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Original Article

Anaesthesia Section

Safety and Efficacy of Ketamine-Dexmedetomidine versus Ketamine-Propofol Combination for Short-term Sedation in Postoperative Obstetric Patients on Mechanical Ventilation: A Randomised Clinical Trial

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ABSTRACT

Introduction: Prolonged mechanical ventilation in postoperative obstetric patients is an important cause of morbidity and mortality. Choosing intravenous sedation for these patients is challenging, as many of these drugs have unique benefits and adverse effects.There are several options are available like benzodiazepines, propofol, alfa-2 agonist, opioids and ketamine. Usually, a combination of sedatives are used to avoid dose dependent adverse effects.

Aim: To evaluate the combination of Ketamine-Dexmedetomidine (KD) and ketamine-propofol for sedation in mechanically ventilated obstetric patients to compare haemodynamic changes. Secondary objectives to assess adverse effects if any, additional opioid (fentanyl) requirement and total length of intensive care unit stay.

Materials and Methods: This randomised clinical study was conducted at King George's Medical University, Lucknow, Uttar Pradesh, India, from May 2018 to August 2019. Total 67 obstetric patients, between 18-45 years of age, requiring postoperative ventilatory support, were included in the study. For sedation, 33 patient received ketamine-dexmedetomidine (group I) combination and 34 patients received ketamine-propofol (group II) combination upto 12 hours of ventilatory support. Target of sedation was to obtain Ramsay sedation scoring between 3-4. Mean Arterial Pressure (MAP) was measured at 0.5 hour, one hour, two hours, four hours, and at every two hourly till 12 hours. Pain was assessed using adult non verbal pain score. Adverse effects (tachyarrhythmia, agitation and hypersalivation) were noted. Total length of Intensive Care Unit (ICU) stay was also recorded.

Results: Age of patients enrolled in the study ranged from 20 to 37 years, the mean age being 27.09±4.61 years. At baseline mean arterial pressure of patients of group I (103.82±19.26 mmHg) was higher than that of group II (96.74±13.49 mmHg) (p-value=0.085). For the rest of the periods of observation, from 0.5 hour to 14 hour, the MAP of group I remained higher as compared to group II. On intragroup comparison, group II had more fluctuation in MAP than group I. Additional requirement of fentanyl was significantly high in Group II, as compared to group I (32.4% vs 12.1%). Mean duration of ICU stay was higher in group II, as compared to group I (30.44±7.26 hours vs 22.91±4.03 hours).

Conclusion: Ketamine-dexmedetomidine is a better combination for sedation in postoperated obstetric patients on mechanical ventilation than ketamine-propofol as it provides stable haemodynamics, significantly lesser opioid requirement and total length of ICU stay.

Keywords: Haemodynamics, Intensive care unit stay, Postoperative ventilation, Sedation

INTRODUCTION

Pregnancy is a biological phase in a woman's life which is associated with unique maternal pathophysiological changes. However, these changes may compel the patients, especially the postoperative obstetric patients, to land up on mechanical ventilatory support. The important pathophysiological changes may lead to morbidity associated with pregnancy and delivery which may result in mortality [1]. To avoid mortality related to such complications, the postoperative patients are put on mechanical ventilation for gradual, uneventful recovery. However, prolonged mechanical ventilation is per se one of the most important causes of morbidity and mortality. Therefore, it is important to select an appropriate sedative which decreases pain and anxiety, decreases cardiac instability favours early extubation, promotes early mobilisation and rapid hospital discharge [2].

There are several options available in Intensive Care Unit (ICU) for sedation like propofol, ketamine, dexmedetomidine etc. Propofolis a sedative agent commonly used for short term sedation in mechanically ventilated patients. Its main advantages include rapid induction and recovery and antiemetic effects. Its main disadvantages are dose-dependent hypotension, bradycardia, and respiratory depression [3]. In the presence of opioids, respiratory depression is more prominent [4].

