

Comparative evaluation of midazolam, dexmedetomidine, and propofol as Intensive Care Unit sedatives in postoperative electively ventilated eclamptic patients

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Abstract

Background and Aims: Eclampsia is a common hypertensive disorder of pregnancy and treatment often includes termination of pregnancy with elective postoperative mechanical ventilation. The present study was aimed to compare midazolam, propofol, and dexmedetomidine for sedation and antihypertensive requirements of such patients admitted to Intensive Care Unit (ICU) after termination of pregnancy.

Material and Methods: A total of ninety eclamptic patients administered general anesthesia for the termination of pregnancy through cesarean section and who also required postoperative ventilation were taken up for the study and were randomly allocated into three groups. All patients received MgSO₄ (loading dose, 4 g intravenous) following first seizure episode followed by a continuous infusion for next 24 h. Midazolam group (GrM) received 0.05 mg/kg loading dose of midazolam, followed by infusion of 0.05–0.3 mg/kg/h, propofol group (GrP) received 1 mg/kg loading dose of propofol followed by infusion of 2–8 mg/kg/h, and dexmedetomidine group (GrD) received dexmedetomidine loading dose at 1 mcg/kg followed by infusion of 0.2–1.2 mcg/kg/h. Postoperatively, patients were assessed for hemodynamic stability, requirement of antihypertensive and analgesics, duration of sedation and stop sedation-discharge, and total time spent in the ICU.

Results: Mean heart rate and mean arterial pressure recorded at different time intervals were lowest in GrD. Nearly 70% ($n = 21$) patients in the GrM required antihypertensive, 50% ($n = 15$) in GrP, and 36.6% ($n = 11$) in the GrD ($P < 0.05$). Duration of stop sedation-discharge from ICU was least in GrD. A number of patients demanding additional analgesics was also least in GrD.

Conclusion: Sedation with dexmedetomidine produced better hemodynamic stability in eclamptic patients, and there was a significant reduction in requirement of additional analgesics ($P = 0.035$) and antihypertensive ($P = 0.004$). Total duration of ICU stay was also less in this group of patients.

Keywords: Dexmedetomidine, eclampsia, Intensive Care Unit sedation, midazolam, propofol

Introduction

Approximately, five to ten percent of all pregnancies are complicated by hypertension.^[1] The hypertensive disorders of pregnancy are a leading cause of maternal death, with an estimated 10%–15% of direct maternal deaths associated

with preeclampsia and eclampsia.^[2] Eclampsia is defined as the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions before, during, or after labor.^[3] The immediate goals are to stop the convulsions, establish a clear airway, and prevent major complications (e.g., hypoxemia and aspiration). Further management includes antihypertensive therapy, induction or augmentation of labor, and expeditious

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_380_15

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How to cite this article: Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as Intensive Care Unit sedatives in postoperative electively ventilated eclamptic patients. *J Anaesthesiol Clin Pharmacol* 2017;33:331-6.

delivery.^[4] Very often general anesthetic technique is used for cesarean deliveries, and these patients are left intubated and shifted to an Intensive Care Unit (ICU) for blood pressure control, assessment of neurologic recovery, and a controlled wean from assisted ventilation.^[5]

Inadequate sedative techniques may adversely affect such patients resulting in unstable hemodynamics and increased morbidity and mortality. Commonly used sedatives in ICUs include midazolam, propofol, and dexmedetomidine. Midazolam is a fast-acting benzodiazepine and has been used for sedation and as an anticonvulsant including eclampsia in the ICU for many years.^[6] Propofol has been used extensively as an anesthetic agent and as a sedative in the ICU where it produces sedation and hypnosis in a dose-dependent manner. The pharmacokinetic properties of propofol are characterized by a rapid onset and short duration of action.^[7] Dexmedetomidine is a highly selective α -2adrenoceptor agonist. It has sedative-, analgesic-, and opioid-sparing effects and is suitable for short- and long-term sedation in an intensive care setting.^[8] Recent literature has demonstrated improved outcome with dexmedetomidine-based versus benzodiazepine-based sedation therapy in select mechanically ventilated ICU patients.^[9,10]

In this clinical study, we compare these commonly used sedative agents for sedation, antihypertensive, and analgesic dose requirement in postoperative electively ventilated eclamptic patients whose pregnancies were terminated through cesarean section and also with regard to their effectiveness, hemodynamic characteristics, and total ICU stay time.

