Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/5253z295

PERIOPERATIVE DEXMEDETOMIDINE INFUSION FOR CARDIAC AND RENAL PROTECTION IN CARDIAC SURGERIES

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ABSTRACT

INTRODUCTION: Cardiac surgeries performed under cardiopulmonary bypass (CPB) are not devoid of adverse effects related to cardiac and renal injuries. Dexmedetomidine, an alpha-2-agonist, is shown to have protective role.

MATERIAL AND METHODS

AIM: To study the role of perioperative dexmedetomidine infusion on cardiac and renal protection during valvular heart surgeries.

This prospective, interventional and randomised study included 50 adult patients scheduled for elective valvular heart surgeries under CPB. The patients were randomised into 2 groups (1 and 2). Group 1 received dexmedetomidine at initiation of CPB at 0.5 mcg/kg bolus over 10 minutes followed by infusion at 0.25 mcg/kg/hr till extubation. Group 2 received standard cardiac anaesthesia care protocol. Cardiac enzymes (CPK-MB, LDH), renal parameters (Blood urea, serum creatinine, creatinine clearance, total urine output) , serum electrolytes (Na/K) ,serum lactate, time to extubation, Ramsay sedation score (RSS) (till 4 hours post-extubation) were compared over a span of 72 hours.

RESULTS: The observations and results of our study revealed that dexmedetomidine imparted cardiac and renoprotective properties as evidenced by significantly lower levels of CPK-MB, LDH, Serum lactate, Blood urea, serum creatinine, serum sodium in Group 1 as compared to Group 2 at all the times on both post-op days ($p<0.05$). Time to extubation and RSS were also significantly less in Group 1.

CONCLUSION: Dexmedetomidine offers cardiac and renoprotective, analgesic sparing, and anxiolytic effects, hence should be used in cardiac surgeries.

KEY WORDS: Dexmedetomidine, cardiac and renal protection, cardiac surgery.

INTRODUCTION

Valve repair and replacement under CPB are routine cardiac surgeries nowadays. CPB has not only made these procedures easier but has also immensely contributed to the outcome of surgeries.[1,2]

The use of CPB puts many vital systems under stress namely- cardiovascular, renal, hematologic, pulmonary & neurologic. The basic pathophysiology is complement activation, immune response, anaphylactic reaction and coagulation cascade activation.

Cardiovascular complications are a result of a demand-supply mismatch. The heart although is arrested during CPB, it still has some metabolic demands. Ischaemia coupled with myocardial edema can lead to a reversible mechanical dysfunction like myocardial stunning. Ionotropic support is required to alleviate this condition.[3]

The kidneys normally receive 21% of cardiac output in a pulsatile manner. The non-pulsatile pattern of CPB along with hypoperfusion due to surgical stress causes a decrease in glomerular filtration (GFR). The use of cold cardioplegia and nonendothelialised tubings of the CPB circuit leads to vasoconstriction and catecholamine release, which activate the renin-angiotensin-aldosterone system and decrease GFR further. If these conditions persist for long, they can lead to acute renal failure.[3]

Hematologic complications occur due to the activation of inflammatory and coagulation cascades by the CPB. Normally, these act as a defence mechanism to protect the body. However, during CPB, the initiation of these pathways is counterproductive. The body treats the entire CPB process as a stress phenomenon and continues this inflammatory process throughout the body, and this is known as a systemic inflammatory response. [3]

Dexmedetomidine an alpha-2 adrenergic receptor has a span of usefulness varying from sedation, analgesic sparing effect, to reduction in delirium and agitation, perioperative sympatholysis, cardiovascular stabilizing effects and preservation of respiratory function.[4] The cardiac and renal protective effects are being studied here in patients undergoing valve replacement surgeries under cardiopulmonary bypass.

METHODS

This prospective interventional randomized study was conducted for 18 months in the Department of Anaesthesia and Intensive care, after obtaining approval from the hospital ethics committee (IEC/VMMC/SJH/THESIS/OCTOBER/2018-161). Written informed consent was obtained from all patients. Adult patients (18-60 years) who fulfilled the criterion of undergoing valvular heart surgeries using CPB were enrolled for the study. Patients with Left Ventricular Ejection Fraction (LVEF) <55%, comorbidities like cardiomyopathies, preoperative atrial fibrillation, diabetes mellitus, hepatic insufficiency, renal disease, cerebrovascular disease, history of use of alpha-2 agonist before surgery and drug dependence were excluded.

