A STUDY OF EFFICACY OF DEXMEDETOMIDINE AND MIDAZOLAM FOR SEDATION OF ECLAMPTIC PATIENTS ON MECHANICAL VENTILATION IN ICU

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ABSTRACT

BACKGROUND

It remains a challenge to provide optimal sedation for eclamptic patients on mechanical ventilation in ICU, who are often irritable. Traditionally, Midazolam, a fast-acting benzodiazepine, has been the most commonly administered sedative drug for ICU patients worldwide. Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, is a newer sedative used for ICU sedation having better haemodynamic stability and no respiratory depressant effect.

Aim- To compare efficacy of dexmedetomidine and midazolam for sedation of eclamptic patients on mechanical ventilation in ICU.

MATERIALS AND METHODS

In a prospective study, 100 eclamptic patients aged more than 18 years who required mechanical ventilation in intensive care unit (ICU) after lower segment caesarean section (LSCS) were divided equally into two groups to receive either midazolam (Group I) or dexmedetomidine (Group II). Vital parameters, level of sedation (Ramsay sedation Score 1-6), any side effects were observed and compared.

RESULTS

Both groups showed decrease in heart rate (HR) and blood pressure (SBP, DBP, MAP) at all-time intervals, but the decrease was statistically significant ($p < 0.005$) in Group II at most time intervals. Both the groups maintained predominantly stable haemodynamics at all times. The Ramsay Sedation Score was also comparable and it maintained at a mean score of 2-3 at most time intervals in both groups. The incidence of bradycardia and hypotension was significantly higher in group II as compared to group I.

CONCLUSION

Dexmedetomidine provided an effective alternative to midazolam in producing and maintaining controlled (RSS 2-3) short-term sedation in mechanically ventilated eclampsia patients and stable haemodynamics.

KEYWORDS

ICU Sedation, Dexmedetomidine, Midazolam, Eclampsia.

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BACKGROUND

Preeclampsia is a multisystem, hypertensive disorder which complicates up to 8% pregnancies,(1) out of which around 25% advance into eclampsia. Eclamptic patients often land up in Intensive Care Unit (ICU) due to complications or for further postoperative care and frequently need mechanical ventilation. Mechanical ventilation is often associated with patient agitation and reduced tolerance hence requiring sedation to alleviate discomfort and improve patient-ventilator synchrony,(2) and also to facilitate nursing care and improve outcome. It is quite a challenge for optimum care of eclamptic patients in ICU who are usually irritable. Various agents are being used for ICU sedation, such as propofol, midazolam, fentanyl and lately dexmedetomidine. Traditionally, Midazolam has been the most commonly administered sedative drug for ICU patients worldwide.(3) Midazolam is a fast-acting benzodiazepine that rapidly penetrates the central nervous system to produce an onset of sedation in 2 to 2.5 minutes.(4) All benzodiazepines reliably cause amnesia, but have no analgesic activity (hence often combined with fentanyl), and produce dose-dependent respiratory depression which is enhanced in combination with opioids. Hence, long-term or high dosage of midazolam in the critically ill patients may lead to oversedation; prolonged mechanical ventilation and longer ICU stay. Dexmedetomidine is a newer sedative used for ICU sedation and has better haemodynamic stability and minimal respiratory depressant effect.(5) Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist. In contrast to other sedative hypnotic agents, dexmedetomidine also has adequate analgesic effect and may induce a sedative state

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similar to physiologic sleep by acting on α_2 receptors in the locus coeruleus.[6] Various studies regarding the efficacy of midazolam and dexmedetomidine for sedation of critically ill patients in ICU have been done globally.[3,7] The studies comparing efficacy of midazolam and dexmedetomidine for sedation in eclamptic patients requiring mechanical ventilation in ICU are minimal.[7]

The aim of this clinical study was to compare the efficacy of dexmedetomidine and midazolam for sedation of eclamptic patients on mechanical ventilation in ICU so that a near ideal sedative agent for eclamptic patients could be determined.

MATERIALS AND METHODS

The present prospective study comprising of 100 eclamptic pregnant women more than 18 years of age undergoing Lower Segment Caesarean Section for termination of pregnancy under general anaesthesia and requiring postoperative mechanical ventilation in ICU at Nehru Hospital, BRD medical college, Gorakhpur was planned. The study period was of one year from September 2014 to August 2015. After the approval of the institutional ethical committee, an informed written consent was taken from all patients' first degree relatives. 100 postoperative patients (LSCS for termination of pregnancy under GA) were selected and distributed randomly into two groups of 50 each (By paper chits prepared in a box) who were sedated either by IV midazolam or dexmedetomidine immediately after admission in the ICU.

