

Dexmedetomidine vs. Propofol for Short-Term Sedation of Postoperative Mechanically Ventilated Patients

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ABSTRACT

Background: Propofol is often used for sedation in the intensive care unit. The aim of this study was to compare the efficacy and endocrine response of propofol vs. the new α_2 -agonist dexmedetomidine for sedation in surgical intensive care patients who need postoperative short-term ventilation.

Methods: Our work is a randomized clinical study conducted on sixty adult patients who required postoperative short term ventilation and sedation. The patients were allocated randomly, to receive IV infusion of either dexmedetomidine 0.2-0.5 $\mu\text{g}/\text{kg}/\text{h}$ or propofol 0.5-1 $\text{mg}/\text{kg}/\text{h}$. Hemodynamic parameters, Ramsay sedation score, extubation time and serum cortisol and interleukin-6 (IL-6) levels were measured.

Results: Ramsay sedation score was 4.1 ± 1 and 4 ± 0.9 for propofol and dexmedetomidine, respectively, ($p=0.59$.) Total fentanyl dose in the propofol group was $75 \pm 15 \mu\text{g}$ compared to $15 \pm 10.5 \mu\text{g}$ in the dexmedetomidine group, ($p=0.0045$). Patients who received dexmedetomidine infusion had significantly lower heart rates compared to patients who received propofol infusion, ($p=0.041$). Pre-infusion serum concentrations of IL-6 were comparable in both groups, while the 24h post-infusion levels were insignificantly decreased in both groups compared to pre-infusion level, ($p=0.36$). There were no intergroup differences in serum cortisol concentrations, ($p=0.231$).

Conclusion: Dexmedetomidine and propofol are safe sedative drugs for postoperative mechanically ventilated patients. Patients were easily aroused to co-operate without showing signs of irritations with less fentanyl analgesia in the dexmedetomidine group. Dexmedetomidine and propofol do not inhibit adrenal function, but they may influence the inflammatory response.

Key Words: *Dexmedetomidine - Propofol - Sedation - Cortisol - IL-6.*

INTRODUCTION

One of the key factors in good patient care is appropriate analgesia and sedation to insure

patient comfort. This is of particular importance in the intensive care unit (ICU) [1].

Intubated mechanically ventilated patients in the surgical ICU require sedation to tolerate the tracheal tube and the ventilator, to suppress cough and prevent respiratory fighting during intensive care procedures such as bronchial suction, physiotherapy and catheter placement. Although opioids can be very useful in the treatment of pain, they alone cannot be appropriate for sedation in critically ill patients [2]. Increasing the degree of sedation in a patient with inadequate pain control is not warranted and similarly, increasing analgesia in an over-anxious patient would not be adequate.

The ideal sedative agent should allow for rapid modification of the sedation level by modifying the dosage (titratable) and should not have depressor effect on the cardiovascular or respiratory systems [2]. It should be cheap and have short duration without cumulative effects, allowing for rapid recovery of effective spontaneous respiration after interruption of its administration in patients undergoing mechanical ventilation [3,4].

Cytokines are important mediators of the immune response. One of these cytokines is IL-6; it has local and systemic effects, which attempt to limit tissue injury, spread of infection and provide a suitable environment for tissue healing and repair [5]. Alterations in pro-inflammatory cytokine production have been implicated in the pathology of systemic inflammatory response syndrome (SIRS) and cancer [6].

Dexmedetomidine is a new, highly selective and potent α_2 -adrenoceptor agonist under investigation as a sedative agent in intensive care unit patients. As well as offering sedation and anxiolysis, α_2 agonists have analgesic qualities and reduce the stress response to surgery and intensive care procedures [7]. At therapeutic doses, dexmedetomidine does not cause any significant respiratory depression [8].

The aim of this study was to evaluate and compare dexmedetomidine-based sedation with the commonly used IV sedative agent in the intensive care unit, namely propofol.

PATIENTS AND METHODS

After approval of the Research Committee at the National Cancer Institute, Cairo University, a randomized control patient-blinded study was conducted on patients admitted postoperatively to the surgical intensive care unit at the National Cancer Institute, Cairo University. Sixty adult patients who were expected to require a minimum of 6-hour postoperative sedation and ventilation after major thoracic, abdominal or pelvic cancer surgeries were included in the study. At the end of surgery, patients were selected randomly using a toss into two equal groups, 30 patients in each group. Exclusion criteria included neurosurgical procedures, known allergy to propofol or dexmedetomidine, known or suspected pregnancy, gross obesity (over 50% above ideal body weight), severe hepatic or renal disease where the neurologic condition was difficult to evaluate, spinal or epidural anesthesia, history of corticosteroid therapy within the last 3 months, or uncontrolled diabetes.