The study was conducted on 50 adult patients who were randomly allocated **into** 2 groups with 25 patients in each group according to the randomization technique.

GROUP 1 (n=25): This group received Dexmedetomidine.

GROUP 2 (n=25): This group received standard care of treatment as per cardiac anaesthesia protocol.

Randomization was done using a sealed envelope system.

SAMPLE SIZE

The sample size calculation was based on the study by **Ammar AS et al (2016)[5]** who observed lower levels of CPK-MB in the dexmedetomidine group at 24 hours post-surgery as compared to the control group. Taking these values as a reference, the minimum required sample size with 90% power of the study and 5% level of significance is 22 patients in each study group. To reduce the margin of error, the total sample size taken is 50 (25 patients per group).

ANAESTHESIA TECHNIQUE:

Written informed consent was taken from all the enrolled patients. The patient was taken **to** the operation theatre. All the monitors were attached. A peripheral line was secured and crystalloid fluid (PlasmaLyte A) was started. The left radial artery was cannulated. The patient was then induced with general anaesthesia. Following induction, right Internal Jugular Vein was cannulated. The priming fluid used in the CPB circuit was PlasmaLyte A. Once the surgery started and the CPB pump was initiated, patients in Group 1 received dexmedetomidine 0.5µg/kg bolus over 10 minutes followed by 0.25 µg/kg/hr infusion till they were extubated in ICU, whereas Group 2 received standard care of treatment as per cardiac anaesthesia protocol.

Demographic details, cardiac enzymes (CPK-MB, LDH), renal parameters (Blood urea, serum creatinine, creatinine clearance, total urine output), S. electrolytes (Na/K), serum lactate, time to extubation, Ramsay sedation score (RSS; at extubation, 2,4 hours post-extubation) were compared over a span of 72 hours (pre-op, post-op day 1, post-op day 2).

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD) and median. The normality of data was tested by the Kolmogorov-Smirnov test. If the normality was rejected, then a non-parametric test was used. Statistical tests applied for quantitative variables were unpaired t-test/Mann-Whitney Test and for qualitative variables, Chi-Square test /Fisher's exact test. A p-value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

The demographic profile and operative characteristics of both groups were similar as shown in Table 1. The other biochemical parameters tested were also compared as shown in table 2.

In group 1, the enzyme CPK-MB had values near the baseline on both post-op days (as depicted in Figure 1). However, in group 2, there was a significant rise on POD 1 (0.013) and 2, but both were clinically non-significant.

In group 1 the enzyme LDH increased significantly on both post-op days 1(0.011) and 2 (0.042) as depicted in Figure 2. Similarly, group 2 also had a significant rise on both days; post-op day 1 (0.012) and 2 (0.001). However, the enzyme had a declining trend in group 1 on the second day as compared to increasing in group 2.

Serum lactate levels as depicted in Figure 3 rose on day 1 to almost double their pre-op values but declined on day 2 however didn't touch the baseline in both groups. A significant fall was observed on day 2 lactate levels in group 1 as compared to group 2.

Serum electrolytes were stable and comparable in both groups on both post-op days 1 and 2.

In Group 1 the level of blood urea increased on post-op day 1 (0.010) followed by a decline on post-op day 2(0.013), which was found to be statistically significant on both days (as depicted in Figure 4). However, in group 2, blood urea showed an increasing trend on both the post-op days, which was statistically significant on post-op day 2(0.019) only.

Renal parameters were comparable in terms of serum creatinine (Figure 5), total urine output and creatinine clearance in both groups on both days.

The Ramsay Sedation score in both the groups was comparable at extubation and 2 hours post-extubation (as depicted in Figure 6), however, it was significantly less in Group 1 at 4 hours post-extubation (0.013).

Group 1 had significantly decreased time to extubation as compared to Group 2 (as depicted in Figure 7).

Although the comparison between groups was statistically non-significant in terms of all parameters, Group 1 had stable parameters clinically as compared to Group 2.

DISCUSSION

The findings of our study showed that dexmedetomidine provided cardiac and renal protection as evidenced by stable and lower values of CPK-MB, LDH, S. urea, S. creatinine and serum lactate in group 1 patients. In addition, it resulted in early extubation and smoother post-operative characteristics.

