DEXMEDETOMIDINE ALONE OR WITH KETAMINE IN ADDITION TO ROUTINE FENTANYL ADMINISTRATION IN POST CARDIAC SURGERY PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: To compare the effects of dexmedetomidine alone (DA) with dexmedetomidine plus ketamine (KD) combination in addition to routine fentanyl administration in post-cardiac surgery patients

Methodology: The trial was conducted at the Department of Anaesthesia and Critical Care, Chaudhary Pervaiz Elahi Institute of Cardiology Multan, from July 2020 to December 2020. A total of 40 patients planned for elective coronary artery bypass grafting (CABG) were randomized by lottery method for dexmedetomidine alone (Group DA, n=20) or dexmedetomidine plus Ketamine (Group KD, n=20) to maintain Ramsay sedation score ≥4 during assisted ventilation. All patients received fentanyl for postoperative analgesia. The mean arterial blood pressure, heart rate, sedation score, pain score, and mean extubation time were compared between two groups and analyzed by using SPSS version 23.

Results: Total fentanyl dose was 45.65 ± 8.23 µg in group KD and 146.01 ± 14.18 µg in group DA (p <0.001). The time of weaning was 344.65 ± 43.89 minutes and 446.60 ± 73.75 minutes in groups KD and DA, respectively (p <0.001). The time of Extubation was 389.90 ± 35.89 minutes and 535.30 ± 36.25 minutes in groups KD and DA, respectively (p <0.001). The ICU stay, heart rate, mean arterial pressure, Ramsay score, and non-verbal Pain score was comparable in both study groups (p>0.05).

Conclusion: Utilizing Ketamine plus dexmedetomidine for sedation post-Coronary Artery Bypass Graft (CABG) procedure gave a brief term of mechanical ventilation and early extubation with less fentanyl requirement than dexmedetomidine alone. Hemodynamic stability was present in both groups.

Keywords: Cardiac Surgery; Dexmedetomidine; Extubation; Hemodynamics; Ketamine; Fentanyl.

INTRODUCTION

Post-cardiac surgery complications influence morbidity and mortality among patients undergoing cardiac procedures. Patients undergoing cardiac surgeries need careful perioperative management to evade unwanted outcomes. Tachycardia is known to be a major cause of post coronary artery bypass graft (CABG) myocardial ischemia but can be managed with sedation and analgesia.[1]

Dexmedetomidine (DMM) is a highly specific α-2-adrenoreceptor agonist.[2] Sedative effects of DMM are better when compared to midazolam but in terms of respiratory and hemodynamic aspects, DMM is more effective than midazolam. DMM is not reported to suppress respiratory drive or reduce arterial oxygen saturation, that is why IV continuous sedation with DMM is not found to adversely affect ventilator weaning or extubation.[2] DMM does not produce unique EEG patterns of sleep resembling normal physiological sleep allowing convenient arousal.[3] Due to all these benefits, DMM is an established 1st line option for cooperative sedation management in the ICU.[4]

Ketamine is known to be a phencyclidine non-barbiturate derivate. Ketamine binds to N-methyl-d-aspartate and Σ opioid receptors producing dissociative anesthetic, analgesic, and amnesic effects while no major respiratory or cardiovascular suppression occurs with the use of ketamine. Ketamine obstructs endothelial nitric oxide synthesis that leads to positive inotropic actions as well as vasoconstriction which in turn preserves hemodynamic stability.[5]

Researchers have found that DMM efficiently and

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safely reduces ketamine-influenced hemodynamic pressor response and psychomimetic effect.[6] DMM is also anticipated to help in preventing tachycardia, hypertension, salivation, and the emergence effect linked with ketamine. On the other hand, ketamine might also help in preventing bradycardia and hypotension linked with DMM as has been reported in the past.[7] A scarcity of data exists comparing a combination of ketamine and DMM versus DMM alone so the present study was planned to compare the effects of DMM alone with DMM plus ketamine combination in addition to routine fentanyl administration in post-cardiac surgery patients

METHODOLOGY

This prospective randomized controlled trial was done at the anesthesia and critical care department of Chaudhary Pervaiz Elahi Institute of Cardiology, Multan Pakistan, from July 2020 to December 2020. Approval from the Institutional Ethical Committee was taken (CPEIC 153). This trial was also registered in the clinical trial registry (No: NCT05218161). Informed consent was sought from all patients.

