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Original Research Article

Optimizing Pain Management Following Cardiac Surgery by Use of I.V. Paracetamol with Tramadol Vs I.V. Paracetamol with Magnesium and Dexamethasone - Randomized Parallel-Group Placebo-Controlled Trial

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Conflict of interest: Nil

Abstract:

Background and Aim: Cardiac surgery demands adequate pain relief, and in recent times there has been a shift toward faster recovery. The use of high and moderate dose opioids in cardiac cases is due to their superior analgesia and hemodynamic stability. Various combinations of drugs and even regional anaesthetic techniques are being tried to limit use of opioids with varying degree of success. In this study, we aimed to investigate whether intravenous Paracetamol with adjuvants helps in blunting the hemodynamic response to intubation and its effect on opioid consumption and extubation**.**

Methods: This is a randomized double-blinded, placebo-controlled study conducted in a State-run tertiary care super specialty hospital. Participants were from the elective list of valve replacement or CABG. They were randomized into three groups: Group M, which received magnesium and dexamethasone along with intravenous paracetamol, Group T, which received tramadol with intravenous paracetamol and Group C, control group which received normal saline. The primary outcome measures noted were total opioid consumption and hemodynamics during intubation.

Results: Opioid consumption was significantly higher in control group compared to other groups. With respect to hemodynamics at intubation, Group M had a better response especially in systolic and mean blood pressure (p value < 0.01) compared to other groups.

Conclusion: Paracetamol with magnesium and dexamethasone (Group M) had lesser opioid consumption and better hemodynamic response to intubation hence, it can be better utilised in cardiac cases in future.

Clinical Trial Registration: This study is registered with the Clinical Trials Registry-India (CTRI) with registration number: CTRI/2020/10/028258.

Keywords: Paracetamol with Adjuvants, Cardiac Surgery, Fast Tracking In Cardiac Surgery.

Introduction

Intravenous paracetamol has gained widespread acceptance as an analgesic and antipyretic, especially in the perioperative period. Many studies are being conducted on the usage of paracetamol along with adjuvants because of its safety profile. Unlike other NSAIDs, there is no increased risk of bleeding and decreased risk of postoperative nausea and vomiting. [1] Tramadol is a proven adjuvant along with paracetamol as an excellent analgesic. [2] Magnesium and dexamethasone [3] also help as adjuvants with paracetamol, and both these combinations have been well tried and found to be useful in non-cardiac surgeries. Magnesium [4] is a known adjuvant that has proven effective in attenuating hemodynamic response to intubation. Magnesium has an antiarrhythmic effect against digoxin-mediated dysrhythmias and torsade's de pointes. Systematic use of magnesium seems to decrease mortality of acute myocardial infarction and is justified during cardiac surgery, because of vasodilation of coronary arteries and prevention of the occurrence of arrhythmias. [5] The trend in cardiac surgery is toward minimizing opioid consumption and facilitating fast-track extubation. Various approaches are being tried toward this aim of fast tracking. [6,7] We wanted to study paracetamol and adjuvants in cardiac surgery, whether they help in attenuating the hemodynamic response to intubation and aiding in early extubation.

Methods

This is a randomized parallel-group, placebo-controlled trial, conducted in a government tertiary care super speciality hospital. After obtaining approval from the institutional ethics committee, the participants were enrolled in the study. The study was conducted in accordance with the principles of Declaration of Helsinki between October 2020 and the end of July 2021.

Inclusion criteria included patients in the age group of 15-75 years of age, both genders and patients scheduled for elective valve repair or CABG.

Patients with severe pulmonary hypertension, severe hepatic or renal dysfunction, morbid obesity and those with left main coronary artery disease were excluded from the study.