The exclusion criteria were patients with baseline HR< 60 bpm, those with hypovolaemia and SBP < 90 mm of Hg, those with Mobitz type 2 and 3rd degree heart block, those with pre-existing comorbidities like cardiac, hepatic, pulmonary, neurological, endocrine or renal diseases, patients with past history of chronic hypertension, those developing Haemolysis, Elevated Liver enzymes and low platelets (HELLP syndrome), having allergy to the study drugs, history of drug abuse, use of antipsychotic or sedative medications. Group I received loading dose of 0.05 mg/kg of midazolam over 10 minutes followed by maintenance dose of 0.1 mg/kg/hour (50 mg of midazolam made to 50 mL with 0.9% NaCl and connected to syringe infusion pump was used). Group II received loading dose of 1 µg/kg of dexmedetomidine over 10 minutes followed by maintenance dose of 0.5 µg/kg/hour (200 µg of dexmedetomidine made to 50 mL with 0.9% NaCl and connected to syringe infusion pump was used). The drug combinations were prepared by an anaesthesiologist not involved in patient monitoring and followup. Vital parameters - Invasive blood pressure (IBP), oxygen saturation (SpO_2), heart rate (HR) and electrocardiography (ECG) of all patients were monitored in the ICU. All patients received $MgSO_4$ 2 g every 4th hourly for 24 hours and rest of the treatment was as per our standard ICU protocol. The Ramsay Sedation Score was assessed hourly with target sedation of 2-3. Visual analogue scale (VAS 0 - 10) was assessed hourly and every patient received injection fentanyl IV 1 µg/kg if VAS >4. Patients with mean arterial pressure (MAP) > 130 mmHg were administered Inj. Labetalol 20 mg bolus as antihypertensive and if response was inadequate it was repeated as per guidelines. Patients were continuously observed for any episode of convulsion and were treated with injection thiopentone. Side effects like hypotension if systolic blood pressure (SBP<90 mmHg), hypertension if mean arterial pressure (MAP>130 mmHg), tachycardia if HR>100 bpm, bradycardia if HR<60 bpm and level 4 sedation were observed and treated in both groups. All parameters and observations were recorded by two anaesthesiologists on rotation basis not involved in preparation of the study drugs. The mode of mechanical ventilation was synchronised intermittent mandatory ventilation (SIMV) and pressure support (PS) in all patients and gradual weaning and extubation was done as per our standard ICU guidelines.

Statistical Analysis

The sample size was calculated considering power of test as 80%, confidence interval of 95%, ratio of sample size (between group II and group I) as one. For this study, it was expected that the difference observed in mean between two groups was ten. SPSS version 21 was used to perform statistical analysis. The data were expressed in mean ± standard deviation (Range). Statistical analysis was done using student t test, paired for intragroup and unpaired for intergroup comparisons. A value of $p<0.05$ was considered to be statistically significant while $p<0.001$ was considered highly statistically significant.

RESULTS

Hundred patients were enrolled in the study and all completed the study. The demographic data in both the groups were statistically insignificant (Table 1). The difference in mean Ramsay Sedation Scores were statistically insignificant in both groups from 2nd to 24 hours. Haemodynamically, there was decrease in pulse rate in both the groups at all-time intervals and this decrease was significant in group II at 8th, 12th, and 24th hour (p value 0.002) in comparison to group I (Table 3). The drop in mean systolic blood pressure (and mean arterial blood pressure) was statistically significant in group II at 1st hour (p value 0.0041) and remained highly significant at 2nd to 24th hour (p value <0.0001) (Table 4 and table 6 respectively). Similarly, the drop in mean diastolic blood pressure in group II was significant at 1st and 2nd hour and it became highly significant (p value <0.0001) from 4th to 24th hour (Table 5). There were 10 patients each of bradycardia and hypotension in group II.

No. of Patients 50 each		
	Group I	Group II
Mean Age (Years)	20.90 ± 2.06	20.94 ± 2.12
Weight (Kg)	52.08 ± 3.96	53.60 ± 2.88
Height (cm)	160.12 ± 3.54	162.24 ± 2.62

Table 1. Showing Patient Characteristics in Both Groups

Time	Group I	Group II	t' Value	p' Value
Pre-drug	1 ± 0	1±0		
1 hr.	1.98 ± 0.31	2.26 ± 0.43	3.73	0.0003**
2 hr.	2.16 ± 0.36	2.2 ± 0.40	0.52	0.60
4 hr.	2.18 ± 0.38	2.24 ± 0.42	0.74	0.45
8 hr.	2.48 ± 0.49	2.52 ± 0.49	0.40	0.68
12 hr.	2.6 ± 0.49	2.64 ± 0.48	0.41	0.67
24 hr.	2.08 ± 0.27	2.18 ± 0.38	1.51	0.1