Ketamine is a phencyclidine non barbiturate derivative that binds with N-methyl-D-aspartate receptor (NMDA) and sigma opioid receptors. It produces dissociative anaesthesia, analgesia, and amnesia without any respiratory or cardiovascular depression. Ketamine preserves haemodynamic instability due to prevention ofendothelial nitric oxide production [5].Major disadvantage with ketamine are tachycardia, hypertension, salivation, and emergence phenomena.

Dexmedetomidine is a highly specific alpha-2 (α2) adrenoreceptor agonist. It does not depress respiratory drive. Therefore, intravenous sedation with dexmedetomidine preserves normal course of ventilator weaning and extubation [6]. Sedation with dexmedetomidineresembles normal physiological sleep and allows easy arousal [7]. It also has analgesic effect [8]. Dexmedetomidine prevents tachycardia,

hypertension, salivation, and emergence phenomena. Major adverse effects of dexmedetomidine are bradycardia and hypotension.

A combination of ketamine and propofol brings about sedation with lower doses of each drug, resulting favourable recovery time profiles [9]. In the same way using Ketamine-Dexmedetomidine (KD) combination is also useful. The haemodynamic response and psychomimetic effects produced by ketamine can beadequately antagonise by dexmedetomidine [10]. On the other hand, bradycardia and hypotension reported with dexmedetomidine can be prevented by ketamine [11].

In this study, combination of KD and ketamine-propofol were used to compare haemodynamic stability among postoperative obstetric patients on mechanical ventilation.Secondary objectives were to find any adverse effects, additional opioid requirementand length of ICU stay.

MATERIALS AND METHODS

This randomised clinical study was conducted in Department of Anesthesiology at King George's Medical University, Lucknow, Uttar Pradesh, India, from May 2018 to August 2019, after obtaining the approval of the Institutional Ethics Committee (ECR/262/Inst/UP/2013/RR-16).

Sample size calculation: Sample size was calculated on the basis of variation in doses of fentanyl in the study groups, using the formula:

$$n=\frac{(z_\alpha+z_\beta)^2(\sigma_1^2+\sigma_2^2)}{d^2}$$

Where, σ_1=20.43, σ_2=51.2. The SD's of doses of fentanyl in the two study groups (according to the reference paper Mohamed M et al.,) [15].

d=mean (σ_1, σ_2) the minimum mean difference considered to be clinically significant.

Type I error α=5% corresponding to 95% confidence level

Type II error β=10% for detecting results with 90% power of study

So, the required sample size (N), was 32 in each group.

Inclusion criteria: Total 67 postoperative obstetric patients on mechanical ventilation, between 18-45 years of age, were included for the study.

Exclusion criteria: Patients with head injury, hepatic or renal failure, patient on vasopressors or inotropes, patients with A-V block on Electrocardiogram (ECG) or those allergic to the drugs under study were excluded from the study.

A CONSORT flow chart for this randomised clinical study is presented in [Table/Fig-1].