Estimation of myocardial injury can be done by measurements of certain enzymes and biomarkers. The myocardial enzymes including LDH and CPK-MB are important biomarkers of myocardial injury, as they have the most sensitive and specific characteristic. Ammar AS et al studied the cardiac protection of dexmedetomidine and found lower levels of myocardial specific proteins cTnI, and CPK-MB in dexmedetomidine group as compared to the saline group.[5] We had similar findings in our study, as levels of CPK-MB remained stable and near baseline in group 1 as compared to its continuously rising levels in group 2, having a significant rise on post-op day 1 ($p=0.013$).

Zhang et al. compared the myocardial protection effects of dexmedetomidine priming vs physiological priming vs intravenous dexmedetomidine infusion on a cardiopulmonary bypass machine after anaesthesia induction. They found LDH was significantly lower in the dexmedetomidine priming group ($p<0.05$) and concluded it was beneficial in alleviating myocardial injury as compared to the other two.[6] In our study intravenous infusion of dexmedetomidine was used, and the results showed that group 1 had a significant increment in the levels of LDH ($p=0.011$) on post-op day 1 followed by a significant decline on post-op day 2 ($p=0.042$). However, in Group 2, LDH had a significant rise on both days (post-op day 1 ($p=0.012$) and day 2 ($p=0.009$)).

Chi et al. studied the cardioprotective effects of continuous administration of dexmedetomidine. They found a low incidence of postoperative myocardial injury and also the levels of cardiac enzymes (cTnI and CPK-MB) and concluded that dexmedetomidine shows an anti-ischaemic effect and improves myocardial oxygen balance. [7] Our study had similar findings as evidenced by stable and near baseline levels of CPK-MB in group 1.

Ammar et al. also studied the renoprotective effects of dexmedetomidine based on kidney-specific urinary proteins which were comparable at all times in both the study groups, one receiving dexmedetomidine and the other normal saline. They monitored creatinine clearance also, which increased significantly on post-op day 1, and was significantly higher in the dexmedetomidine group. [5] In our study we monitored blood urea, serum creatinine, urine output and creatinine clearance and had similar findings.

Munoz et al tried to study the correlation of a rise in lactate during CPB and its impact on morbidity and mortality in 174 patients undergoing surgery for congenital cardiac disease and concluded that hyperlactatemia occurring during CPB was an early indicator of postoperative morbidity and mortality. [8] In our study we saw that the values of lactate increased in both the groups on post-op day 1 and in group 2 on postop day 2 as compared to the pre-op values. The values clearly show us that dexmedetomidine leads to stable lactate levels in group 1. Lactate is a marker of hypoperfusion of the body. Dexmedetomidine causes vasodilation and improves the perfusion in the body leading to a decrease in the anaerobic metabolism and a decrease in lactate levels.

Biccard et al. conducted a systematic review and found that dexmedetomidine was associated with improved trends in cardiac outcomes, mortality, non-fatal myocardial infarction and myocardial ischaemia. However, there was a significant rise in the incidence of hypotension ($p<0.0001$) and bradycardia ($p<0.00001$).[9] The side effects of dexmedetomidine observed during our study were insignificant overall. There was an occurrence of hypotension in both groups, which could be due to the operative procedure itself, blood loss and massive fluid shifts. The hypotension was reversible in nature and was corrected by fluid boluses. There was arrhythmia in both the groups which was ventricular tachycardia. It was relieved by cardioversion in one patient, whereas it resolved spontaneously in the other two within a few seconds. All three occurred at the time when the patient was coming off bypass, and resuming normal circulation. Bradycardia also occurred in Group 1 patients.

Abd Aziz et al. conducted a study regarding the efficacy and safety of dexmedetomidine versus morphine in postoperative cardiac surgery patients and concluded that dexmedetomidine reduced the

length of ICU stay as compared with other sedatives. [10] In our study, dexmedetomidine was initiated while going on CPB and continued till the time of extubation. We found that patients in group 1 had better sedation scores, easy arousability, and a significant decrease in time to extubation. There was not a single case that reported excessive sedation or delirium.

CONCLUSION

This study demonstrated that patients undergoing cardiac surgeries, using cardiopulmonary bypass had varied sets of complications occurring throughout, especially comprising cardiac and renal tissues. Dexmedetomidine addition had a benefit in offering protective action to these varied complications and helping improve patient profile and prognosis. We found that patients who received dexmedetomidine had stable post-op parameters, decreased time to extubation and a better Ramsay sedation score.

DECLARATIONS:

Funding statement: There is no funding source for this study/publication.
Conflict of interest: The author reports no conflict of interest relevant for this study.

