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# Comparison Of Midazolam Propofol And Dexmedetomidine For Sedation And Antihypertensive Requirement Inpost Operative Electively Ventilated Eclamptic Patients In The Intensive Care Unit.

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**ABSTRACT**

**Introduction-** Eclampsia a complication of severe preeclamsia is characterized by new onset of seizures which is not attributable to any other cause in a pregnant female whose fetus has crossed age of viability i.e. 20 wks.

**Objective-** To compare the effectiveness of midazolam, propofol and dexmedetomidine for the sedation of eclampsia patients admitted to our intensive care unit (ICU).

**Material and Methods –** A study of 60 eclamptic patients was taken up who required mechanical ventilation in ICU and were randomly divided into three groups. All patients received MgSO4 2 g/h for 24 hours. GrM group received 0.05mg/kg loading dose followed by infusion of 0.1mg/kg/hr. GrP received propofol loading dose 1mg/kg followed by infusion of 3mg/kg/hr and GrD group received dexmedetomidine at 1mcg/kg over 20 mins followed by infusion 0.7mcg/kg/hr. patients were maintained on Ramsay sedation score of 2-3 and their mean arterial pressure was maintained between 90-130mmhg . If it exceeded the range NTG and SNP were added. Standard criteria were followed for weaning from ventilator.

**Results -** Dexmedetomidine produced better hemodynamic stability in eclamptic patients. There was significant reduction in requirement of additional analgesics ($p< 0.035$) and antihypertensives ($p<0.004$). Duration of ICU stay was less in eclampsia patients ($p<0.0029$) who required dexmedetomedine. We believe that the better results of patient in GrD group was because of ability of dexmedetomidine to denervate sympathetic nervous system.



## INTRODUCTION

Ten percent of all pregnancies are complicated by hypertension. Eclampsia and preeclampsia account for about half of these cases worldwide and remain a major cause of maternal morbidity and mortality in both developed and developing countries. 1Eclampsia, which is considered a complication of severe preeclampsia, is commonly defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia.It typically occurs during or after the 20th week of gestation or in the postpartum period. Nonetheless, eclampsia in the absence of hypertension with proteinuria has been demonstrated.

The main focus of treatment remains to stabilize the patient; control derangements of the cardiovascular, hematological, renal, pulmonary, and central nervous systems; and prevents potential future problems [2]. It is thus life threatening condition for both mother and baby and the new onset seizures should be effectively controlled; they are usually treated with magnesium sulphate, intramuscularly or intravenously, but may still occur, exacerbating maternal morbidity and mortality and for controlling seizures thus several anticonvulsant drugs havebeen tried. [3]

Midazolam is a fast-acting benzodiazepine with a short elimination half-life; has powerful anxiolytic, amnesic, hypnotic, skeletal muscle relaxant properties and has been used for sedation and as an anticonvulsant including eclampsia in the intensive care unit (ICU) for many years.Midazolam undergoes extensive oxidation in the liver via the cytochrome P450enzyme system to form water soluble hydroxylated metabolites, which are excreted in urine.

However, the primary metabolite, namely,1-hydroxy methyl imidazolam has mild central nervous system depressant activityand may accumulate in t

he critically ill patient, especiallyin the case of kidneyfailure [4-5].

Dexmedetomidine is a centrally acting alpha2 agonist with sedative and analgesicproperties that has demonstrated efficacy in managing pain, agitation, and delirium in a variety of critically ill patient populations. Dexmedetomidine has demonstrated the ability to provide a mild to moderate level of sedation indiverse ICU populations compared to conventional sedative regimens. Recent literature has demonstrated improved outcomes with dexmedetomidine based vs. benzodiazepine based sedation therapy in select mechanically ventilated ICU patients. [6,7].

Propofol is a phenolic derivative that is structurally unrelated to other sedative hypnotic agents. It has been used extensively as an anaesthetic agent and as a sedative in the intensive care unit (ICU) where it produces sedation and hypnosis in a dose dependent manner. Propofol also provides control of stress responses and has anticonvulsant and amnesic properties. Importantly, its pharmacokinetic properties are characterised by a rapid onset and short duration of action

Because of the potential for hyperlipidaemia and the development of tolerance to its sedative effects, the usefulness of propofol in long term situations is less well established.[8]

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

**Material and methods:** After obtaining ethics committee approval, and a written and informed consent from patients' first degree relatives,a prospective, randomized controlled study was done in 60 patients whose pregnancies were terminated via caesarean delivery because of eclampsia and who needed ventilatory support. Exclusion criteria included chronic hypertension; cardiac, neurological, hepatic, renal, or endocrinal disease; or allergic reactions to the medicine used during the treatment or Hemolysis, Elevated Liver Enzymes and Platelets (HELLP) syndrome.