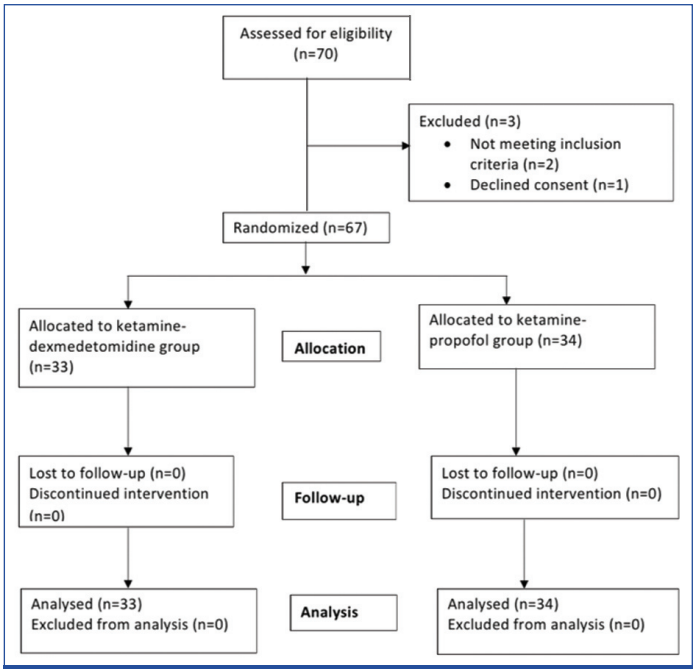
Study Procedure

All the 67 patients were put on Pressure Regulated Volume Control (PRVC) mode of mechanical ventilation. Target minute volume was set at 6-8 mL/kg of ideal body weight. All these patients were sedated using ketamine 1 mg/kg intravenous (i.v) bolus, followed by 0.25 mg/kg/h infusion combined with either dexmedetomidine or propofol to maintain Ramsay sedation score 3-4 during assisted ventilation.

Based on simple random sampling,

- Group I received ketamine+dexmedetomidine (1.0 µg/kg over 20 minutes and then 0.2-0.7 µg/kg/h).
- Group II received ketamine+propofol (1 mg/kg bolus followed by 25-50 µg/kg/min) [15].

Haemodynamic parameters like heart rate, mean arterial pressure, and electrocardiographic changes were measured at 0.5 hour, one hour, two hours, four hours, and at every two hour interval till 14 hours. Hypersalivation or agitation, if present in any patient, was noted. Pain was assessed hourly using adult non verbal pain score (total score-10) [12]. Patients having pain score more than 5 on hourly assessment, were supplemented withstat dose of inj. fentanyl (1 µg/kg) intravenously. Number of patients requiring fentanyl were counted in both the group.The total length of ICU stay was measured precisely.



[Table/Fig-1]: CONSORT diagram.

STATISTICAL ANALYSIS

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. All parametric values are represented in number (%), and mean±SD. To test the significance of two means the student's t-test was used. The p-value <0.05 was considered significant.

RESULTS

Age of patients enrolled in the study ranged from 20 to 37 years, the mean age being 27.09±4.61 years. Difference in mean age of patients of group I (27.09±4.61 years) and group II (27.03±3.61 years) was not significant statistically [Table/Fig-2].

Variables	Group I (N=33)	Group II (N=34)	p-value (t-value)
Age (years) Mean±SD	27.09±4.61	27.03±3.61	0.952 (0.061)
ASA II	14 (42.4%)	21 (61.8%)	0.113
ASA III	19 (57.6%)	13 (38.2%)	

[Table/Fig-2]: Inter-group comparison of age (in years) and American Society of Anesthesiologists (ASA) grading.

Proportion of American Society of Anesthesiologists (ASA) grade III patients was higher in group I (57.6%) while proportion of ASA grade II patients was higher in group II (61.8%), but this difference was not found to be significant statistically [Table/Fig-2].

Majority of the patients of both the groups achieved Ramsay sedation score 3 (69.7% and 55.9%). Score of 4 was achieved by higher proportion in group II compared to group I (35.3% vs 21.2%), rest of the patients of both the groups achieved sedation score of 2 (9.1% and 8.8%). Difference in sedation scores of both the groups was not found to be significant [Table/Fig-3].

Ramsay sedation score	Group I (n,%)	Group II (n,%)	Total (n,%)
Ramsay 2	3 (9.1)	3 (8.8)	6 (9)
Ramsay 3	23 (69.7)	19 (55.9)	42 (62.7)
Ramsay 4	7 (21.2)	12 (35.3)	19 (28.3)

[Table/Fig-3]: Inter-group comparison of Ramsay Sedation Score. Z=1.071; p-value=0.284 (Mann-Whitney U test)

At baseline mean arterial pressure of patients of group I (103.82±19.26 mmHg) was higher than that of group II (96.74±13.49 mmHg)

(p-value=0.085). For the rest of the periods of observation, from 0.5 hour to 14 hour, the MAP of group I remained higher as compared to group II. In group I, a subsequent decline in baseline MAP was observed at 0.5 hour to 14 hour, minimum change was observed at 0.5 hour (6.36%) followed by at one hour (11.56%) while maximum change was observed at 14 hour (40.79%). In group I changes in baseline MAP were statistically significant at all the periods of observation, except at 14 hour. Range of change in baseline MAP among patients of group I was 6.36% to 40.79%.