ETHICS APPROVAL:

Approval was obtained from the Instituitional Ethics Committee for Human Research- S. No.- IEC/VMMC/SJH/THESIS/OCTOBER/2018-161. Dated-29/10/2018.

FUNDING: NONE

ACKNOWLEDGEMENTS: NONE

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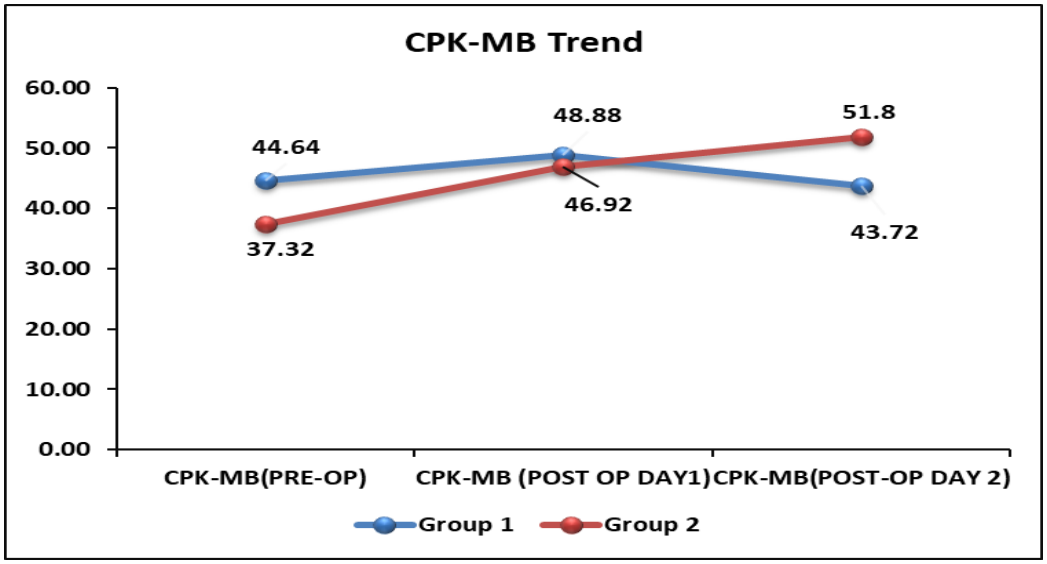

Figure 1: Trend of enzyme CPK-MB.
CPK-MB: Creatinine phosphokinase- Mycocardial specific.

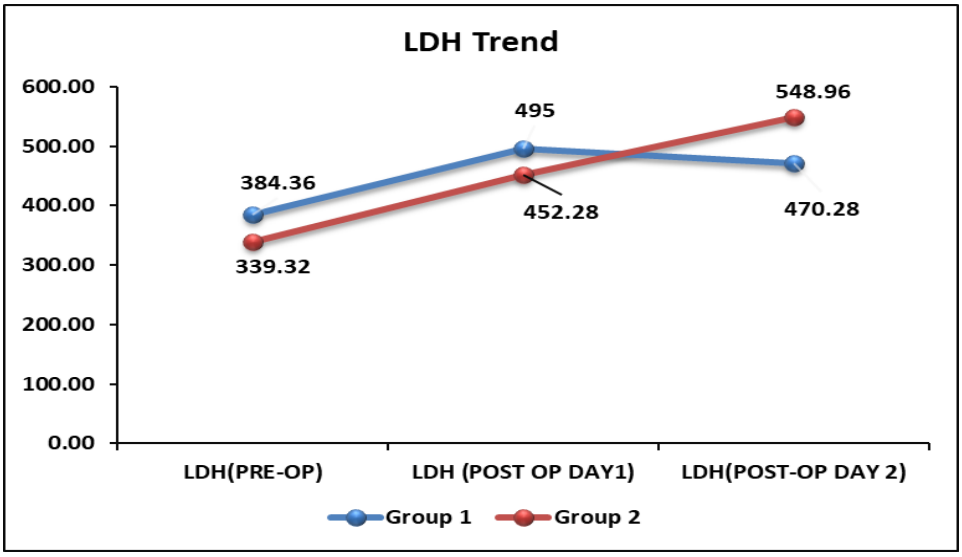

Figure 2: Trend of enzyme LDH.
LDH: Lactate dehydrogenase.