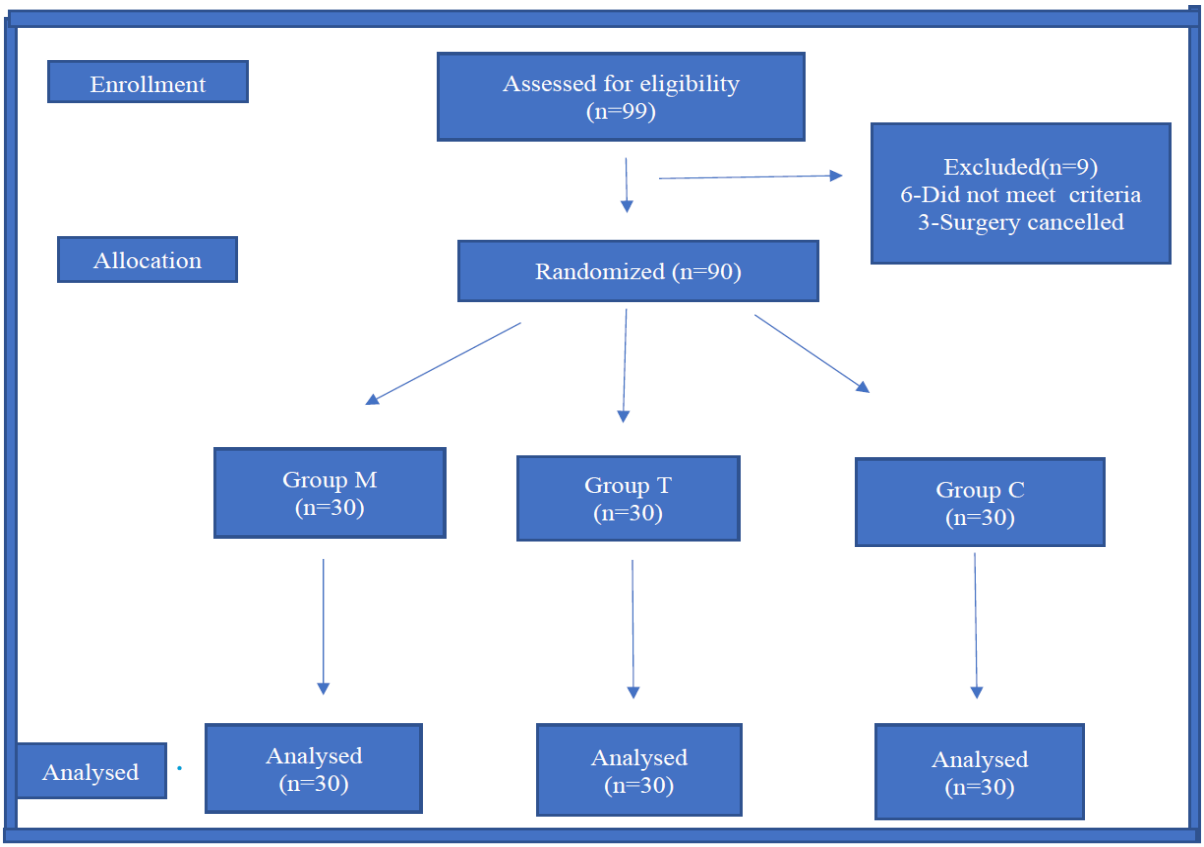

Figure 1: CONSORT flow chart

Written informed consent was obtained from all patients. Parental consent was obtained from patients less than 18 years of age. The participants were from the elective list of valve replacement or CABG. The patients were randomized based on a computer-generated sequence. The investigator and participant were blinded to the study drug. The patients were kept nil oral for 8 hours before surgery. All cases received oral diazepam 5mg, on the previous night of surgery. On the morning of surgery, the patient was wheeled into the operation theatre and the pre-induction monitors were attached such as pulse oximetry, NIBP, five lead ECG and BIS. The baseline hemodynamic parameters and BIS were noted (HR, BP, MAP). A wide-bore I.V. line was secured. The technician prepared the infusion of the study drug in OT who does not further take part in the study. These preparations were covered with non-transparent cover in order to prevent their identity. Study group M received magnesium 500mg and dexamethasone 4mg mixed with 1gram of intravenous paracetamol (100ml). Group T received tramadol 50mg mixed with 1gram of intravenous paracetamol (100ml). Control group C received 100ml of normal saline. The infusion was started to run over a period of 20mins. While the study drug infusion was on, radial artery canulation was done under local anaesthesia. After arterial cannulation, under local anaesthesia using ultrasound guidance, the right internal jugular vein canulation was done. After securing the lines, and confirming the completion of the infusion, General anaesthesia was commenced. This is usually 30 mins after the start of the study drug infusion. Premedication was done with Inj. Midazolam 0.05mg/Kg, Inj. Fentanyl 4mic/kg, Inj. Loxicard1.5mg/kg. Induction with Propofol 2mg/kg titrated to effect, Vecuronium 0.05mic/kg, Mask ventilation with 100% oxygen and sevoflurane 2%. After 3mins, we intubated the

patient with a 7mm /7.5mm cuffed oral endotracheal tube in females and an 8mm cuffed oral endotracheal tube in males.

