Comparison between dexmedetomidine and midazolam for sedation of eclampsia patients in the intensive care unit

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Abstract

Purpose: This study compares the effectiveness of midazolam and dexmedetomidine for the sedation of eclampsia patients admitted to our intensive care unit (ICU).

Patients and Methods: Forty women with eclampsia requiring termination of pregnancy by caesarean delivery were randomized in to 2 groups of 20 to receive either midazolam or dexmedetomidine. The midazolam group received a loading dose of 0.05 mg/kg followed by an infusion of 0.1 mg kg\(^{-1}\) h\(^{-1}\). The dexmedetomidine group loading dose was 1 μg/kg per 20 minutes, followed by continuous infusion at 0.7 μg kg\(^{-1}\) h\(^{-1}\). Heart rate, blood pressure, Ramsey sedation score, antihypertensive need, convulsion fits, and duration in ICU were monitored and recorded all through the ICU stay.

Results: Dexmedetomidine markedly reduced heart rates for the first 24 hours (\(P < .05\)) compared with midazolam, but there were no differences at 48 and 72 hours. Mean arterial blood pressures were similar in the 2 groups (\(P > .05\)), although in the dexmedetomidine group, it was lower at 5, 6, 12, and 24 hours compared with the first 4 hours (\(P < .05\)). Moreover, fewer patients given dexmedetomidine required nitroglycerine and nitroprusside (\(P < .05\)). The duration of ICU stay was less in the dexmedetomidine group, 45.5 hours (range, 15-118 hours), than in the midazolam group, 83 hours (minimum-maximum, 15-312 hours).

Conclusion: Dexmedetomidine sedation in eclampsia patients is effective in reducing the demand for antihypertensive medicine and duration of ICU stay.

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1. Introduction

Preeclampsia is characterized by hypertension diagnosed after 20 weeks gestation plus proteinuria. In severe cases, the diastolic blood pressure is 110 mm Hg or more, there is a persistent proteinuria of 2 or more, and any of the following can be present: headaches, visual disturbances, upper abdominal pain, oliguria, increased serum creatinine, thrombocytopenia, increased liver enzymes, fetal growth retardation, and pulmonary edema. Eclampsia is the new onset of seizures before, during, or after labor, which is not attributable to other causes, in a woman with preeclampsia. Eclampsia, a complication of pregnancy characterized by seizures and accompanied by severe hypertension, brain and lung edema, aspiration pneumonia, and acute renal failure, remains a major cause of maternal morbidity and mortality in both developed and developing countries. Proteinuria and acute respiratory distress syndrome can also follow [1].

The main goals of treatment are to stabilize the patient; control derangements of the cardiovascular, hematological, renal, pulmonary, and central nervous systems; and prevent
potential future problems [2]. It is critical for both mother and baby that new seizures be effectively controlled; they are usually treated with magnesium sulfate, intramuscularly or intravenously, but may still occur, exacerbating maternal morbidity and mortality [1].

Several anticonvulsant drugs have been tried. Midazolam is a fast-acting benzodiazepine with a short elimination half-life; has powerful anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties; and has been used for sedation in the intensive care unit (ICU) for many years. Its use has been proposed for the treatment of eclampsia. Midazolam undergoes extensive oxidation in the liver via the cytochrome P450 enzyme system to form water-soluble hydroxylated metabolites, which are excreted in urine. However, the primary metabolite, namely, 1-hydroxymethylmidazolam, has mild central nervous system depressant activity and may accumulate in the critically ill patient, especially in the case of kidney failure [3-5].

Dexmedetomidine is a centrally acting α2-agonist with sedative and analgesic properties; it is similar to clonidine but has much greater α2 to α1 binding affinity. The sedative properties are facilitated through the locus coeruleus site in the central nervous system, and the analgesic effects may occur via activation of the α2-receptors by accentuating the action of opioids. After extensive metabolism in the liver, dexmedetomidine is eliminated as methyl and glucuronide conjugates, mainly (95%) via renal excretion [6].

Dexmedetomidine used in intensive care as a sedative without respiratory depressive effects has analgesic properties and controls stress, anxiety, and pain [7].

In this clinical study, we compare dexmedetomidine and midazolam for sedation in eclampsia patients with regard to their effectiveness, hemodynamic characteristics, and ICU discharge time.

