Hemodynamic Effects of Propofol Versus Midazolam in Mechanically Ventilated ICU Patients

MAGED ABULMAGD, M.D.; TAMER FAHMY, M.D.; TAREK EL GOHARY, M.D. and MOAEMEN YEHIA, M.Sc.
The Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

Objective: To compare the efficacy, hemodynamic effects, days on mechanical ventilation, ICU length of stay, ICU mortality, and the ICU cost of two commonly sedatives, propofol and midazolam in mechanically ventilated ICU patients.

Design: Randomized prospective study.

Setting: Department of Critical Care Medicine, Cairo University.

Patients: A total of 20 critically ill patients with respiratory failure and expected to require mechanical ventilation for more than 48 hours. Patients were randomly assigned to one of two groups, ten patients will receive intravenous infusion of propofol (group P), and the other group will receive intravenous infusion of midazolam (group M).

Interventions: None.

Measurements and Results: A total of 20 critically-ill patients with respiratory failure, expected to require mechanical ventilation for more than 48 hours were enrolled in our study. Base-line demographic data, Acute Physiology and Chronic Health Evaluation (APACHE IV) score, and the reason for admission to the intensive care unit were recorded for all patients. An intravenous infusion of either propofol or midazolam was administered by a physician-implemented protocol to achieve a target Riker’s Sedation-Agitation Scale [SAS], with a brief daily “wake-up”.

For hemodynamic assessment, a pulmonary artery catheter (PAC) was inserted in all patients. Compared to midazolam, propofol caused a significant reduction in both MAP (89.1 ±5.32 to 54.6±2.72, p<0.0001 vs 69.90±8.44 to 69.10±8.06, p : NS), and SVR (1889.76±990.2 to 1109.46±630.09, p<0.05 Vs 1579.58±598.84 to 1522.96±567.55, p : NS). There was no significant difference between both groups in duration of mechanical ventilation (7.2±5.25 days in Group P versus 6.3±6.11 days in Group M, p : NS). Compared to midazolam, patients on propofol have significantly longer hospital stay. The overall ICU mortality was comparable in both groups (6 in group P Vs 5 in Group M, p: NS).

Conclusions: To achieve a target level of sedation in critically ill ventilated patients, MAP and SVR were significantly depressed with propofol infusion, but not with midazolam. In both groups, there was insignificant difference in days of mechanical ventilation or ICU mortality. Despite the less time for wake up in propofol group, the ICU cost for propofol sedation is significantly higher than midazolam.

Key Words: ICU sedation – Propofol – Midazolam.

Introduction

SEDATION in intensive care unit is part of treatment strategy in critically ill patients. Ideally, sedation in ICU allows for a comfortable and cooperative patient, decreases levels of anxiety and stress, reduces insomnia and the risk of awareness during stressful interventions, and normalizes metabolism and hemodynamics. The ideal hypnotic should have favorable kinetics that enable rapid onset, easy targeting of sedation, and quick offset from sedation. This hypnotic, when having a limited adverse effect profile, is expected to shorten the ICU stay and thus decrease cost, reduce morbidity and even mortality [1].

Propofol and midazolam are IV hypnotics that modulate the gamma amino butyric acid type A receptors [2,3]. Favorable characteristics of propofol are lack of accumulation and a short recovery time, both of which are essential for early neurological examination after discontinuation [4]. Adverse effects of propofol include pain on injection [5], arterial hypotension [6], bradycardia, blood stream infection [7], increase in serum lipids, and excitation...
Hemodynamic Effects of Propofol Versus Midazolam

of CNS up to inducing seizures in susceptible patients [7].

Midazolam is not painful on injection and with no increase risk of bradycardia, blood stream infection, hypertriglyceridemia [8], or excitation of CNS. However drug accumulation may occur particularly in patient with renal failure [9], and in patient receiving antimycotics [16], this may lead to prolonged weaning from mechanical ventilation. Despite the numerous reports that have been published about the relative benefit and side effects of propofol and midazolam in ICU patients, this issue however remains controversial [10,11]. This may be related to difference in study population, varying trial sizes, inconsistent evaluation of the level of sedation, and variability of end points among trials.