All patients received MgSO4 2 g/h for 24 hours. Invasive blood pressure, heart rate, oxygen saturation, central venous pressure and sedation score were recorded hourly. The patients were randomly divided into 3 groups. 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 immediately after admission. A dexmedetomidine loading dose was administered at 1 µ g/kg per 20 minutes, followed by a continuous infusion at 0.7 µ g $kg^{-1}$ $h^{-1}$ (400 µ g dexmedetomidine is put in 100 mL physiological saline). The third group, GrP (n=20) received propofol of loading dose 1mg/kg followed by maintenance infusion dose of 3mg/kg/hr. Fentanyl was given for pain at dose of 1 µgm/kg if score was more than 2 on FACES Scale. The sedation and analgesic scores were assessed at 1-hour intervals. If patient became agitated sedation dose of drugs was increased to meet the RamseySedation Scale 2-3 criteria (Table 1 ).

Table 1 - **Ramsay scale for the assessment of the level of sedation**

| LEVEL OF ACTIVITY | POINTS |
|---|---|
| Patient anxious, agitated or restless | 1 |
| Patient cooperative, orientated and tranquil | 2 |
| Patient responding only to verbal commands | 3 |
| Patient with brisk response to light glabella tap or loud auditory stimulus | 4 |
| Patient with sluggish response to light glabella tap or loud auditory stimulus | 5 |
| Patient with no response to light glabella tap or loud auditory stimulus | 6 |

After admission to the ICU, mean arterial pressure (MAP) was maintained between 90 and 130 mm Hg. If it exceeded this, nitroglycerin (mean dose, 0.5-5 µ g $kg^{-1}$ $min^{-1}$ ) was infused. If this was insufficient, it was replaced with sodium nitroprusside (mean dose 0.5-5 µ g $kg^{-1}$ $min^{-1}$ ).

Standard criteria were followed for weaning from ventilator, extubation and discharge from the ICU.

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

Table 1- DEMOGRAPHIC PROFILE OF PATIENTS IN THREE GROUPS

| PARAMETER | GrD {n= 20} | grP {n = 20} | grM {n = 20} |
|---|---|---|---|
| Age (years) | 27.95 ± 2.46 | 27.51 ± 4.51 | 26.95 ± 4.22 |
| Weight (kgs) | 64.25± 3.19 | 65.00 ± 2.24 | 65.15 ± 2.08 |
| Height (cms) | 155.45 ± 6.16 | 154.65 ± 5.44 | 157.48 ± 3.81 |
| operation (mins) | 39.05 ± 3.05 | 39.35 ± 3.92 | 38.70 ± 4.10 |

Dexmedetomidine reduced heart rates at for the first 24 hours more than propofol and much more than midazolam did ( Fig. 1). The difference in heart rates disappeared at 48 and 72 hours between GrM, GrP andGrD group.

Table 2

| Number of patients requiring antihypertensives | Gr D { n=20} | grP {n=20} | grM {n=20} | P VALUE |
|---|---|---|---|---|
| **NTG** | 8 | 12 | 18 | 0.004 |
| **NITROPRUSIDE** | 3 | 5 | 14 | 0.007 |

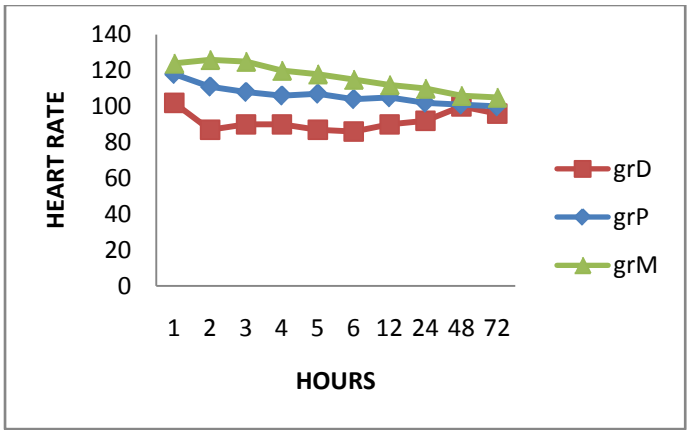


Figure 1

Mean arterial pressure was similar in the 3 groups(GrD, GrP and GrM) at 1, 2, 3 hrs but was lower in GrP and lowest in GrD at 6, 12, and 24 hours.

Decrease in mean arterial pressure was more in GrD than G rP group.