Material and Methods

After obtaining Institutional Ethics Committee approval (Ref. No. 13/ETH/GMC dated May 4, 2012), a prospective, randomized, observational study was done between 2012 and 2015 in the ICU of a tertiary care maternity hospital on ninety patients whose pregnancy were terminated following eclampsia. A written and informed consent from patient's first-degree relatives was taken for the study. Inclusion criteria included patients delivered through cesarean section following general anesthesia within 24 h of the first seizure episode and who needed postoperative ventilatory support. Patients with a prior history of chronic hypertension; cardiac, hepatic, renal, or endocrinal disease; chronic headache; seizure disorder; or any neurological disorder were excluded from the study. Furthermore, patients having allergic reactions to any medicines used during the treatment or hemolysis, elevated liver enzymes, and low platelet syndrome were also excluded from the study.

All patients received a loading dose of MgSO₄ (4 g intravenous [IV]) following first seizure episode followed by a continuous infusion of 2 g/h for next 24 h. The patients were randomly divided into three groups of thirty each as per computer-generated random number list. The midazolam group (GrM; *n* = 30) received midazolam immediately after admission to ICU in a loading dose of 0.05 mg/kg in 100 ml of isotonic saline, followed by continuous infusion at a rate of 0.05–0.3 mg/kg/h. The second group, dexmedetomidine group (GrD; *n* = 30) received dexmedetomidine in a loading dose of 1 μ g/kg in 100 ml isotonic saline over 20 min, followed by a continuous infusion at 0.2–1.2 μ g/kg/h. The third group, propofol group (GrP; *n* = 30) received propofol in a loading dose of 1 mg/kg, followed by maintenance infusion dose of 2–8 mg/kg/h. Sedation dose of the drugs was adjusted to meet the Ramsay sedation scale of 2–3 [Table 1]. Baseline hemodynamic parameters were comparable between the three groups. Injection morphine 0.1 mg/kg every 6 hourly was given to all three groups as an analgesic. Invasive blood pressure (mean arterial pressure [MAP]), heart rate (HR), and oxygen saturation were recorded at hourly intervals. The sedation and analgesic scores were also assessed at 1 h intervals till the time patients were discharged from ICU. Injection fentanyl was given as a rescue analgesic for pain at a dose of 1 μ g/kg if the pain score was 3 or more on the FACES pain scale (0–5).

After admission to the ICU, MAP was maintained between 90 and 120 mmHg. If it exceeded this, the patient was administered injection labetalol 10 mg IV bolus followed by infusion of 20–80 mg/h. If this was insufficient, infusion of nitroglycerin (NTG) in a dose of 0.5–5 mcg/kg/min was added. Standard criteria were followed for weaning from ventilator, extubation, and discharge from the ICU.

Postoperatively, in the ICU patients were assessed by an independent observer primarily for hemodynamic stability (HR and MAP) at hourly intervals for first 6 h followed by 6, 12, and 24 hourly intervals, thereafter till discharge from ICU. Patients were also assessed for

Table 1: Ramsay scale for the assessment of the level of sedation

Level of activity	Points
Patient anxious, agitated, or restless	1
Patient-cooperative, oriented, and tranquil	2
Patient responding only to verbal commands	3
Patient with brisk response to light glabellar tap or loud auditory stimulus	4
Patient with sluggish response to light glabellar tap or loud auditory stimulus	5
Patient with no response to light glabellar tap or loud auditory stimulus	6

secondary outcomes including requirement of antihypertensive (labetalol and NTG) and analgesics (fentanyl), duration of sedation and stop sedation-discharge from ICU, and total time spent in the ICU.