Aim of the work:

The aim of the current work was to compare the efficacy, hemodynamic effects, weaning from mechanical ventilation, ICU length of stay, ICU mortality, and lastly the ICU cost of two sedatives—propofol and midazolam—in mechanically ventilated ICU patients.

Patients and Methods

The study included 20 critically-ill patients having respiratory failure and expected to require mechanical ventilation for more than 48 hours, admitted to the critical care department, Cairo University between November 2007 to June 2008. The protocol was approved by the local Ethics Committee and informed consent was obtained from the next of kin of the patients before inclusion in the study. Excluded from the study were terminally-ill patients who are not suspected to survive longer than 1 week, patients transferred from an outside institution where sedatives had already been administered, patient with refractory shock, treated with neuromuscular blockers, or admitted after resuscitation from cardiac arrest.

Patients were randomly assigned to one of two groups; the first group received continuous infusion of propofol (group P), and the second group received continuous infusion of midazolam (group M). For propofol, mean starting dose was 2.58mg/kg/hr with maximum dose reached 3.67mg/kg/hr, while the mean starting dose for midazolam was 0.047mg/kg/hr with a maximum dose reached 0.062mg/kg/hr to achieve target sedation level.

The intravenous infusion of either drugs was administered using a physician-implemented protocol, to achieve a target sedation level, according to the Riker’s Sedation-Agitation Scale [SAS], with brief periods of interruption of infusion for repeated “wake-up” assessment.

Patients were sedated with an initial bolus dose given to reach a targeted sedation level most frequently 3 or 4 SAS [which measures sedation on a scale of 1 (unarousable) to 7 (dangerous agitation)]. Then the physician adjusts the rate of infusion with the aim of achieving the prescribed sedation level. The level of sedation was reassessed every 3-4 hrs and recorded on the ICU nursing chart.

A pulmonary artery catheter was inserted for all patients for monitoring of pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR) and cardiac indices (CI).

Base-line demographic data, Acute Physiology and Chronic Health Evaluation (APACHE IV) score, and the reason for admission to the intensive care unit and cause of respiratory failure were recorded for all patients.

Statistical analysis:

The data were summarized by descriptive statistics [i.e., mean, standard deviation (SD), frequencies]. Mean values and standard deviation were compared using simple t-test (2 variables). Percentages are compared using Chi-square test or Fisher’s exact test. The software used on the analysis is (Version 11; SPSS Institute, Cary, NC, USA, Graph pad instat 2008) and a p-value less than 0.05 is considered to be statistically significant.

Results

Our study included 20 pts who were divided into group P (propofol group, 10 pts) and M (midazolam group, 10 pts). There was no significant difference between the age of both groups. The RSAS was between 3 to 4 and the APACHE score was not significantly different in P-group and M-group. Demographic data is shown in Table (1).

<table>
<thead>
<tr>
<th>Table (1): Demographic data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group P</td>
</tr>
<tr>
<td>Age (yrs) (mean)</td>
</tr>
<tr>
<td>Male / female</td>
</tr>
<tr>
<td>Indication for ventilation:</td>
</tr>
<tr>
<td>Cardiac cause</td>
</tr>
<tr>
<td>Pulmonary cause</td>
</tr>
<tr>
<td>Other causes</td>
</tr>
<tr>
<td>Admission APACHE IV (mean)</td>
</tr>
</tbody>
</table>
Hemodynamic parameters:

a- Blood pressure:

The mean arterial blood pressure before drug administration in P-group (MABP 1) was significantly higher than MABP 1 in M-group (89.1 ± 5.32 vs 69.90 ± 8.44 mmHg, *p*-value 0.0001). MABP2 (MABP after drug administration in P-group) was significantly lower than MABP1 (54.6 ± 2.72 vs 89.1 ± 5.32 mmHg, *p*-value 0.0001).

b- Central venous pressure (CVP):

CVP in P group and M group did not change significantly before & after drug infusion.

c- Pulmonary capillary wedge pressure (PCWP):

PCWP didn’t change significantly before & after drug infusion.

d- Cardiac index (CI):

The two groups showed non significant difference in the cardiac index before & after infusion of propofol & midazolam.

e- Systemic vascular resistance (SVR):

There was a significant decrease in SVR in P-group after drug infusion (1889.76 ± 990.2 to 1109.46 ± 630.09 dyn S/cm$^2$m) and the percent of change was (–41%), *p*-value 0.049). In M-group, there was no significant difference after midazolam infusion, also, there was no significant difference between the two groups in SVR.