A total of 40 hemodynamically stable patients having a normal or moderate impairment of left ventricular functioning (ejection fraction more than 40%) and who had elective CABG surgery adopting high-dose opioid anesthesia on mechanical ventilation were included and groups were made on randomized lottery method as explained in Figure 1. Pregnant women or those patients with neurological disorders, hepatic or renal impairment, or intraoperative hemodynamic instability were not excluded. Patients using vasopressors or inotropes were also excluded. The sample size calculation was done using a study by Mogahd et al.[8]

In all patients, sedation was done adopting DMM 1 µg per kg IV bolus, followed by 0.25 µg per kg per hour infusion with a combination of either ketamine or alone aiming for the attainment of Ramsay sedation score ≥4 during assisted ventilation. Group DMM alone (DA) received DMM alone as 1 µg per kg bolus that was followed by 0.3-0.7 µg per kg per min. Group DMM plus ketamine (KD) were given ketamine plus DMM 1.0 µg per kg over 20 min and then 0.2–0.7 µg per kg per hour. Ten percent variability in heart rate, blood pressure and mean arterial pressure from baseline was termed normal. Assessment of sedation was graded as per the Ramsay sedation scale.[8] Fentanyl was used as analgesia in all cases starting at 1 µg per kg per h infusion which was adjusted as per the adult nonverbal pain score.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for data analysis. Numeric data were shown in mean and standard deviation (SD). Categorical variables were represented as frequency and percentage. The Chi-square test was employed for the comparison of the 2 groups considering $p \leq 0.05$ as significant.

RESULTS

There were 11 (55.0%) male and 9 (45.0%) female in group KD, whereas 10 (50.0%) males and 10 (50.0%) females in group DA ($p = 0.752$). Age, weight, and height were statistically similar in both study groups as shown in table-I ($p>0.05$). The total fentanyl dose was 45.65 ± 8.23 µg in group KD and 146.01 ± 14.18 µg in group DA ($p <0.001$). The time of weaning was 344.65 ± 43.89 minutes and 446.60 ± 73.75 minutes in groups KD and DA, respectively ($p <0.001$). The time of Extubation was 389.90 ± 35.89 minutes and 470.90 ± 66.65 minutes in groups KD and DA, respectively ($p <0.001$). The ICU stay heart rate and mean arterial pressure were not significantly different ($p>0.05$). There was no statistically significant difference in Ramsay score and non-verbal Pain score between both the groups (p-value 0.427 and 0.516, respectively). Table 1 is showing baseline and outcome data between study groups.

DISCUSSION

In the cardiothoracic centers, Coronary Artery Bypass Graft (CABG) constitutes the highest percentage of cardiac surgeries. Elongated mechanical ventilation is one of the major causes of mortality and morbidity postoperatively.[9] The sedation type affects the period of mechanical ventilation after a surgical procedure. Factors such as the drug's onset of action, its side effects, and duration of recovery of cognitive functions after discontinuation of the drug help

Table 1: Baseline and outcome data

Variable	Group KD* (n=20)	Group D+ (n=20)	p-value
Age (years)	53.65 ± 6.97	55.75 ± 5.65	0.302
Weight (kg)	65.35 ± 7.89	67.30 ± 7.82	0.438
Height (cm)	173.05 ± 10.75	171.60 ± 11.86	0.688
Gender (male/female)	11 / 9	10 / 10	0.752
Total fentanyl dose (µg)	45.65 ± 8.23	57.50 ± 9.73	<0.001
Time of weaning (min)	344.65 ± 43.89	446.60 ± 73.75	<0.001
Time of Extubation (min)	389.90 ± 35.89	470.90 ± 66.65	<0.001
ICU stay (hours)	45.45 ± 2.60	46.50 ± 2.42	0.194
Heart rate (bpm)	77.10 ± 2.61	77.95 ± 4.03	0.434
MAP (mmHg)	74.80 ± 6.63	77.35 ± 7.07	0.247
Ramsey score	3.35 ± 1.09	3.65± 1.27	0.427
Pain score	4.90 ± 2.05	4.45 ± 2.28	0.516