Anesthetic technique prior to entry into the ICU was 5 mg/kg thiopental sodium, 3-4 μ g/kg fentanyl and atracurium 0.5 mg/kg. After endotracheal intubation, maintenance of anesthesia was provided by isoflurane N_2O in O_2 . Additional atracurium was administered as required. At the end of the surgical procedure, neuromuscular blockade was not reversed and artificial ventilation was continued. On arrival to the ICU, patients were immediately artificially ventilated with synchronized intermittent artificial ventilation (SIMV) with pressure support mode. When the patients could open their eyes on command, they were allocated randomly, to

receive IV infusion of either dexmedetomidine (Group-D, n=30), or propofol (Group-P, n=30) whilst being mechanically ventilated. All patients received short acting fentanyl infusion 0.25-0.5 μ g/kg/h. The infusion rate was adjusted by the ICU staff as required by the patient to relieve pain. No muscle relaxants were given during the study period. Dexmedetomidine was supplied in 2-ml ampoules at a concentration of 100 μ g/ml. It was diluted with normal saline to a concentration of 4 μ g/ml. Patients received a loading infusion dose of dexmedetomidine 2.5 μ g/kg/h over 10 minutes followed by maintenance infusion at a rate of 0.2-0.5 μ g/kg/h into a peripheral vein, with the dosage adjusted to achieve the desired level of sedation. On the other hand, propofol was given undiluted as a bolus dose of 1 mg/kg initially, followed by an infusion of 0.5-1 mg/kg/h, with the dosage adjusted to achieve the desired level of sedation. The degree of sedation was measured by ICU residents and recorded hourly using the Ramsay sedation score (RSS) [9] and continuously using the bispectral index (BIS) [10]. The Ramsay sedation score consists of the following six grades (1) Anxious, (2) Cooperative and tranquil, (3) Responding to commands only, (4) Brisk response to light glabellar tap, (5) Sluggish response to light glabellar tap, (6) No response to light glabellar tap. Three levels of sedation were considered: adequate (sedation level was grade 2, 3, 4 or 5), insufficient (sedation level was 1) and excessive (sedation level was grade 6). The overall sedation adequacy was determined according to the cumulative number of hours under each of the three sedation levels defined above.

The dose of both drugs was adjusted by varying the dose by 10% increase or decrease in infusion rate in order to maintain the level of sedation within the range previously considered adequate. The total amount of fentanyl consumption and the quality of sedation were recorded. BIS levels in the range 61-88 were required to maintain a state of sedation. Patients were ventilated mechanically with oxygen-enriched air to attain acceptable blood gases. Registration of total time on mechanical ventilation (hours) was recorded. Continuous oxygen saturation was controlled by a pulse oximeter as well as end-tidal CO_2 pressure. Heart rate (HR), mean arterial blood pressure (MAP) and central venous pressure (CVP) were monitored

continuously and recorded hourly. Ten milliliters of central venous blood samples were obtained into heparinized syringes from all patients immediately on arrival to the ICU and before administration of sedative infusions and 24 hours after commencement of sedative infusions. These samples were used for measurement of cortisol and interleukin-6 (IL-6) level. Samples were centrifuged immediately and serum was stored at 70°C. IL-6 was estimated using Solid phase Sandwich enzyme linked assay (ELISA) (Diaclone-research, France). Cortisol level was estimated using ADVIA Centour cortisol assay (ADVIA, Centour, Ready Pack and ACS1180-Bayer Corporation).

The sedative infusion was discontinued, in preparation for extubation. Extubation was undertaken when there was no evidence of bleeding and the patient was alert, cardiovascularly stable, normothermic and with an arterial oxygen tension ≥ 10 kPa on an inspired oxygen concentration $\leq 35\%$ and had positive end-expiratory pressure < 5 cm H₂O, spontaneous respiration had been established with pressure support < 10 cm H₂O, a tidal volume of > 6 ml/kg and respiratory rate ≥ 10 breaths/min but < 20 breaths/min. Extubation time, i.e. weaning time (the time from cessation of sedative infusion to extubation) was recorded. Cardiovascular and respiratory adverse events were also recorded and treated accordingly (hypotension is defined as a decrease in arterial pressure of $\geq 40\%$ from baseline, bradycardia ≤ 50 beats/min, tachyarrhythmia and a respiratory rate < 8 or > 25 breaths/min) after extubation.