In P-group, there were 4 pts on either dobutamine or noradrenaline or both at baseline. After propofol infusion, one more pt needed adding noradrenaline with concurrent dobutamine infusion. In M-group, there was no need to add another yasopressor drug to the concurrent treatment (2 pts were on dobutamine at baseline).

All hemodynamic parameters are shown in Table (2).

Mechanical ventilation duration and hospital stay:

a- Days of mechanical ventilation:

There was no significant difference between the 2 groups as regard duration of mechanical ventilation (7.2 ± 5.25 days in P-group vs 6.3 ± 6.11 days in M-group, *p*-value >0.05).

b- Liberation from mechanical ventilation:

Five out of 10 (50%) in each group were successfully liberated from the ventilator.

c- ICU stay:

Patients of group P stayed significantly longer in the ICU than M-group (22.3 ± 16.59 vs 10.3 ± 6.52 days respectively, *p*-value 0.04).

d- Time to awakening:

After stoppage of infusion, time to awakening was significantly shorter in P-group (33.5 ± 13.75 minutes) vs (91.5 ± 23.22 minutes) in M-group, *p*-value 0.0001).

Mortality:

There was no significantly difference in mortality between the two groups (6/10 died in P-group vs 5/10 in M-group).

Sedation cost and total cost:

The total cost for hospitalization was not statistically different while the sedation cost was significantly higher in P-group.

---

Table (2): Hemodynamic measurements.

<table>
<thead>
<tr>
<th></th>
<th>Group P</th>
<th></th>
<th></th>
<th>Group M</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td><em>p</em>-value</td>
<td>Before</td>
<td>After</td>
<td><em>p</em>-value</td>
</tr>
<tr>
<td>MAP</td>
<td>89.1±5.32</td>
<td>54.6±2.72</td>
<td>0.0001</td>
<td>69.90±8.44</td>
<td>69.10±8.06</td>
<td>NS</td>
</tr>
<tr>
<td>SVR</td>
<td>1889.76±990.2</td>
<td>1109.46±630.09</td>
<td>0.049</td>
<td>1579.58±598.84</td>
<td>1522.96±567.55</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>3.89±1.78</td>
<td>3.63±1.8</td>
<td>NS</td>
<td>3.42±1.27</td>
<td>3.51±1.28</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP</td>
<td>12.1±5.57</td>
<td>11.1±5.55</td>
<td>NS</td>
<td>10.8±2.39</td>
<td>10.5±2.37</td>
<td>NS</td>
</tr>
<tr>
<td>CVP</td>
<td>14.46±6.32</td>
<td>15.33±4.47</td>
<td>NS</td>
<td>10.2±2.39</td>
<td>9.71±5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table (3): Total and sedation cost in both groups.

<table>
<thead>
<tr>
<th></th>
<th>P – group</th>
<th>M – group</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost LE</td>
<td>14901±12904</td>
<td>10021±6252</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation cost LE</td>
<td>588±131</td>
<td>138±47</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
**Discussion**

In our study, propofol has decreased systemic arterial pressure. This decrease in arterial pressure seemed to be caused mainly by a decrease in systemic vascular resistance and not due to a decrease in cardiac output. The effect of propofol on the pulmonary vasculature was relatively less evident than that on the systemic vasculature.

Several studies have evaluated the haemodynamic effects of short-term propofol sedation after cardiac surgery [12,13,14]. In these studies, the effects of propofol have been compared with midazolam in a non-blinded design with no control groups used. In within-groups analyses, a decrease in systemic arterial pressure has been consistently observed with propofol [13,14]. With the decrease in arterial pressure, a significant or non-significant [14] decrease in systemic vascular resistance has been observed. The decrease in cardiac index was not found to be significant [14,15].