### 2. Patients and methods

This is a prospective, randomized, and controlled study. After obtaining ethic committee approval from Erciyes University Hospital, patients’ first-degree relatives were informed about the study, and their written consent was taken. Forty patients whose pregnancies were terminated via caesarean delivery because of eclampsia and who needed ventilatory support were included in the present study. All patients who had chronic hypertension; cardiac, neurological, hepatic, renal, or endocrinal disease; or allergic reactions to the medicine used during the treatment or developed the Hemolysis, Elevated Liver Enzymes and Platelets (HELLP) syndrome were excluded from the study.

All patients received MgSO4 2 g/h for 24 hours. Invasive blood pressure, heart rate, oxygen saturation, central venous pressure (Hewlett Packard system no. M1205A), and sedation score were recorded hourly. The patients were randomly divided into 2 groups using coin toss. The group GrM (n = 20) received midazolam immediately after admission. After delivering a loading dose of 100 mg in 100 mL 0.9% NaCl at 0.05 mg/kg, it was continued at 0.1 mg kg⁻¹ h⁻¹. The other group, GrD (n = 20), received dexmedetomidine (Precedex Abbott Labs, North Chicago, Ill) immediately after admission. A dexmedetomidine loading dose was administered at 1 μg/kg per 20 minutes, followed by a continuous infusion at 0.7 μg kg⁻¹ h⁻¹ (400 μg dexmedetomidine is put in 100 mL physiological saline). The sedation and analgesic scores were assessed at 1-hour intervals. Sedation was maintained to meet the Ramsey Sedation Scale 2-3 criteria (Table 1). When sedation became inadequate (Ramsey sedation score <2), propofol was given as a bolus (0.5 mg kg⁻¹) in both groups. Pain of the patients was assessed by Visual Analog Scale, when Visual Analog Scale greater than 4 fentanyl was administered in the dose of 1 μg kg⁻¹.

After admission to the ICU, mean arterial pressure (MAP) was maintained between 100 and 126 mm Hg. If it exceeded this, nitroglycerin (mean dose, 0.5-5 μg kg⁻¹ min⁻¹) was infused. If this was insufficient, it was replaced with sodium nitroprusside. Patients were continuously monitored for convulsions. Thiopental was used as an anticonvulsant in each group.

The weaning process was started if there were no signs of respiratory (PaO₂ >60 mm Hg, fraction of inspired oxygen <0.4, and positive end expiratory pressure (PEEP) ≤5 mm Hg) or hemodynamic impairment and if the patient was able to cough. Extubation was performed if there were no signs of respiratory (tidal volume ≥4 mL/kg, respiratory rate 10 to 25/ min, PaO₂ >95 mm Hg, PacO₂ <50 mm Hg, and fraction of inspired oxygen ≤0.4) or hemodynamic (MAP at 100-126 mm Hg without vasodilators) impairment and if the patient was able to follow commands.

Discharge from the ICU was performed if there were no signs of neurological (cooperative, oriented, and tranquil), respiratory (PaO₂ >69 mm Hg, PacO₂ 35-45 mm Hg, and inspired O₂ <3 L/min), hemodynamic (MAP at 100-126 mm Hg without vasodilators), or surgical impairment.

#### 2.1. Statistical analysis

The power analysis was calculated by the demand of antihypertensive (df = 1, α = .05, power = .88). Statistical analysis was performed using SPSS (version 10.0, SPSS, Inc).

### Table 1 Ramsey sedation scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Nervous, agitated, and/or restless</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented, quite patient</td>
</tr>
<tr>
<td>3</td>
<td>Only obeying the orders</td>
</tr>
<tr>
<td>4</td>
<td>Sleeping, suddenly responding to hitting the glabella, and high voice</td>
</tr>
<tr>
<td>5</td>
<td>Sleeping, slowly responding to hitting the glabella, and high voice</td>
</tr>
<tr>
<td>6</td>
<td>No response to any of these stimulations</td>
</tr>
</tbody>
</table>
Analysis of hemodynamic values, demographic data, operation time, and Acute Physiology and Chronic Health Evaluation (APACHE II) values was carried out using Student t test between the groups and repeated-measure analysis of variance within the groups. Duration of ICU stay was analyzed using Mann-Whitney U test. Requirements for antihypertensive medicine, additional propofol, and analgesics were assessed using χ² test. A P value < .05 was considered statistically significant.