Statistical analysis

The primary outcome measure was hemodynamic variables (MAP) and total ICU stay. Based on the previous data and with power of study at 80% ($\alpha = 0.05$), a sample size of ninety (30 in each group) was considered adequate. Statistical analysis was done using SPSS for windows, Version 15.0. Chicago, SPSS Inc. software. Data collected were compiled and analyzed using Pearson Chi-square to compare nonparametric data and ANOVA for parametric data. All data were presented as a mean \pm standard deviation, median (interquartile range [IQR]), and number (%) where appropriate. $P < 0.05$ was considered statistically significant.

Results

Out of the total 97 patients enrolled for the study, 7 patients were excluded because of recurrent postoperative convulsions requiring either additional anticonvulsants or neurosurgical intervention [Figure 1]. There were no statistically significant differences between the GrM, GrD, and GrP with respect to operation time, age, and weight of the patients ($P > 0.05$) [Table 2].

Postoperatively, in the ICU, mean HRs were lower in patients receiving dexmedetomidine as compared to propofol and midazolam ($P < 0.05$) [Figure 2]. This difference is HRs among the groups was more significant during the first 12–24 h and later disappeared. Furthermore, among the three groups, GrM had highest HR.

MAP recorded at different time intervals was lower in GrP and lowest in GrD. Furthermore, the decrease in MAP was

more in GrD. The significantly lower mean MAP in the GrD means that dexmedetomidine produced better hemodynamic stability among the three groups [Figure 3].

In our study, 70% ($n = 21$) patients in the GrM required antihypertensive, 50% ($n = 15$) in GrP, and 36.6% ($n = 11$) in the GrD ($P < 0.05$). GrD also had 30% reduction in the dose of antihypertensive, and the use of additional antihypertensive (NTG) was least in GrD followed by GrP [Table 3].

The mean duration of sedation in the three groups was 18 h (GrD), 16.9 h (GrP), and 18.4 h (GrM), and this was statistically insignificant. However, statistically significant differences were noted in the median duration of stop sedation-discharge from ICU. GrD had the least median duration of 16.7 h [IQR: 11.00–24.75], GrP had 23.4 h [IQR: 18.00–33.25], and GrM had the highest median duration of 31.1 h [IQR: 23.25–43.00] This translated directly into total time spent in the ICU with GrD having the least median duration of ICU stay (44.6 h [IQR: 33.50–52.00])

Table 2: Demographic profile of patients in three groups

Parameter	GrM (n=30)	GrD (n=30)	GrP (n=30)	P
Mean age (years)	28.6 \pm 6	27.3 \pm 7.2	27 \pm 6.3	0.273 (NS)
Mean weight (kg)	67.3 \pm 10	65.2 \pm 8.2	65.9 \pm 10.1	0.153 (NS)
Mean duration of surgery (min)	43.1 \pm 8.1	42 \pm 7	44.4 \pm 7.3	0.504 (NS)

NS=Not significant, GrP=Propofol group, GrM=Midazolam group, GrD=Dexmedetomidine group

Table 3: Antihypertensive requirements

Antihypertensive	GrM (n=30)	GrD (n=30)	GrP (n=30)	P
Labetalol	11	15	21	0.004
Nitroglycerin	3	5	10	0.007