* Dexmedetomidine plus ketamine group
+ Dexmedetomidine group

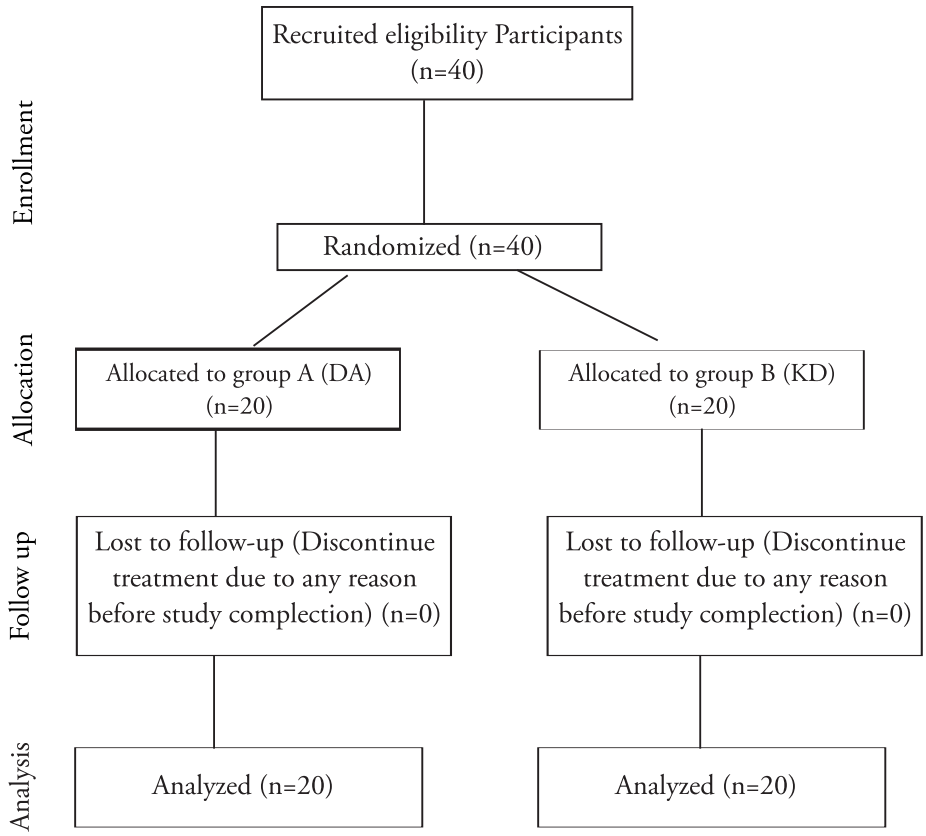

Figure 1: CONSORT diagram showing the flow of participants through each stage of the trial

choose the sedative.[10] If the duration of stay is reduced, it causes less cost of ICU and hospital stay due to short-acting sedatives and opioids, favouring the prompt tracheal extubation and reducing pain anxiety and cardiac instability from sympathetic output.[11] Pneumonia related to the ventilator, stress ulcer, GI bleeding, reduced cardiac output, and pulmonary barotrauma due to elongated mechanical ventilation enhances rates of morbidity and mortality.[12]