## 3. Results

There were no statistically significant differences between the GrM and GrD with respect to operation time, age, weight, or height of the patients (P > .05; Table 2).

<table>
<thead>
<tr>
<th></th>
<th>GrM (n = 20)</th>
<th>GrD (n = 20)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>26.8 ± 7.1</td>
<td>25.1 ± 4.8</td>
<td>.370</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.1 ± 10.1</td>
<td>68.0 ± 7.5</td>
<td>.462</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.3 ± 2.6</td>
<td>158.0 ± 3.2</td>
<td>.714</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>42.5 ± 8.9</td>
<td>39.7 ± 14.2</td>
<td>.470</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>6.0 ± 2.7</td>
<td>5.1 ± 3.1</td>
<td>.371</td>
</tr>
</tbody>
</table>

Dexmedetomidine reduced heart rates at 1, 2, 3, 4, 5, 6, 12, and 24 hours much more than midazolam did (P < .05; Fig. 1). The difference in heart rates disappeared at 48 and 72 hours.

Mean arterial pressure was similar in the 2 groups initially but was lower in the GrD at 5, 6, 12, and 24 hours (P < .05; Fig. 2).

The need for nitroglycerine infusion differed between groups: 18 (90%) patients in the GrM and 9 (45%) in the GrD (P < .05, Table 3). Similarly, 13 patients in the GrM but only 2 in the GrD needed nitroprusside (P < .05, Table 3). The duration of ICU stay was 83 hours (range, 15-312 hours) in the GrM and 45.5 hours (range, 15-118 hours) in the GrD (P < .05, Table 4). Duration of sedation in the 2 groups is shown in Table 4. The time of the interval (stop sedation-extubation) in the 2 groups was not assessed because in GrD, some patients were extubated during dexmedetomidine sedation. There was no difference between groups regarding propofol or additional analgesic requirements (P > .05, Table 4). No patient had convulsions after commencing either treatment.

## 4. Discussion

An ideal ICU sedation agent should rapidly act and have analgesic and sedative properties to prevent anxiety and unpleasant recall. It should generate only mild cognitive impairment, allowing easy communication between physician and patient. Moreover, it should not accumulate in the body. It should not demonstrate tachyphylaxis or cause withdrawal symptoms when its use is terminated [8]. In our study, dexmedetomidine allowed a shorter ICU stay and reduced antihypertensive use compared with midazolam in eclampsia patients requiring sedation in the ICU.

Benzodiazepines are widely used in the ICU because of their sedative, anxiolytic, anticonvulsant, and amnestic properties, which are mediated by slowing down the central nervous system. Midazolam is a widely used benzodiazepine with rapid onset time in adults (0.5-5 minutes), and its effects after a single dose disappear quickly. However, infusion for more than 1 hour increases its deposition in peripheral tissues and the amount accumulated exceeds the amount metabolized. The effects of midazolam thus continue after the infusion has been stopped, owing to release from peripheral tissues to blood. Moreover, paradoxical reactions to midazolam have been reported.

<table>
<thead>
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<th>GrM (n = 20)</th>
<th>GrD (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients needing nitroglycerine</td>
<td>18</td>
<td>9</td>
<td>.006</td>
</tr>
<tr>
<td>No. of patients needing nitroprusside</td>
<td>13</td>
<td>2</td>
<td>.001</td>
</tr>
</tbody>
</table>
benzodiazepines and hemodynamic changes may be experienced [9]. It is an effective sedative for ICU use [3,4,10-13].

Dexmedetomidine is also used in the ICU and has hypnotic, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the preoperative period. In addition, it possesses selective α2-adrenoceptor agonism, especially for the 2A receptor subtype, and reduces opioid requirements without causing significant respiratory depression. Mild cognitive impairments with integrated anxiolytic and amnesic effects are generated by α2-agonists. Dexmedetomidine sedation allows the physician to wake the patients for easy communication, while generating only mild cognitive impairment.

In addition, it inhibits kainic acid–induced convulsions and has neuroprotective effects in rats in status epilepticus. However, there are no data to show that dexmedetomidine can reduce convulsions in humans [14]. Eser et al [15] showed that dexmedetomidine has a neuroprotective effect on the hippocampus and dentate gyrus of rats after transient global cerebral ischemia-reperfusion injury. Ma et al [16] showed that the neuroprotective effect of dexmedetomidine is mediated by the activation of the α2A-adrenergic receptor subtype.