After confirmation of correct placement, we placed the patient on a ventilator with air/oxygen 1:1, with isoflurane 1-2%. The hemodynamic disturbances were managed as follows- hypertension treated with a bolus of fentanyl 1mic/Kg, tachycardia treated with esmolol 0.5mg/kg intravenously, hypotension with iv fluids 50ml increments/ ephedrine 3mg/ml or phenylephrine 10mcg/ml. The hemodynamic parameters including heart rate, blood pressure, mean arterial pressure, and BIS were monitored at the following intervals–baseline, induction, at intubation, 5 mins after intubation later every 30mins till the end of surgery. The total opioid consumption until the end of surgery was also noted. The primary outcome measures noted are total opioid consumption and hemodynamics during intubation. The secondary outcomes measured were the time taken for extubation, duration of surgery, cross-clamp and bypass durations.

Statistical Analysis:

Statistical analysis was performed using SPSS software, and the results are represented as Mean ± SD. Statistical analysis of the data was performed within and between the groups using Analysis of variance (ANOVA) and Repeated Measures ANOVA (RM ANOVA) with pair-wise comparison. A p-value of less than 0.05 was considered significant. A sample size of 90 (30 in each group) was used to detect the mean difference of hemodynamic parameters between the three different groups with 80% statistical power and a 5% level of significance with 10% attrition.

Result

We summarize the patient demographic data and the number of cardiac surgery procedures in Figure1 (a) 1 (b) and 1 (c). There is no statistically significant difference among the groups since they all are almost similar concerning gender, the average age and procedures involved among the groups.

This study has 63% of male and 37% female subjects, then there are 32% people aged between 21-40, 50% aged around 41-60 and 18% people aged above 60 and most of the people (47%) undergone CABG procedure.

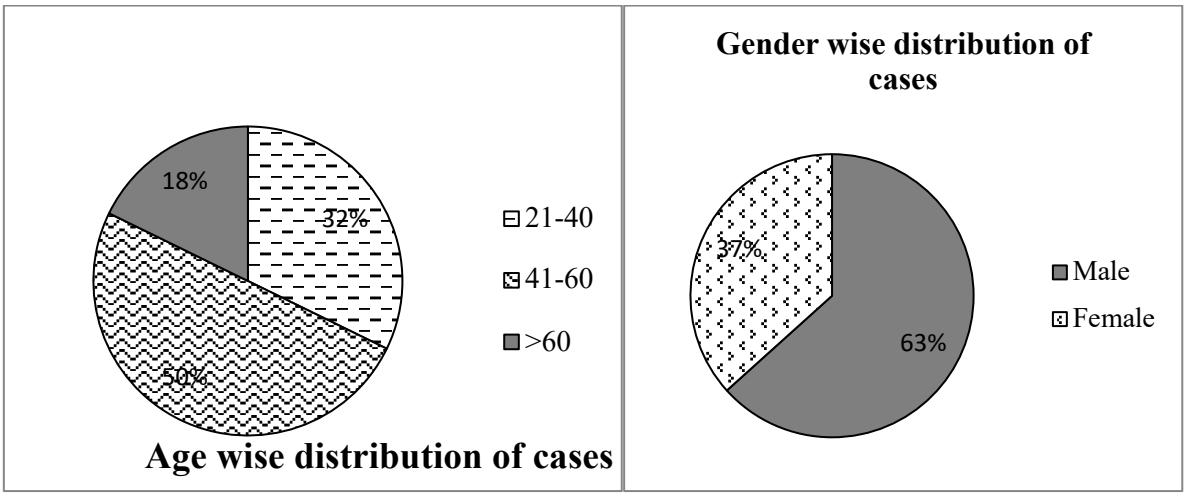

Figure 1(a) Figure 1(b)

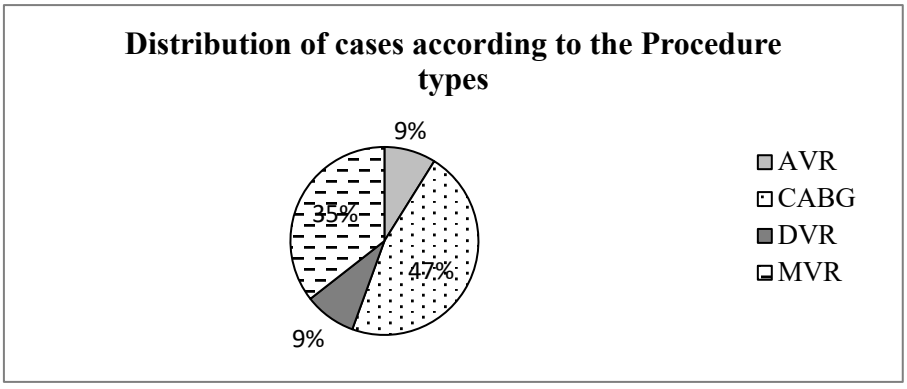

Figure 1(c)

