with hemodynamic stability, normothermia and normal ventilator criteria on 40\% oxygen, discontinuation of sedative agents was done and extubation the patient was achieved. Extubation time which was defined as the time from cessation of sedative infusion till extubation was also recorded. Monitoring of heart rate, mean arterial blood pressure, central venous pressure thereafter, was continued for another two hours and was included in the study database. All hemodynamic and sedation data were collected and analyzed by using student t test using the software version 4.57; Abacus Concepts, Berterly, CA.USA.
RESULTS

There was no statistically significant difference between both groups with regards to age, body weight and duration of operation (1).

The mean time of sedation in propofol group was 7.5 ± 1.7 hrs. With only two patients required 6 hrs. sedation only, while in dexmedetomidine group the mean time of sedation was 8 ± 1.7 hrs. with 5 patients required early extubation after 6 hours only. As for the hemodynamic variables, the mean arterial blood pressure as shown in fig. (1) showed no statistical difference between both groups (P = 0.75). No adverse effects recorded in both groups. No patient required addition of inotropes or exhibited a hypertensive or hypotensive response to the loading dose of both drugs. However, with respect to mean heart rate as shown in fig (2), the dexmedetomidine group exhibited a significant lower heart rates compared with propofol group (P = 0.026) but this did not affect mean arterial blood pressure but 4 patients required small dose of atropine 0.4mg especially after loading dose as heart rate dropped (53-54 beat/min), but after all, they recovered rapidly and with adjustment of the infusion rate thereafter, mean heart rate went up to acceptable ranges.

No significant difference were observed with regards to central venous pressure changes as recorded during sedation period, as shown in fig (3).

Recording the depth of sedation using bispectral index score showed that the mean value for propofol group was 56 (44-67) and 49 (42-57) for dexmedetomidine group with non significant difference between both groups (p=0.41) table (1). Although propofol group showed deeper sedation and less communicability with the patients than the other group, yet this was statistically insignificant. On the other hand, propofol group required much more additional doses of analgesics (nalbuphine) 240mg versus only 80mg for the dexmedetomidine group which was statistically significant. (P=0.002). Mechanical ventilation variables, airway and lung dynamics and arterial blood gas analysis were all similar in both groups for the whole period of mechanical ventilation. The mean extubation time as measured from the start of discontinuation of sedation until extubation was 33 min in propofol group versus 32 min in dexmedetomidine group with no statistical difference (p=0.7) while no patient required re-intubation table (1).

DISCUSSION

The present study had shown 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. Both agents produced almost equivalent depth of sedation with non significant statistical difference. In spite of this, dexmedetomidine group patients showed more co-operative behavior of patients with ICU staff and easier weaning and endotracheal extubation. However, extubation time was almost similar with insignificant difference which could be explained by the shorter elimination half-life of propofol which is approximately three times shorter than dexmedetomidine(30-60min vs. 100-150min)(8). The mean bispectral index values of patients of both groups suggested low incidence of recall(9), however, the lower figures seen in dexmedetomidine group implied that any amnesic properties of dexmedetomidine would disappear rapidly after
Table 1: Demographic data and some study parameters of both groups (mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Propofol Group</th>
<th>Dexmedetomidine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ys)</td>
<td>34-62 (47 ±9.8)</td>
<td>33-59 (45 ± 8.6)</td>
</tr>
<tr>
<td>Body (kg)</td>
<td>80-165 (118 ± 24.8)</td>
<td>75-170 (119 ± 23.2)</td>
</tr>
<tr>
<td>Types of Operations</td>
<td>* 4 cases of gastric banding</td>
<td>* 6 cases of gastric banding</td>
</tr>
<tr>
<td></td>
<td>* 3 cases of radical cystectomy</td>
<td>* 2 cases of radical gastrectomy</td>
</tr>
<tr>
<td></td>
<td>* 3 cases of Werteim</td>
<td>* 1 case of Werteim</td>
</tr>
<tr>
<td>Duration of ICU Sedation (hs)</td>
<td>6-11 (7.5± 1.7)</td>
<td>6-12 (8.0±1.7)</td>
</tr>
<tr>
<td>Duration of operations (hs)</td>
<td>5-7 (5.5 ±0.8)</td>
<td>5-7 (5.5±0.8)</td>
</tr>
<tr>
<td>Dose of Nalbuphine (mg)</td>
<td>200-260 (240±12.4)</td>
<td>60-100 (80±6.5)</td>
</tr>
<tr>
<td>Bispectral index score</td>
<td>44-67(56±5.9)</td>
<td>42-57(49±4.9)</td>
</tr>
<tr>
<td>Extubation time(min)</td>
<td>25-39(33±3.9)</td>
<td>25-36(32±3.8)</td>
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P < 0.05 = significant