Statistical methods:

Data were analyzed using SPSS statistical package version 11. Student's *t* test was used for inter-group comparison of baseline demographic data. Inter-group comparison and changes with time of plasma interleukin-6 (IL-6) and cortisol were tested using a two-way ANOVA test with repeated measures on one factor. All data were reported as mean \pm standard deviation (SD). *p* value ≤ 0.05 was considered significant.

RESULTS

No intergroup differences were found with respect to demographic data (Table 1). The patients of these surgical procedures were found

to need short term ventilation (< 24 h), either because of intraoperative massive bleeding, prolonged surgery > 6 h in critically cardiac patients, or patients with COPD.

Over the whole study period, the RSS was 4.1 ± 1 for the propofol group (group-P) and 4 ± 0.9 for the dexmedetomidine group (group-D) ($p = 0.59$) and BIS was 64 ± 10 and 60 ± 12 for propofol and dexmedetomidine, respectively ($p = 0.36$). The mean percentage of hours of adequate sedation under ventilator was $92 \pm 1.8\%$ in group-P vs. $93 \pm 1.5\%$ in group-D ($p = 0.23$).

Patients receiving propofol infusions required significantly more fentanyl (75 ± 15 μ g) compared to patients receiving dexmedetomidine (15 ± 10.5 μ g), $p = 0.0045$. Twelve patients in the dexmedetomidine group and thirteen patients in the propofol group received sedation for only 6-8 hours because extubation was clinically indicated. Eighteen patients in the dexmedetomidine group and seventeen in the propofol group received sedation for more than 12 hours, but less than 36 hours.

There were no intergroup statistically significant differences in MAP (Fig. 1, $p = 0.45$). No patient in both groups needed inotropic support. The mean values of HR during sedation with dexmedetomidine were significantly lower compared with the propofol group, but did not need intervention, (Fig. 2, $p = 0.041$). CVP was well maintained in all patients throughout the study period.

Mechanical ventilation variables, oxygen saturation and end-tidal CO₂ were similar in both groups. There were no adverse respiratory events seen in either group-D or group-P. Mean extubation times were comparable in both groups, 30 ± 15 min for group-D vs. 35 ± 12 min for group-P ($p = 0.32$).

Pre-infusion (baseline) levels of serum concentrations of IL-6 were comparable in the two groups (Table 2). Twenty four hours post infusion, IL-6 decreased in both groups, but there were no intergroup statistical significant differences ($p = 0.36$). The reference range for cortisol was 4.3-22.4 μ gm/dL. Pre-infusion and post-infusion concentrations of cortisol were comparable and there were no intergroup significant differences ($p = 0.231$).

Table (1): Demographic data of the patients

	Dexmedetomidine group	Propofol group	<i>p</i> Value
Age (Y)	65±6.5	67±5.7	0.37
Weight (kg)	62±1.5	61±3.7	0.85
<i>Type of surgery:</i>			
Hepatectomy	8	4	
Whipple	7	7	
Radical hystrectomy	3	2	
Oesophagectomy with gastric pull up	10	8	
Total gastrectomy	2	9	
Operative time (h)	5.5±2.1	4.5±3.2	0.1
Intraoperative fentanyl (ug)	500±70	550±90	0.16

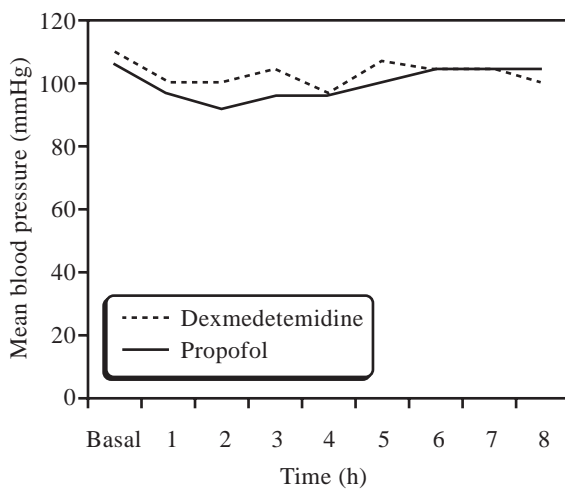


Fig. (1): Mean blood pressure (mmHg) in the dexmedetomidine (D) and propofol groups (P) during the first 8 hours of injection.