Table 1: Average opioid consumption among 3 groups

Variable	Drug T		Drug M		Drug C		P value
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
Duration of surgery	30	4.44 ± 0.98	30	4.37 ± 1.04	30	3.93± 0.45	0.54
Opioid consumption (fent mcg)	30	352.33 ± 80.3	30	387.33 ± 91.99	30	472.67 ± 86.2	<0.01*
Cross clamp time	18	1.24 ± 0.6	15	1.07 ± 0.26	15	1.06 ± 0.18	0.861
Bypass time	18	1.66 ± 0.78	15	1.42 ± 0.35	15	1.35± 0.18	0.917
Time for extubation	30	8.60 ± 6.38	30	8.53 ± 5.38	30	7.70 ± 5.60	0.227

Table 1 reveals that the average opioid consumption has a significant difference ($p < 0.05$) between the three different drug groups and it clearly shows that the Drug C group has more opioid consumption compared with other groups. (i.e.) Drug C > Drug T ≅ Drug M. The table also coveys that the Average Duration of surgery, Cross clamp time, Bypass time, and Time for extubation have no significant difference between the groups.

Table **2** shows the hemodynamic parameter's average value (Mean ± Standard Deviation) obtained in different stages of time according to the three different groups with p values for the within and between group analysis.

Table 2: Hemodynamic parameters of 3 groups in different stages

Drug T Group (n=30), Drug M Group (n=30) and Drug C Group (n=30) [N=90]																
	Baseline			Induction			Intubation			5 mins after intubation			Every 30 mins			P value (between)
	Drug T	Drug M	Drug C	Drug T	Drug M	Drug C	Drug T	Drug M	Drug C	Drug T	Drug M	Drug C	Drug T	Drug M	Drug C	0.37
HR	75.93 ±11.52	74.47 ±16.06	78.63 ±12.93	71.00 ±11.87	67.67 ±13.56	72.70 ±8.84	74.00 ±12.99	64.93 ±12.11	74.23 ±11.09	70.27 ±14.63	66.37 ±11.42	72.64 ±10.76	69.37 ±14.37	66.97 ±11.82	73.23 ±11.96	
P value	<0.01$ <0.05# <0.05&															
SYS BP	136.50 ±22.38	133.83 ±18.02	131.23 ±21.43	112.63 ±17.38	101.33 ±20.81	108.30 ±16.91	112.07 ±22.23	97.40 ±15.71	114.80 ±21.48	105.77 ±16.96	95.00 ±15.36	106.63 ±19.93	98.56 ±16.03	95.77 ±14.21	102.53 ±15.81	0.04*
P value	<0.01$ <0.01# <0.01&															
DIA BP	72.07 ±12.33	74.10 ±11.13	72.93 ±15.44	62.10 ±12.99	60.17 ±12.59	67.43 ±10.73	64.93 ±15.44	58.50 ±11.95	67.43 ±12.51	62.73 ±10.82	59.07 ±13.15	64.00 ±14.56	57.13 ±10.01	58.03 ±12.02	60.43 ±11.11	0.16
P value	<0.01$ <0.01# <0.01&															
Mean BP	93.33 ±12.29	94.13 ±10.32	71.33 ±41.39	78.87 ±12.71	73.87 ±13.71	62.50 ±36.31	80.40 ±16.88	70.97 ±12.72	64.10 ±38.22	77.03 ±11.76	71.03 ±13.17	60.53 ±36.75	70.77 ±10.79	70.40 ±11.63	57.40 ±33.82	<0.01*
P value	<0.01$ <0.01# <0.01&															
BIS	94.80 ±3.71	94.87 ±3.15	95.87 ±1.68	58.93 ±9.47	57.20 ±10.78	63.70 ±5.43	47.60 ±6.61	43.60 ±6.99	49.10 ±6.94	43.80 ±6.69	41.97 ±8.38	43.57 ±6.57	44.47 ±8.55	38.87 ±5.75	41.77 ±5.41	0.03*
P value	<0.01$ <0.01# <0.01&															