To the best of our knowledge, dexmedetomidine has not been previously used in eclampsia patients admitted to the ICU, but it is an effective ICU sedative [17-19].

Herr and coworkers [17] compared dexmedetomidine and propofol sedation in the ICU in patients undergoing coronary artery bypass graft surgery. Although they found no significant difference in sedation levels, propofol-sedated patients required 4 times as much morphine while in the ICU. The mean blood pressure slightly increased initially in both groups, then decreased by 12 mm Hg more in propofol-sedated patients compared with dexmedetomidine-sedated patients. Furthermore, ventricular tachycardia occurred in 5% of the propofol-sedated patients but none of the dexmedetomidine-sedated patients.

Ickeringill and coworkers [18] administered dexmedetomidine without a loading dose in 50 patients who had had complex major surgery (n = 9), multiple trauma (n = 8), and cardiac surgery (n = 33). The mean ± SD APACHE II score in their study was 13 ± 5. Dexmedetomidine slightly decreased mean systolic blood pressure and mean heart rate and was an effective sedative and analgesic. The cardiac surgery group benefited the most. They confirmed that dexmedetomidine is effective and practical in a number of different patient groups, suggesting that it can be used effectively in eclampsia patients as well. Venn and colleagues [19] compared dexmedetomidine with propofol in 20 adults expected to require artificial ventilation. Patients sedated with dexmedetomidine required 3 times less analgesia than did those receiving propofol. They also found no differences in arterial pressures between groups, but heart rate was significantly lower in the dexmedetomidine group. They also reported that patients sedated with dexmedetomidine could be easily roused, without showing irritation, and cooperate with procedures such as physiotherapy, despite artificial ventilation.

Bhagwanjee and coworkers [20] studied maternal morbidity and mortality in 105 patients with eclampsia admitted to the ICU. Patients were treated with magnesium sulfate or phenytoin plus a midazolam infusion, and none had seizures after admission to the ICU. The mortality rate was 10.5%. Mean age, gestation, parity, number of preadmission seizures, and duration of stay were similar in survivors and nonsurvivors, although the APACHE II score was significantly greater in nonsurvivors. Respiratory failure was the most important cause of death in this study. In our study, no patient had convulsion or died in either treatment group after admission to the ICU, and only one had a seizure en route to the ICU before receiving any treatment.

There are some limitations of this study. This study is not blinded, and the time of the interval (stop sedation-extubation) in the 2 groups was not assessed because in GrD, some patients were extubated during dexmedetomidine sedation. Another limitation of this study is the inquiry that has not been performed about the cost-effectivity.

We have shown that, compared with midazolam, dexmedetomidine notably reduced heart rate and nitroglycerine infusion demand and decreased the ICU stay in eclampsia patients. We believe that this results from the ability of dexmedetomidine to denervate the sympathetic system. Eclampsia patients present with a hyperdynamic circulation, and large increases in blood pressure and heart rate are often accompanied by serious complications. Our immediate interventions stabilized blood pressure, as indicated by the similarity in blood pressure between the groups. Dexmedetomidine use results in less need for antihypertensives.

In conclusion, the results suggest that dexmedetomidine infusion in eclampsia patients reduces the amount of antihypertensive use and shortens the duration of the ICU stay.

**Table 4** Duration of sedation, stop sedation-discharge from ICU, time spent at ICU, number of patients propofol requirements, and number of patients demanding additional analgesic

<table>
<thead>
<tr>
<th></th>
<th>GrM (n = 20)</th>
<th>GrD (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sedation, median (range) (h)</td>
<td>21 (4-48)</td>
<td>25 (5-74)</td>
<td>.445</td>
</tr>
<tr>
<td>Stop sedation-discharge from ICU, median (range) (h)</td>
<td>52 (6-288)</td>
<td>21 (1-150)</td>
<td>.000</td>
</tr>
<tr>
<td>Time spent in ICU, median (range) (h)</td>
<td>83 (15-312)</td>
<td>45.5 (15-118)</td>
<td>.021</td>
</tr>
<tr>
<td>No. of patients propofol requirements</td>
<td>12</td>
<td>9</td>
<td>.527</td>
</tr>
<tr>
<td>No. of patients demanding additional analgesic</td>
<td>12</td>
<td>8</td>
<td>.343</td>
</tr>
</tbody>
</table>
References