DISCUSSION

Dexmedetomidine is a highly selective α_2 agonist with an affinity 8 times that of clonidine for the adrenoceptors (α_2 : α_1 ratio 1600:1) [7]. Propofol is widely used as a sedative drug in the surgical ICU. In-adequate sedative technique may adversely affect morbidity and even mortality in the ICU. In addition, the sedative drug used can modulate the neuroendocrine stress and the inflammatory response to surgery, which is more important in improving recovery [11]. Recent studies suggest that longer term admin-

Table (2): Serum levels of cortisol and IL-6 in the studied groups.

	Dexmedetomidine group	Propofol group	Group <i>p</i> value
<i>Cortisol</i>			
(μ g/dl)			
Pre-infusion	16.1±6	14.3±8	0.23
After infusion	12.6±7	11.9±9	
Time <i>p</i> value	0.25		
<i>IL-6</i>			
(pg/ml)			
Pre-infusion	313±110	314±130	0.48
After infusion	260±100	267±140	
Time <i>p</i> value	0.36		

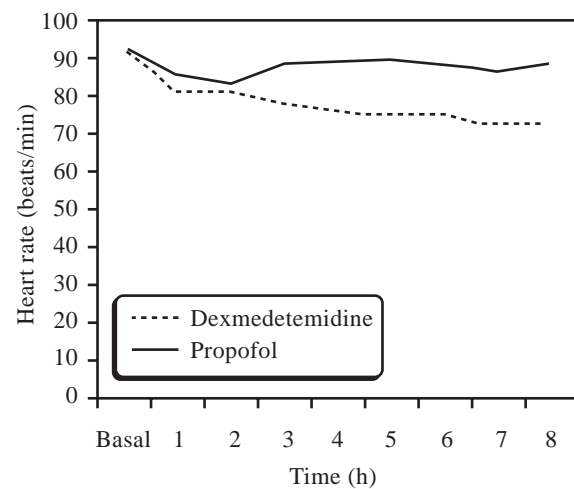


Fig. (2): Mean heart rate (beats/min) in the dexmedetomidine (D) and propofol (P) groups during the first 8 hours of injection.

istration of those drugs might be associated with significant risks and adverse effects [11].

We elected not to mask the tested drug because the physical appearance of propofol (formulated in a white lipid emulsion) is different from dexmedetomidine (clear liquid) and any leakage of solution would unmask the study drug. Also, when necessary to administer bolus infusions for acute agitation, knowledge of the treatment groups would prevent potentially hazardous hemodynamic changes through appropriate care with drug infusion rates.

BIS monitoring of sedation was used in addition to Ramsay scale because it is an objective monitor and does not depend on the evaluating person. The results show that both propofol and dexmedetomidine are effective agents for postoperative sedation in ICU. The BIS values of patients receiving both infusions in this study suggest a low incidence of recall [10]. The extubation times were similar and rapid with the use of both sedative agents. Despite ventilation and intubation, patients sedated with dexmedetomidine could be easily aroused to co-operate without showing irritation. An equivalent depth of sedation between dexmedetomidine and propofol was achieved, with the advantage that the fentanyl requirement was reduced by over 54% in patients who received dexmedetomidine. The hypotension and bradycardia that occurred in the dexmedetomidine group were predictable from the known properties of α_2 agonists, and have been confirmed from previous studies in volunteers [12,13], medical ICU patients [14] and in surgical ICU patients [15]. The numerous adverse cardiovascular events seen previously with the loading infusion of dexmedetomidine [16] were not seen in this study, due to reduction of the loading infusion dose. However, the significantly lower HR seen with the dexmedetomidine group compared with the propofol group may lower the stressful ICU episode, in particular over the extubation periods. Previous studies have shown sustained higher HR, similar to this study, for patients receiving propofol in the ICU [3].

There were no statistical differences between intraoperative fentanyl doses and although fentanyl may attenuate the endocrine response to surgery, [17,18] this only occurs at doses much greater than those used in this study [18].

Our study showed that there were no differences in basal and 24h post-infusion serum cortisol between patients of both groups. Propofol infusions had no significant effects on cortisol level. The same results have been shown previously [4]. These findings indicate that propofol have no significant effects on adrenal steroid-genesis in critically ill patients [4] and our findings imply that dexmedetomidine acts similarly.

IL-6 is the principal cytokine released after surgery, [19] and its circulating concentrations reflect the inflammatory response to surgical

trauma [19]. The similarity of baseline concentrations in both groups indicates that the severity of surgery has been equivalent in both groups. Post-infusion concentrations of IL-6 in both groups indicate that both sedative drugs have insignificant effects on inflammatory response to surgical trauma.

Conclusion: Dexmedetomidine is a safe sedative agent with patients easily aroused to co-operate without showing irritation. Dexmedetomidine significantly reduced the requirement for fentanyl analgesia.

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