Abbreviations: HR- Heart Rate, SYS BP- Systolic Blood Pressure, DIA BP- Diastolic Blood Pressure, BP- Average Blood Pressure and BIS-Bispectral Index

*p<0.05 between the groups

$- Drug T #- Drug M &- Drug C p<0.05 within the groups (from baseline)

The comparison of the parameters between the three groups shows a significant difference only in Systolic blood pressure, mean blood pressure and BIS values. Group M, shows a significant decrease at all different stages of time from baseline compared to other groups. All three drugs performed similarly regarding heart rate and diastolic blood pressure values.

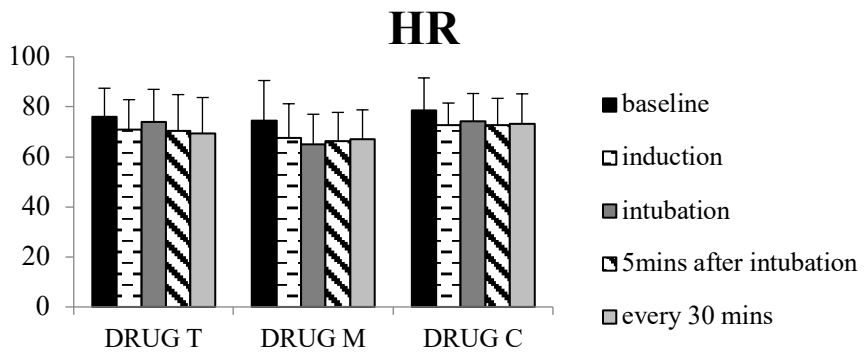

Figure 2: HR

Figure 2 shows the mean HR in the different time periods among the three different groups. In all three groups, there is a significant decrease from baseline in comparison to other time periods.

Figure 3 shows the mean SYS BP in the different time periods. The graph shows that Drug T has a significant decrease in all the stages from the baseline but comparable between induction and intubation whereas, Drug M group shows a statistically significant decrease in all different stages of time from the baseline, the Drug C group also has significant decrement from baseline but increases during intubation period. Therefore comparatively, it seems that Drug M performs in a better way.

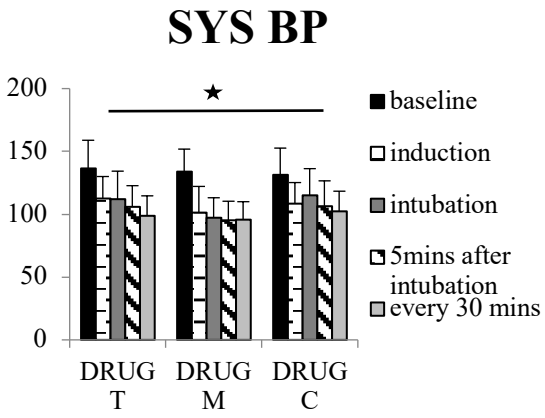

Figure 3: SYS BP

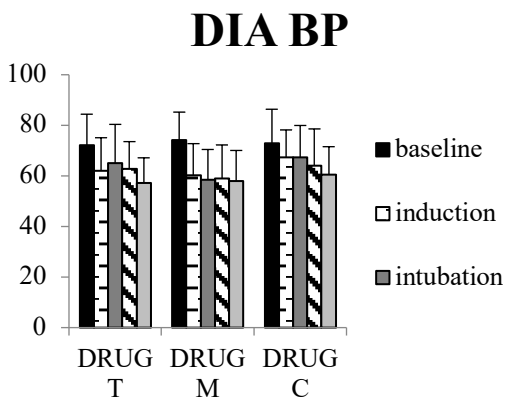

Figure 4: DAI BP

Figure 4 images the level of mean DIA BP between the groups at different stages of time. All three Drug shows a significant difference with respect to the different time period from baseline. **Figure 5** shows the average BP level among the different groups and at different stages of time. The graph shows that there's a significant difference in average BP levels among the groups and within the time period. Specifically, Drug M has a significant decrease from baseline to each stage while others have fluctuation. **Figure 6** shows the mean BIS level between the groups. In the Drug T group, it has a significant decrease in BIS level up to 44.47 ±8.55 at every 30 mins observation, and in the Drug M group it has a significant decrement which went up to 38.87 ±5.75 at every 30 mins observation where the Drug C group also has the significant impact in BIS which decreased up to 41.77 ±5.41. Comparatively Drug M reading is lower than Drug T and Drug C.