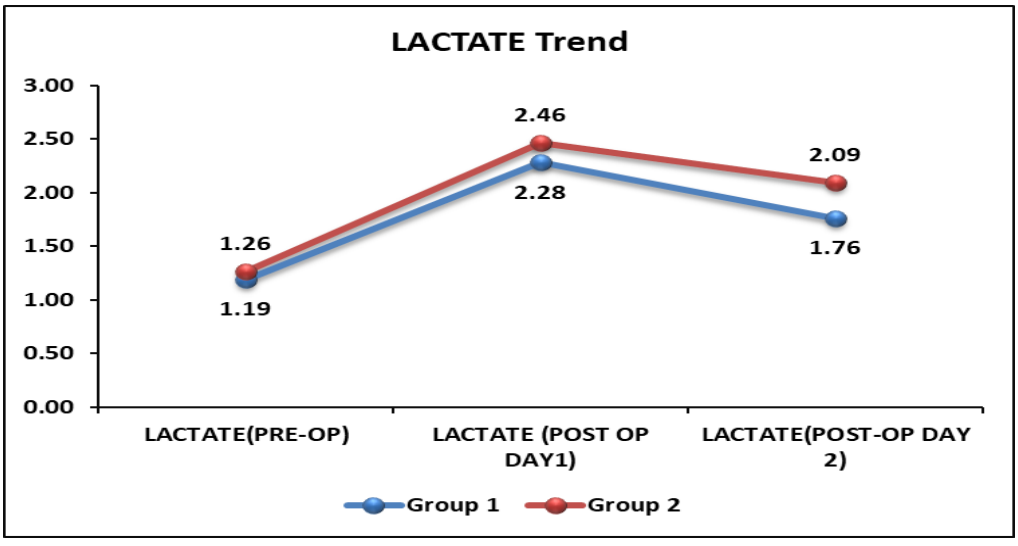

Figure 3: Trend of lactate.

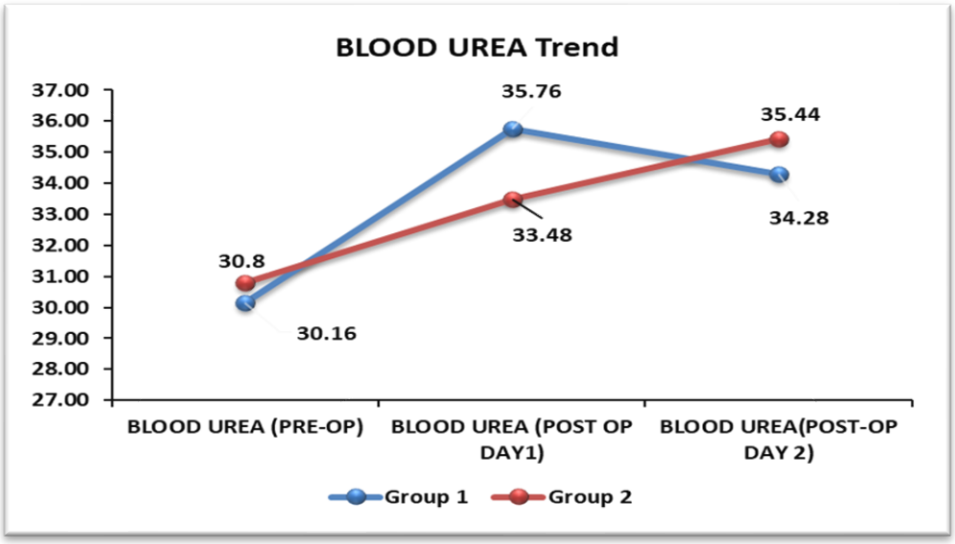

Figure 4: Trend in blood urea.