In group II also, a subsequent decline in baseline MAP was observed during 0.5 hour to six hour, and thereafter during 8 hour to 14 hour. Minimum change in baseline MAP was observed at 0.5 hour (7.42%), followed by at one hour (10.95%), while maximum change was observed at 14 hour (31.18%) followed by at 12 hour (30.26%). In group II changes in baseline MAP were statistically significant at all the periods of observation. Range of change in baseline MAP among patients of group II was 7.42% to 31.18% [Table/Fig-4].

Time interval (hours)	Group I Mean±SD	Group II Mean±SD	Student's t-test	
			t-value	p-value
Baseline	103.82±19.26	96.74±13.49	1.748	0.085
0.5 h	97.21±15.07	89.56±10.49	2.418	**0.018**
1 h	91.82±15	86.15±9.64	1.847	0.069
1.5 h	88.21±12.88	82.82±11.45	1.811	0.075
2 h	83.06±11.63	80.85±8.76	0.880	0.382
4 h	81.82±10.44	76.88±8.20	2.156	**0.035**
6 h	81.26±10.24	75.33±6.95	2.579	**0.013**
8 h	82.69±11.07	76.46±6.91	2.195	**0.034**
10 h	85.25±9.54	75.89±7.51	2.702	**0.012**
12 h	79.25±10.84	71.83±7.51	1.541	0.146
14 h	82±9.90	74.50±10.72	0.823	0.457

[Table/Fig-4]: Inter-group comparison of mean arterial pressure at different time intervals.
p-value <0.05 was considered significant

Proportion of patients of group II was higher as compared to group I in whom adverse effects like tachyarrythmia (5.9% vs 0.0%), hypersalivation (23.5% vs 12.1%), and agitation (35.3% vs 18.2%) were observed, but none of the differences were found to be significant statistically. Additional fentanyl was required in significantly higher proportion of patients of group II as compared to group I (32.4% vs 12.1%) [Table/Fig-5].

Complications	Total	Group I (n,%)	Group II (n,%)	Significance of difference	
				χ^2	p-value
Tachyarrhythmia	2	0	2 (5.9)	2.001	0.157
Hypersalivation	12	4 (12.1)	8 (23.5)	1.482	0.223
Agitation	18	6 (18.2)	12 (35.3)	2.496	0.114
Patients requiring inj. Fentanyl for pain relief (non verbal pain score >5)	15	4 (12.1)	11 (32.4)	3.945	**0.047**

[Table/Fig-5]: Inter-group comparison of adverse effects and additional fentanyl requirement (N=67).
p-value <0.05 was considered significant

Range of duration of ICU stay of group I was 18-34 hours while that of group II was 18-46 hours. Mean duration of ICU stay of patients of group II (30.44±7.26 hours) was found to be significantly higher than that of group I (22.91±4.03 hours) [Table/Fig-6].

Duration	Group I Mean±SD	Group II Mean±SD	Student's t-test	
			t-value	p-value
ICU stay (Range: 18-46 h)	22.91±4.03 (18-34 h)	30.44±7.26 (18-46 h)	-5.228	**<0.001**

[Table/Fig-6]: Inter-group comparison of duration of ICU stay.
p-value <0.05 was considered significant

DISCUSSION

Critically ill mothers, who have been operated under general anaesthesia, mostly need intensive care and ventilatorysupport postoperatively. An ideal sedative agent plays a vital role in the recovery of the postoperative obstetric patients. So, the selection of sedative should be such that it leads tohaemodynamic stability, analgesic effect,lesser adverse effects, early extubation and shorter stay in ICU.