Table 2. Comparison of Ramsay Sedation Score in Both Groups

p>0.05 = insignificant, p<0.05 = significant*, p<0.001 = highly significant **

Time	Mean PR/minute		t Value	p Value
	Group I	Group II		
Pre-drug	118.69 ± 14.36	121.02 ± 22.02	0.62	0.532
1 hr.	111.65 ± 15.40	110.89 ± 17.84	0.22	0.821
2 hr.	106.21 ± 15.41	101.55 ± 18.23	1.38	0.17
4 hr.	101.38 ± 14.73	95.11 ± 19.61	1.80	0.073
8 hr.	95.49 ± 16.49	84.44 ± 19.53	3.05	0.002*
12 hr.	90.45 ± 15.67	78.79 ± 14.69	3.83	0.002*
24 hr.	89.21 ± 14.20	77.15 ± 12.05	4.57	<0.0001**

Table 3. Statistical Analysis of Mean PR per minute in Both Groups

p>0.05 = insignificant, p<0.05 = significant*, p<0.001 = highly significant **

Time	Mean SBP		t Value	p Value
	Group I	Group II		
Pre-drug	151.57 ± 18.10	147.76 ± 16.83	1.08	0.278
1 hr.	144.76 ± 18.96	134.32 ± 16.47	2.93	0.0041*
2 hr.	140.50 ± 17.98	123.30 ± 18.58	4.70	<0.0001**
4 hr.	137.19 ± 18.55	111.31 ± 15.91	7.48	<0.0001**
8 hr.	130.68 ± 23.98	109.05 ± 15.48	5.35	<0.0001**
12 hr.	129.14 ± 16.19	109.22 ± 12.69	6.84	<0.0001**
24 hr.	127.48 ± 20.94	109.58 ± 11.07	5.34	<0.0001**

Table 4. Comparison of Mean SBP in Both Groups

p>0.05= insignificant, p<0.05 = significant*, p<0.001 = highly significant **

Time	Mean DBP		t' Value	p' Value
	Group I	Group II		
Pre-drug	93.80 ± 12.07	91.72 ± 11.81	0.87	0.3851
1 hr.	90.16 ± 14.41	83.89 ± 10.53	2.48	0.0147*
2 hr.	85.50 ± 12.50	77.68 ± 11.94	3.19	0.0019*
4 hr.	83.54 ± 13.34	74.06 ± 12.11	3.72	0.0003*
8 hr.	85.80 ± 13.99	74.94 ± 13.09	4.26	<0.0001**
12 hr.	82.94 ± 10.24	72.19 ± 9.71	5.38	<0.0001**
24 hr.	82.85 ± 11.37	71.60 ± 9.98	5.25	<0.0001**

Table 5. Comparison of Mean DBP in Both Groups

p>0.05 = insignificant, p<0.05 = significant*, p<0.001 = highly significant **

Time	Mean MAP		t' Value	p' Value
	Group I	Group II		
Pre-drug	114.91 ± 12.29	111.60 ± 10.59	1.44	0.152
1 hr.	110.87 ± 14.45	102.40 ± 10.71	3.32	0.0012
2 hr.	106.23 ± 11.03	94.19 ± 12.15	5.18	<0.0001**
4 hr.	104.92 ± 12.45	88.34 ± 11.79	6.83	<0.0001**
8 hr.	102.41 ± 14.21	88.16 ± 13.36	5.16	<0.0001**
12 hr.	101.40 ± 11.81	86.60 ± 9.36	6.94	<0.0001**
24 hr.	100.37 ± 9.60	87.52 ± 14.76	5.16	<0.0001**

Table 6. Comparison of Mean MAP in Both Groups

p>0.05 = insignificant, p<0.05 = significant*, p<0.001 = highly significant **

Side-Effects	Group I	Group II
Bradycardia	1	10
Hypotension	0	10
Level 4 sedation	0	0

Table 7. Table Showing Side-effects among Two Drugs used

DISCUSSION

The eclamptic patients often need to be mechanically ventilated in the ICU postoperatively after LSCS. Sedation in ICU is of paramount importance in such patients. The goals and standards for analgesia cum sedation of mechanically ventilated ICU patients have undergone considerable changes in the past few years. While excessively deep levels of sedation resulted in increased morbidity due to prolongation of mechanical ventilation and ICU stay, on the other hand inadequate sedation increased the risk of accidental extubation and other adverse events. The goal of sedation in ICU in present scenario is to have a calm, but arousable patient, with stable haemodynamics. Midazolam continues to be the most commonly administered sedative drug for ICU patients worldwide, including our hospital. On the other hand, dexmedetomidine is a newer, effective and safe sedative agent finding its way into the ICU.