Other studies have also demonstrated that anaesthetic doses of propofol decrease systemic arterial pressure mainly by decreasing systemic vascular resistance [16,17]. How-ever, propofol may also have a direct cardiac depressant effect [18,19], although this issue is controversial [20]. In Hammaren et al., study the stroke volume tended to decrease with propofol. Although the decrease in preload of the left ventricle, as indicated by the decrease in pulmonary artery occlusion pressure, may explain the decrease in stroke volume, Hammaren et al. could not exclude a direct depressant effect of propofol on the myocardium [21].

In our study there was a significant decrease in the mean arterial blood pressure in the propofol group after infusion of the drug. Another German study evaluated the effects of both agents on cardiovascular function using a bolus and same dose of infusion for propofol used in our study (2mg/kg/h) and a higher dose for midazolam (0.1mg/kg/h) and despite of that, a significant decrease in blood pressure was particularly observed in patients with masked hypovolaemia, however, this decrease was easily controlled by volume administration [22]. Also in concordance to our study they found no significant difference in heart rate or CVP before and after infusion of both agents.

In our study there was no significant change in pulmonary artery occlusion pressure or central venous pressure. Grounds et al. [21] noticed a decrease in the right ventricle afterload (pulmonary vascular resistance) without changes in the right ventricle preload (right ventricular end-diastolic volume and pressure, and central venous pressure) with propofol; however, right ventricular performance (right ventricular ejection fraction) was not improved. This may reflect a direct cardiac depressant effect of propofol. (was this consistent with our study in the RV function?).

In our study, the time to wake up from sedation with propofol ranged from 21 minutes to 47 minutes after cessation of infusion. While it ranged from 68 to 114 minutes with Midazolam. In other studies the time to wake up from sedation with propofol varied with the depth and duration of sedation and the patient’s body weight. The deeper the sedation (i.e. the lower the sedation score), the longer the time to wake-up (34 minutes for a Ramsay score 3 vs 59 hours for a Ramsay score 5); the longer the period of sedation, the longer the wake-up time; and the more obese the patient, the longer the wake-up time [23].

Interestingly, there was insignificant difference in the days of mechanical ventilation and the average weaning duration from the ventilator between the two agents and this was in agreement with Walder et al., who have systematically reviewed randomized controlled trials comparing midazolam and propofol for sedation in mechanically ventilated, critically ill patients, where data from 27 trials (1624 adults) were analysed [24]. In 8 trials, sedation lasted 54-339h; there was no difference in weaning duration between the two drugs. The efficacy of these two sedative drugs was therefore very similar. In 13 trials (chiefly postoperative), sedation lasted 4 to 35 hours; in 9 of these, average days of mechanical ventilation and weaning time from mechanical ventilation with propofol was less but not statistically significant than that of midazolam [25].

In our study patients of group P had significantly longer ICU stay than Group M. In a Canadian multicenter trial, critically ill patients requiring continuous sedation while receiving mechanical ventilation have been enrolled to determine whether sedation with propofol would lead to shorter times to tracheal extubation and ICU length of stay than sedation with midazolam. Pooled results showed that patients treated with propofol (n=46) were extubated earlier than those treated with midazolam (n=53) (6.7 vs 24.7h, respectively; p<0.05) following discontinuation of the sedation but were not discharged from ICU earlier (94.0 vs 63.7h, respectively; p=0.26). Using a treatment-received analysis, propofol sedation either did not differ from midazolam sedation in time to tracheal extubation or ICU discharge (sedation duration, <24h) or was associated with earlier tracheal extubation but
longer time to ICU discharge (sedation duration, >24h, <72h, or 72h). They have concluded that the use of propofol sedation allowed for more rapid tracheal extubation than when midazolam sedation was employed. This did not result in earlier ICU discharge [26].

Conclusion:
To achieve the target level of sedation from 3 to 4 RSAS in the critically ill patients on mechanical ventilation, MAP and SVR are significantly depressed by propofol infusion and not midazolam. Compared to midazolam, patients on propofol had significantly longer ICU stay with insignificant difference in days of mechanical ventilation or ICU mortality. Despite the less time for wake up in propofol group, the ICU cost for propofol sedation is significantly higher.

References