GrP=Propofol group, GrM=Midazolam group, GrD=Dexmedetomidine group

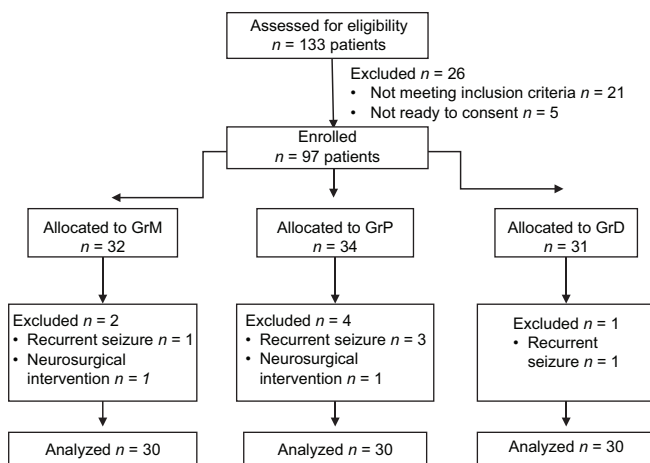


Figure 1: Consort diagram of number of patients assessed done at start of results

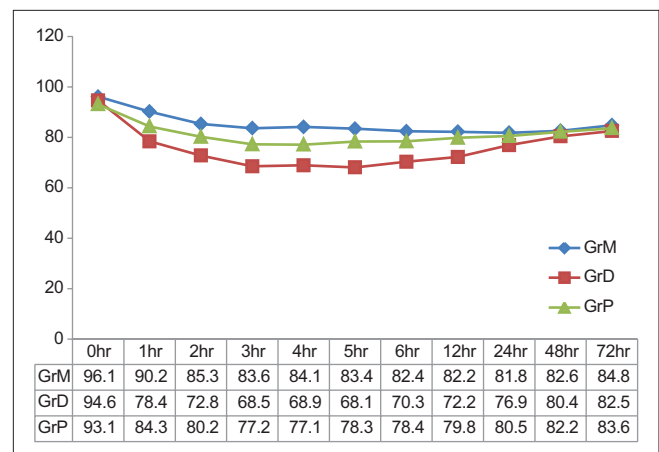


Figure 2: Mean heart rates among variable groups recorded at different time intervals. Mean heart rates recorded postoperatively were lower in patients receiving dexmedetomidine as compared to propofol and midazolam ($P < 0.05$). This difference is heart rates among the groups

followed by GrP (52.5 h [IQR: 39.75–68.00]), whereas GrM had the maximum ICU stay among the three groups (58.8 h [IQR: 41.00–73.25]), and the difference was statistically significant ($P < 0.05$). Furthermore, the number of patients demanding additional analgesics was more in GrM (24) followed by GrP (16) and least in GrD (12) [Table 4 and Figure 4].

Discussion

Sedation of ICU patients is often essential to maximize survival, reduce ICU and hospital stay, and facilitate mechanical ventilation. In this study, dexmedetomidine appeared to be a superior sedative for eclamptic patients not only in terms of better hemodynamic profile but also in terms of less need of additional analgesics, antihypertensives, and also early discharge times once sedation was stopped.

In eclamptic patients admitted to ICU, anxiety, agitation, and restlessness can negatively impact the hemodynamic stability.^[4] Common implicated factors for pathogenesis of seizures in eclamptic patients include cerebral vasospasm,

ischemia, edema, hemorrhage, hypertensive encephalopathy, and disseminated intravascular coagulopathy.^[11] However, the causes are poorly understood, and no single process accounts for the clinical features of eclampsia.^[12]

Magnesium plays a role in almost every physiological system and has been successfully used as an anticonvulsant in eclampsia; its action is secondary to antagonism at N-methyl-D-aspartate (NMDA) receptors.^[13] Marked antiadrenergic and antinociceptive effects are also attributed to magnesium due to antagonism of NMDA and calcium channels in various studies.^[14,15] In the present study, under the highlights of magnesium effects, we aimed to find out a better sedative among propofol, midazolam, and dexmedetomidine in eclamptic patients admitted to ICU for postoperative ventilation.