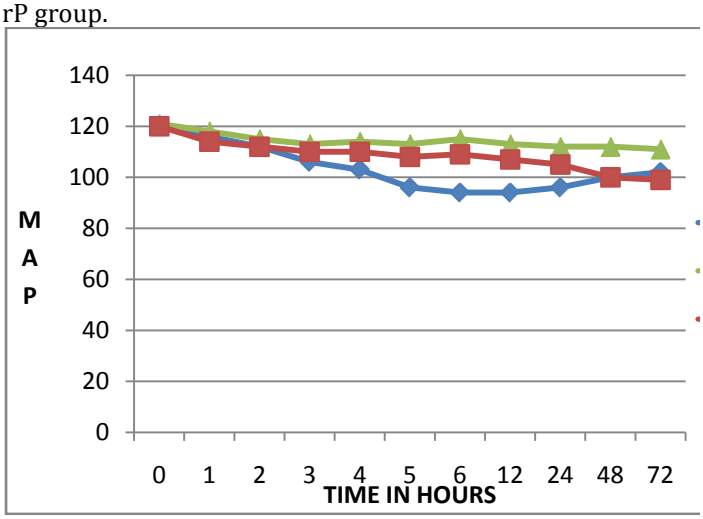


**Figure 2**

**In our study 90% patients in the GrM, required antihyp ertensives, 60% in GrP and 40% in the GrD .**

**Discussion**

Anxiety, agitation and restless movements can negatively i mpact the hemodynamic stability of eclampsia patients in intensive ca re units. Sedation is often required to reduce hemodynamic instability, anxiety and agitation and prevention of further seizures in ICU patients.

Midazolam is an effective sedative for ICU use. It 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 amou nt accumulated exceeds the amount metabolized. The effects of midazolam thus continue after the infusion has been stopped, owing to release from perip heral tissues to blood.

Moreover, paradoxical reactions to benzodiazepines and he modynamic changes may be experienced [9].

Dexmedetomidine is used in the ICU and has hypnotic, anal gesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses. In addition, it possesses selective α 2-adrenoceptor agonism, especially for the 2A receptor subtype, and reduces opioid requirements withou t causing significant respiratory depression. Dexmedetomdine is primarily meta bolized in the liver by glucuronidation with small amount hydroxylated by the cyt ochrome P-450 (CYP-450) enzyme system via the 2A6 pathway.Basic science mo dels have eluded towards at potential neuroprotective effect of dexm edetomidine through several mechanisms. Improvement in cerebral oxygen dem and during cerebral ischemia, reduction in astrocytic glutamate release, increas e in anti-apoptoticfactors, and blocking of pro apopotic pathways m ay evoke a neuroprotective effect [11, 12].

Dexmedetomidine sedation allows the physician to quickly wake the patients for easy communication, while generating only mild cognitive i mpairment.

Propofol has a rapid onset and offset of sedation even after prolonged administration, thus allowing for greater control over the le vel of sedation and more rapid weaning from mechanical ventilation. In additio n, long-term administration of propofol does not appear to be associated with the development of tolerance, addiction, or withdrawal followi ng discontinuation.

Propofol suppresses cellular oxygen consumption and carb on dioxide production without increasing anaerobic metabolism. Final ly, the use of propofol may reduce or eliminate the need for other medications in t hese patients such as muscle relaxants, antihypertensives, lipid nutritional suppl ements, and analgesics, thereby simplifying their medication regimens and reducin g the overall cost of their care while in the ICU. [14]

Table 3 Duration of sedation, stop sedation-discharge from ICU, time spent at ICU and number of patients demanding additional analgesic.

| | GrD (n = 20) | GrP (n = 20) | GrM (n = 20) | P val ue |
|---|---|---|---|---|
| Duration of sedation, average (hrs) | 22 [4-75] | 19.5 [5-79] | 22 [5 -96] | 0.820 4 |
| Stop sedation-discharge from ICU, (median range) (h) | 18.5[3-159] | 26 [4-190] | 34.5 [4-275] | 0.002 9 |
| Time spent in ICU (median range) (h) | 42.5[14-234] | 50 [14-269] | 56.5[9-371] | 0.141 0 |
| No. of patients demanding additional analgesic | 8 | 11 | 16 | 0.035 |

Aliye Esmaoglu MD and coworkers studied 40 eclamptic patients in ICU and compared the effectiveness of midazolam and dexmedetomidine for the sedation. They

observed that dexmedetomidine markedly reduced heart rates for the first 24 hours compared withmidazolam, but there were no differences at 48 and 72 hours. Mean arterial blood pressures were similar in the 2 groups, although in the dexmedetomidine group, it was lower at 5, 6, 12, and 24 hours compared with

the first 4 hours . Moreover, fewer patients given dexmedetomidine required nitroglycerine and nitroprusside. 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). A. Weinbroum, P. Halpern compared prolonged sedation incritically ill patients with midazolam and propofol and concluded that these drugs were reliable, safe, and controllable for longterm 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, while propofol caused more cardiovascular depression during induction. In our study, 3 patients had convulsion after admission to t he ICU and required

anticonvulsants to control seizure even after effective contr ol of MAP, 2 patients had cerebral edema and thus these 5 patients were excluded from study.

The limitation of our study was that this study is not blinded.

We conclude that, compared with midazolam and propofol, dexmedetomidine notably reduces heart rate, MAP and nitroglycerine infusion demand and decreases the ICU stay in eclampsia patients due to its central sympatholytic action.

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