In our study, the study groups were comparable in all patient characteristics (Table 1). On comparison of Ramsay Sedation Score, both Group I and group II had mean Ramsay Sedation Score of 1 ± 0 before starting the study drug and was maintained at a mean score of 2 at most times in both groups. On statistical evaluation, it was found that the p value was highly significant at 1st hour but by 2nd to 24th hour it was not significant (p value >0.05), meaning that both group I and group II are comparable in sedation levels (Table 2).

Riker et al (2009), Jacob et al (2012), Adams et al (2013), S. Gupta et al (2015) observed no statistically significant difference between dexmedetomidine and midazolam regarding levels of sedation with the two study drugs.[3,8,9,10]

The pulse rate decreased in both the groups at all-time intervals and this decrease in group II at 8th, 12th, and 24th hour was significant (p value 0.002) in comparison to group I (Table 3). Esmaoglu et al (2009) observed that dexmedetomidine markedly reduced the heart rates in the first 24 hours (P<0.05) compared to midazolam.[7] S Gupta, et al (2015) observed that the fall in heart rate in dexmedetomidine group was not significant in first 15 hours but by 16th hour it became significant till 24th hour. They had observed a 28% reduction in pulse rate from the baseline in dexmedetomidine group whereas 7% reduction was seen in midazolam group. In our study, we observed 29.48% reduction in pulse rate in group I and 43.87% reduction in group II.[10] This could be due to the fact that our patients were eclamptic and hence high intracranial tension (ICT) lead to accentuated decrease in heart rate. There was decrease in mean systolic blood pressure in both the two groups, but it was more pronounced in group II and was statistically significant at 1st hour (p value 0.0041) and remained highly significant at 2nd to 24th hour (p value <0.0001) (Table 4). There was a decrease in mean diastolic blood pressure in both groups but more decrease was seen in group II and was significant at 1st and 2nd hour but by 4th to 24th hour it became highly significant (p value <0.0001) (Table 5). There was reduction in mean arterial blood pressure in both groups but more decrease in blood pressure was seen in group II. And the decrease in MAP was significant in 1st hour (p value 0.0012) and remained highly significant by 2nd to 24th hour (p value <0.0001) (Table 6). Venn et al (1999) observed that 18 of the 66 patients receiving dexmedetomidine experienced significant hypotension (Mean arterial pressure <60 mmHg or >30% fall from pre-infusion values).[11] A randomised

controlled trial by Jakob et al in 2012 observed that dexmedetomidine group had more decrease in blood pressure (26%) as compared to midazolam group (11.6%).[8]

Comparing the side-effects of the two drugs administered, it was observed that 1 patient (2%) in group I had arrhythmic events while group II had none. Bradycardia (HR<60) was observed in 1 patient (2%) in group I whereas group II had 10 patients experiencing bradycardia (20%). Finally, hypotension (Systolic BP<90 mmHg) was not noted in group I, but was observed in 10 patients (20%) among group II patients (Table 7).

A study by Riker et al (2009) observed that dexmedetomidine treated patients were more likely to develop bradycardia i.e. 42.2% versus 18.8% as compared to midazolam.[3]

Similar results were observed by Prasad et al (2012) who compared dexmedetomidine with fentanyl for postoperative sedation in cardiac surgical patients and observed that the frequency of bradycardia in dexmedetomidine group was significantly higher.[12]

A meta-analysis by Jen A. Tan et al observed that dexmedetomidine was associated with increased risk of bradycardia and hypotension.[6]

It was observed that 3 patients (6%) in group I needed antihypertensive drug (IV labetalol) while it was not required in group II. Esmaoglu et al in 2009 observed that in patients who were given dexmedetomidine only few required nitroglycerin and nitroprusside as compared to midazolam.[7]

It was observed that 1 patient (2%) of group II had convulsion episode whereas it was not observed among group I patients.

Comparing the ICU stay in hours in both group I and group II, it was observed that group I had mean duration of 39 hours whereas that of group II was 38.48 hours and were almost comparable.

Also a study by Stephen M Jacob et al (2012) observed that length of ICU stay was similar in both dexmedetomidine and midazolam groups.[8]

In this study, we found that dexmedetomidine is as effective as midazolam for producing and maintaining adequate short-term sedation of mechanically ventilated eclampsia patients and also has good haemodynamic control.

Limitations of the Study

The study included a small number of participants. Secondly, there was use of magnesium sulfate liberally in the study patients which can also cause sedation along with hypotension. Thirdly, only mean duration of ICU stay was observed but extubation time was not included in the study.

CONCLUSION

In this study, we found that dexmedetomidine is as effective as midazolam for producing and maintaining adequate short-term sedation of mechanically ventilated eclampsia patients and also has good haemodynamic control. The risk of bradycardia and hypotension although higher than traditional sedatives, it may not increase length of hospital stay. Thus, dexmedetomidine could be a safe and efficacious sedative agent in eclamptic patients in ICU.

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