Midazolam is a widely used benzodiazepine sedative with rapid onset time in adults (0.5–5 min), and its effects after a single dose disappear quickly. It acts through gamma-aminobutyric acid-benzodiazepine receptor complex and undergoes extensive oxidation in the liver through the cytochrome P450 to form water-soluble hydroxylated metabolites, which are excreted in urine.^[6] However, infusion for more than 1 h increases its deposition in peripheral tissues, and effects of midazolam thus continue after the infusion has been stopped, owing to release from peripheral tissues to blood. Moreover, paradoxical reactions to benzodiazepines and hemodynamic changes may be experienced.^[16]

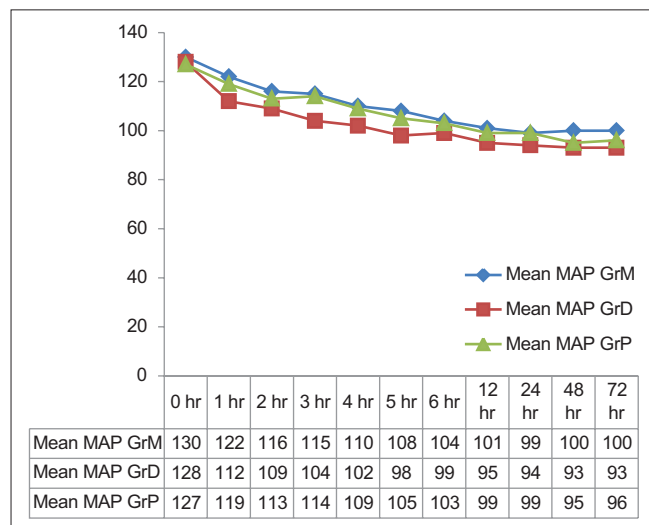


Figure 3: Mean arterial pressure recorded at different time intervals. Mean arterial pressure recorded at different time intervals was lower in propofol group and lowest in dexmedetomidine group. Furthermore, the decrease in mean arterial pressure was more in dexmedetomidine group. The significantly lower mean arterial pressure in the dexmedetomidine group means that dexmedetomidine produced better hemodynamic stability among the three groups

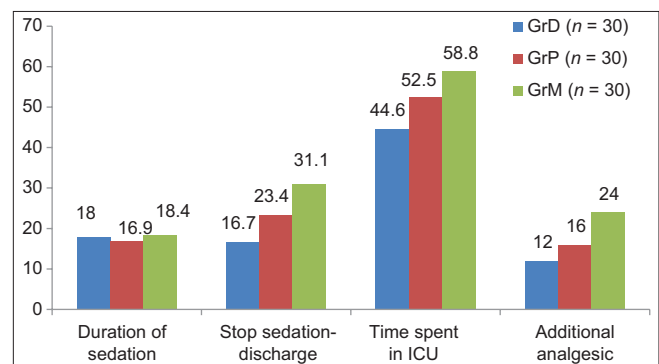


Figure 4: Duration of sedation, stop sedation-discharge from Intensive Care Unit, time spent at Intensive Care Unit, and number of patients demanding additional analgesic

Table 4: Duration of sedation, stop sedation-discharge from Intensive Care Unit, time spent at Intensive Care Unit, and number of patients demanding additional analgesic

Parameter recorded	GrM (n=30)	GrD (n=30)	GrP (n=30)	P
Mean duration of sedation (h)	18 (6-67)	16.9 (5-74)	18.4 (7-91)	0.8203
Stop sedation-discharge from ICU (median range) (h)	16.7 (11-24.75)	23.4 (18-33.25)	31.1 (23.25-43)	0.0029
Time spent in ICU (median range) (h)	44.6 (33.5-52)	52.5 (39.75-68)	58.8 (41-73.25)	0.0142
Number of patients demanding additional analgesic	12	16	24	0.0351

ICU=Intensive Care Unit, GrP=Propofol group, GrM=Midazolam group, GrD=Dexmedetomidine group

The efficacy of propofol in the sedation of adults in the ICU is well established. Because of a rapid distribution and clearance, the duration of action of propofol is short and recovery is rapid. Emergence from sedation is more rapid with propofol than with midazolam, even after long-term administration (>72 h), which enables better control of the depth of sedation in response to titration and more predictable recovery times.^[17] Furthermore, the use of propofol may reduce or eliminate the need for other medications in these patients such as muscle relaxants, antihypertensive, lipid nutritional supplements, and analgesics, thereby simplifying their medication regimens and reducing the overall cost of their care while in the ICU.^[18]