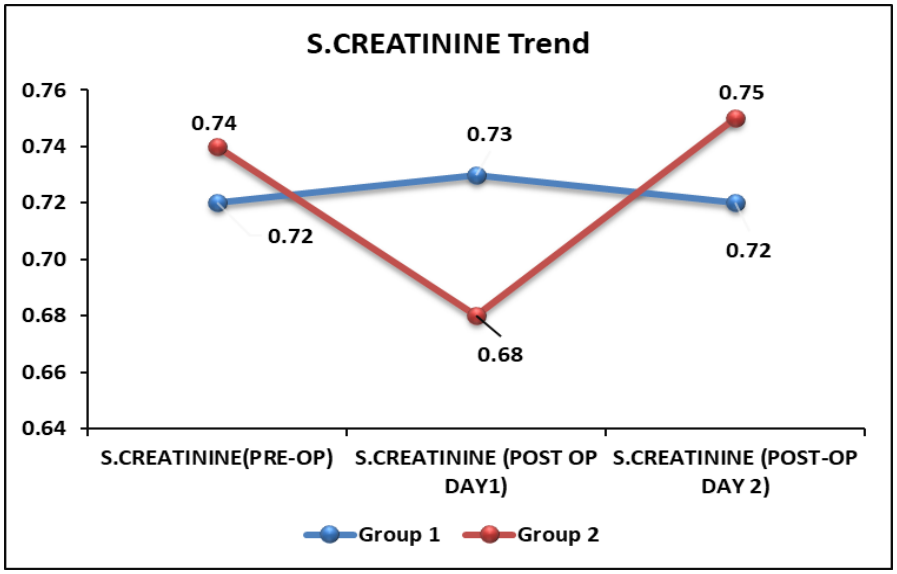

Figure 5: Trend in Serum creatinine.

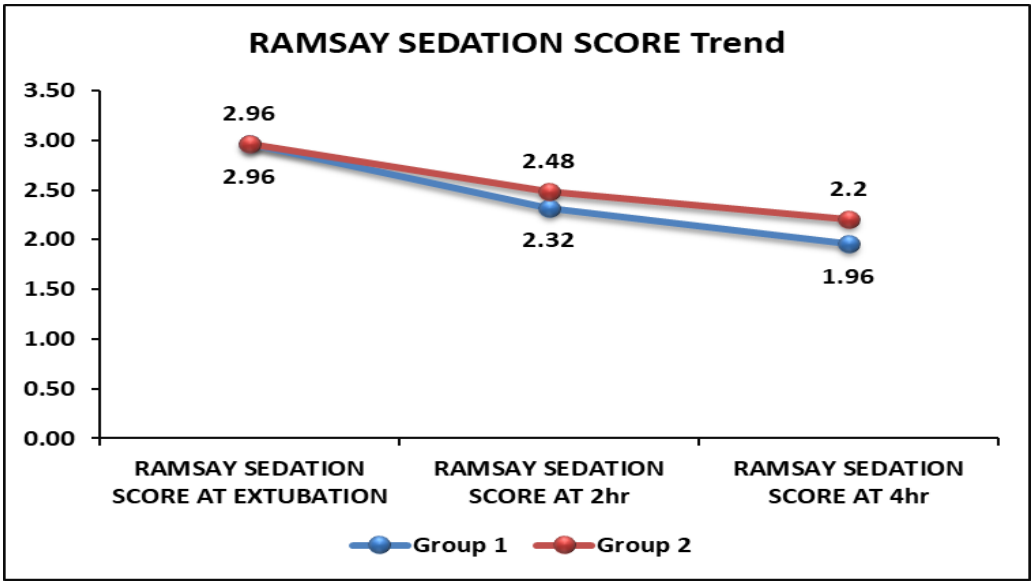

Figure 6: Trend in Ramsay sedation score.

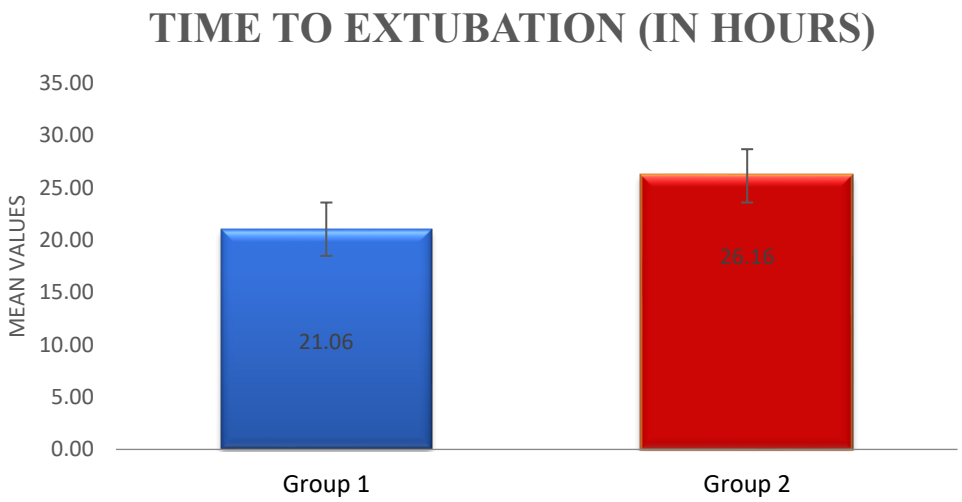

Figure 7: Time to extubation