Shurtleff V et al., observed that patients receiving ketamine experienced more days without delirium than patients who received non ketamine sedation [13]. However, ketamine has sympathomimetic effects like tachycardia and hypertension, hypersalivation which compels it to be combined with other sedatives which can counterbalance its side-effects. Hamimy W et al., concluded that ketamine-propofol combination may provide adequate and safe short term sedation (less than 24 h) for critically ill patients in the intensive care units, with rapid recovery and no clinically significant complication [14]. Mogahd MM et al., showed that ketamine at dose of 1 mg/kg i.v. bolus followed by 0.25 mg/kg/hr infusion, when combined with propofol at the dose of 1 mg/kg bolus followed by 25-50 mcg/kg/min or dexmedetomidine at the dose of 1 mcg/kg over 20 min followed by 0.2-0.7 mcg/kg/hr leads to less complications, early extubation and more pain relief [15]. They concluded that combination is better option for sedation, early weaning, early ambulation in postoperativeobstetric patients on mechanical ventilation.

In the present study, a total 67 postoperative obstetric patients, admitted in ICU for mechanical ventilation, were included and divided into two groups to receive combination of KD and ketamine-propofol. On analysis, it was found that ketamine could be combined with dexmedetomidine for sedation while counteracting each other's side-effects. Similarly, ketamine and propofol can be combined for sedation while nullifying each other's undesirable effects.

Fall in mean blood pressure from baseline was significant in both the group at all intervals. KD group had higher mean blood pressure value on follow-up but this was found to be non significant on inter-group comparison. KD group had more haemodynamic stability. This result was similar to the study by Gupta B et al.,who compared the sedo-analgesic effects of dexmedetomidine (group DEX) and KD (group KD) in electively mechanically ventilated patients in surgical ICU [16]. They found that group DEX experienced brief episode of hypotension and bradycardia but group KD were haemodynamically stable. In this regard, the study done by Mogahd MM et al., who compared group KD and group Ketamine-propofol for sedation and analgesia in patients after coronary artery bypass surgery, found that there was insignificant difference between both the groups as regards haemodynamic stability [15].

Majority of the patients of KD and Ketamine-propofol achieved Ramsay sedation score 3 (69.7% and 55.9%). However, Ketamine-propofol patients were more sedated than KD group but it was found to be statistically insignificant (p-value=0.284).

It was found that ketamine-propofol group required additional fentanyl doses in significantly higher (p-value=0.047) doses than group I (32.4% vs 12.1%). Mogahd MM et al., also found that KD showed significant decrease in fentanyl consumption as compared to ketamine-propofol [15]. Herr DL et al., compared dexmedetomidine based versus propofol based sedation regimens and found that propofol group patients required 4 times total dose of morphine than dexmedetomidine group, proving that dexmedetomidine is better analgesic and sedative causing early recovery than propofol [17].

The index study, also found that the mean duration of ICU stay of patients of ketamine-propofol (30.44±7.26 hr) was found to be significantly very high (p-value <0.001) than that of ketamine-dexmedetomidine (22.91±4.03 hr Dasta JF et al., concluded that continuous sedation with dexmedetomidine tend to significantly

reduced mechanical ventilation duration and total length of ICU stay in comparison to midazolam infusion for intensive care unit sedation [18]. Curtis JA et al., also found that postoperative cardiac surgery patients receiving dexmedetomidine-based sedation were extubated earlier and spent lesser days in ICU than patients receiving propofol-based sedation [19].

Limitation(s)

It was a single-centered study. Some organ dysfunction scoring system {like Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA)} should be applied before and during ICU admission which is lacking in the present study. Further multicentered, larger sample size studies are required.

CONCLUSION(S)

Ketamine and dexmedetomidine combination provides better haemodynamic stability, lesser adverse effects (tachyarrhythmia,hypersalivation, agitation), less fentanyl dose required, lesser stay in ICU, as compared to ketamine and propofol combination. Authors conclude that KD combination is better than ketamine-propofol combination in postoperated obstetric patients on mechanical ventilation in ICU.

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