Dexmedetomidine has hypnotic, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses. In addition, it possesses selective α 2A-adrenoceptor agonist and reduces opioid requirements without causing significant respiratory depression.^[19] Basic science models have eluded toward potential neuroprotective effect of dexmedetomidine. Improvement in cerebral oxygen demand during cerebral ischemia, reduction in astrocytic glutamate release, increase in antiapoptotic factors, and blocking of proapoptotic pathways may evoke a neuroprotective effect.^[20,21] Dexmedetomidine sedation allows the physician to quickly wake the patients for easy communication while generating only mild cognitive impairment. Dexmedetomidine offers effective means to acquire desirable sedation and also appears to be superior in terms of better hemodynamic profile, least requirement of analgesics and antihypertensive, and shorter ICU stays.^[22]

Eser *et al.* showed that dexmedetomidine has neuroprotective effects after transient global cerebral ischemia-reperfusion injury and later it was showed that the neuroprotective effect of dexmedetomidine is mediated by the activation of the α 2A-adrenergic receptor subtype.^[23] Herr *et al.* compared propofol and dexmedetomidine sedation in patients undergoing coronary artery bypass graft and found no significant difference in sedation levels; however, propofol-sedated patients required four times more morphine in ICU when compared to GrD.^[24] In our study also, GrP needed a higher number of rescue analgesics. Pandharipande *et al.* compared dexmedetomidine sedation with lorazepam sedation in acute brain dysfunction in mechanically ventilated patients and concluded that dexmedetomidine sedation resulted in more days alive without delirium or coma.^[25]

Venn *et al.* compared dexmedetomidine with propofol in twenty adults requiring artificial ventilation and found that patients sedated with dexmedetomidine required three times less analgesia and had significantly lesser HRs compared to GrP as was the case in our study. They also reported that patients sedated with dexmedetomidine could be easily

aroused, without showing irritation and cooperate better with procedures such as physiotherapy, despite mechanical ventilation.^[26]

Our study is also in concordance with that of Esmoğlu *et al.* who studied forty eclamptic patients in ICU for sedation and observed that dexmedetomidine markedly reduced HRs for the first 24 h compared with midazolam. Mean arterial blood pressures were similar in the two groups although in the GrD, it was lower at 5, 6, 12, and 24 h compared with the first 4 h. Moreover, fewer patients given dexmedetomidine required NTG and nitroprusside. The duration of ICU stay was also less in the GrD, 45.5 h (range, 15–118 h), than in the GrM, 83 h (minimum–maximum, 15–312 h).^[4]

Memis *et al.* in his study on thirty adult patients demonstrated that magnesium sulfate infusion decreases sufentanil infusion requirements in mechanically ventilated patients without causing a significant difference in bispectral index values between the groups.^[15]

Weinbroum *et al.* compared prolonged sedation in critically ill patients with midazolam and propofol and concluded that these drugs were reliable, safe, and controllable for long-term sedation in ICU patients and rapid weaning from mechanical ventilation. Midazolam depressed respiration, allowed better maintenance of sedation, and yielded complete amnesia at a lower cost, whereas propofol caused more cardiovascular depression during induction.^[27]

The limitations of the study were that it was not blinded and total number as well as total duration of preoperative seizures was not taken into account. Furthermore, serum magnesium levels were not monitored. Larger observational studies with individual sedative agents in the backdrop of serum magnesium levels need to be carried out.

Conclusion

We conclude that propofol, midazolam, and dexmedetomidine are all effective means to acquire desirable sedation in electively ventilated patients. However, compared with midazolam and propofol, dexmedetomidine notably reduces HR, MAP, opioid, and antihypertensive requirement in eclamptic patients and decreases the total ICU stay due to its central sympatholytic action.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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