Fig. 1. Comparison between the two studied groups regarding MAP

Fig. 2. Comparison between the two studied groups regarding heart rate
Discontinuation of the infusion. Also, additional use of narcotic analgesics was more in propofol than in dexmedetomidine patients with high level of significance which again could be attributed to the central analgesic properties of dexmedetomidine. The sedative and analgesic profile in our study were consistent with the study done by Hall et al(10) who stated in that small dose of dexmedetomidine infusion over 12 hours postoperatively was the best sedative and analgesic technique they ever used and they added that amnesia was excellent in their study for all patients as they did not recall. Gertler et al(11) 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. They continued dexmedetomidine infusion for 4 hours post-operatively and recorded excellent amnesic properties as measured by Hewitt questionnaire(12).

An interesting study published by Triltsch et al(13) found that bispectral index-guided sedation in ICU was well maintained by dexmedetomidine infusion. They maintained bispectral index ranges between 60-70 during mechanical ventilation before weaning, 65-90 during weaning and 85-95 postextubation. They concluded that dexmedetomidine reduced additional propofol and morphine requirements and improved hemodynamic stability.

Martin et al(14) confirmed the importance of the analgesic sparing effect of dexmedetomidine with an “easier to manage” judgment of nursing staff when describing dexmedetomidine sedated patients.

Hemodynamically, in the present study, both groups showed similar nonsignificant central venous pressure and equivalent non significant reduction of mean arterial blood pressure with significantly manifested bradycardia in dexmedetomidine group. No adverse cardiovascular events with the loading doses or infusions have been observed.

However, the significantly lower heart rates seen with dexmedetomidine in comparison with propofol patients may be beneficial in lowering the risk of ischemia events during the stressful ICU
stay time and mechanical ventilation periods and particularly during extubation time.

Thomas et al\textsuperscript{(15)} studied the respiratory and cardiovascular effects of dexmedetomidine in ICU patients and found out that all patients showed good cardiovascular stability with no adverse respiratory effects. On the contrary, Venn et al\textsuperscript{(6)} studied the hemodynamic effects of dexmedetomidine in postoperative ICU patients and they found that most patients developed significant hypotension and bradycardia in response to loading dose, this difference from the present study may be attributed to the use of higher loading dose of dexmedetomidine 0.5ug/kg over 5 minutes, while the present study used 0.3ug/kg over 10min. In another study done by Eckerngill et al\textsuperscript{(16)} a statistically significant but clinically unimportant reduction in the mean heart rate and mean systolic blood pressure was observed over the first 6 hours. The authors of the later study came to the conclusion that dexmedetomidine was an effective sedative and analgesic, however, omitting the loading dose avoided undesirable hemodynamic effects without compromising sedation and analgesia.

In a similar study, Rain and Ebert\textsuperscript{(17)} used dexmedetomidine for sedation and compared it with propofol for intraoperative sedation level equivalent to a bispectral index score of 60-70. They found that sedation was achieved more rapidly with propofol but was similar in both groups after 25 minutes after initiation of the infusions. Also, they stated that the previous use of dexmedetomidine resulted in more sedation, lower blood pressure and improved analgesia (less morphine use in recovery). Lastly, they reported a slower onset and offset of sedation with dexmedetomidine compared with propofol which in fact was not recorded in the present study. By comparing the present results with previously done works we concluded that dexmedetomidine is considered an excellent, effective and safe sedative agent to be used regularly in ICU mechanically ventilated, postoperative patients with good cardiovascular safety profile.

REFERENCES