We noted that the combination of DMM and ketamine resulted in less duration of mechanical ventilation and earlier extubation than DMM alone. We did not note any significant differences in terms of sedation scores and hemodynamic aspects in both study groups. Early weaning and more limited term of mechanical ventilation with DMM might be added to the missing respiratory depressant impact, notwithstanding its better pain-relieving impact that diminished the aggregate sum of fentanyl utilization. Barletta and colleagues[13] found DMM to be an efficient sedative option among post-cardiac surgery cases as it was found to have no adverse influence on respiratory functioning and reduced sympathetic discharge which in turn decreased the duration of extubation and ICU stay. The utilization of DMM in post-cardiac surgery is becoming popular as it is found to influence a shorter duration of extubation in comparison to propofol.[13] The reasons may be different; it does not affect respiration as well as had sympatholytic activity thus it decreases the opiate dose.[13] Researchers comparing DMM versus propofol have revealed that patients using propofol-based regiments needed four times more morphine for sedation which shows that DMM is significantly more effective than propofol.[14-16] Contrary to this, a study found that DMM increases the use of morphine from 3.6% to 39.3% whereas ketorolac increased the use of morphine from 3.6-% to 25% among post-cardiac procedure cases.[17] In many previous studies, several beneficial effects of the combination of DMM ketamine as compared to alone DMM were found in earlier extubation and lesser time of the stay in ICU. James et al. revealed that the time of post-operative extubation, as well as the stay in ICU, was shorter with the sedation that was DMM-based.[10]

According to Stephan et al., DMM is an excellent option for permanent sedation with fewer spans of automated ventilation in ICU patients. Patients with DMM had a lesser extubation period and a lesser span of mechanical ventilation than propofol and midazolam. DMM did not affect the length of hospital stay or ICU stay. It causes hypotension and bradycardia more than midazolam but is equal to propofol.[18] In contrast, a previous study revealed that the extubation time in the patients receiving propofol and DMM was the same.[19] The propofol has a fast return of cognition while stopping the sedation because it has a short duration of action.[20] In 2011, the effect of DMM substitution was studied during the nationwide shortage of propofol in 70 patients that underwent CABG surgery. There were no differences between the DMM and propofol sedated patients for the time of extubation and opioid requirement in the first 12 hours after the admission to ICU.[21] Janette used the mixture of Ketamine and DMM throughout the procedure in children. The association of both drugs can avoid the limitations of these two drugs. There are several unfavourable adverse effects of DMM, such as hypotension, xerostomia, and bradycardia. During sedation, Ketamine, along with its reaction profile of tachycardia, enhanced secretion, and hypotension, appears to be the best option. It can abolish the unfavourable effects of DMM and vice versa. Besides, Ketamine has no respiratory depressant effect and powerful analgesic properties.[22] Our hemodynamic data,

including HR and MAP, disclosed an inconsequential change between the two groups. The ketamine use with the combination of DMM for the drowsiness remained linked by some prevalence of hemodynamic changes. Both produce hypotension, as well as DMM, produce bradycardia. During our study, no patient required chronotropic or inotropic medicine. The use of alone DMM in some studies produces unfavourable outcomes in hemodynamics.[23] The research of 300 sedated patients admitted to ICU after coronary bypass surgery revealed that DMM is related to more reduction in blood pressure than propofol.[14] In addition to this, in a meta-analysis, marked bradycardia was noticed while loading the dose and high maintenance dose that exceeds 0.7 µg/kg/h.[24] The reason is the selective nature of DMM. It may also be due to DMM being potent alpha 2 receptor agonist with dual vasomotor effects.

According to previous research, the hemodynamic effects of DMM in cardiac surgery are different; some results revealed that the incidence of hypotension was not worse, while others reported a significant reduction in BP that necessitates the vasopressors.[25] The sedation of ketamine and DMM combination with propofol was compared by Tosun et al. According to them, propofol-ketamine regularity was superior.[26] Researchers have discovered that the grouping of DMM as well as Ketamine produced the effective sedation for cardiac catheterization in the children without ventilator effects or marked hemodynamics infants.[27] Janette et al. revealed that the combination of Ketamine and DMM enhances favorable outcomes instead of using the DMM alone.[22]

CONCLUSION

Utilizing Ketamine plus dexmedetomidine for sedation post-CABG procedure gave a brief term of mechanical ventilation and early extubation with less fentanyl dose requirement compared to dexmedetomidine alone. Hemodynamic parameters were stable in both groups.

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Author's Contribution

SAR conceived the Idea and contributed to manuscript supervision. AF helped in manuscript writing and performed the statistical analysis. MIK helped in the collection of the data. KUF helped in the interpretation of data. AA and WA helped in finding the Literature. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.