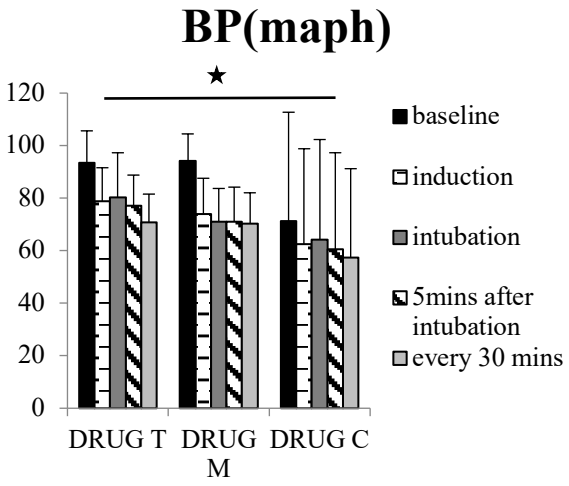

Figure 5: BP (maph)

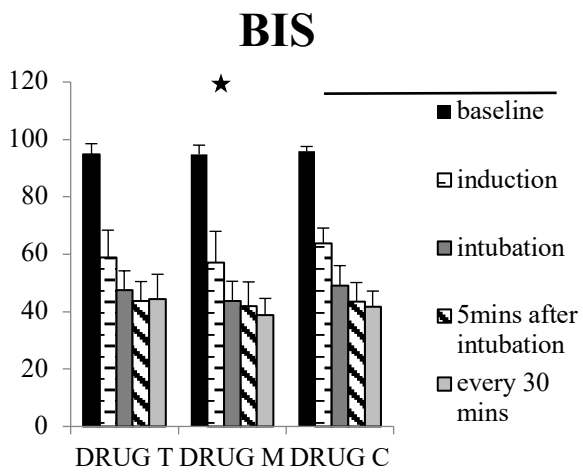

Figure 6: BIS

Discussion

There was no change in the demographic parameters between the groups. Opioid consumption was significantly higher in the control group. Group M performed significantly better with respect to systolic, mean blood pressure and BIS values. There was no difference between the groups with respect to the average duration of surgery, cross clamp and bypass times, and time for extubation.

Pain management in surgeries is often multimodal and involves the use of regional techniques. The use of high-dose and moderate-dose opioids in cardiac anesthesia is because they provide favourable hemodynamics in patients with limited circulatory reserves who might have been unable to tolerate conventional anaesthetic agents. [8] Although laryngoscopy and intubation separately result in sympathetic stimulation, the catecholamine rise with intubation exceeds that with laryngoscopy alone. [9] Fentanyl, beta-adrenergic receptor blockers, and lignocaine have all been used with varying results. [10,11] In our hospital, we have used intravenous paracetamol with tramadol combination routinely as post-operative medication for all cardiac surgery cases once they are shifted to ICU. In a study [12] on opioid free anesthesia in spine surgeries, the preoperative use of shiv mix-3(involving paracetamol, magnesium, and dexmedetomidine) proved to be an excellent combination that provided better perioperative hemodynamic stability and post-operative pain score. Dexamethasone [13] is also a proven adjuvant as part of the multimodal regimen, and also in the prevention of postoperative nausea, vomiting, and sore throat.

About the parameters, Group C had a significant increase in opioid consumption compared with the other groups. This is similar to the study in which paracetamol reduced opioid consumption in the first 24 hours after cardiac surgery. [19] Another interesting observation is females had a lesser opioid consumption than males in the study. In a study by Memis et al, they demonstrated that intravenous paracetamol after major surgery, not only decreased opioid consumption but also had shortening of extubation and ICU stay. [20] In our study, although opioid consumption was less, there was no difference among the groups with respect to extubation. This is probably explained by the fact that since we use only short-acting opioids like fentanyl in the post-operative period unlike other centres that use morphine, there was probably no difference with respect to the time of extubation.

In our study, although heart rate appears to be decreased after baseline at all-time points, there is no significant difference between the groups. This is in contrast to another study, where intravenous paracetamol administered before caesarean section reduced tachycardia response after intubation. [14,15] This can be explained by the fact that all induction agents do blunt the hemodynamic response and in general, because cardiac patients are already invariably on beta blockers, may be the tachycardia response is not profound. Another study showed that administration of intravenous paracetamol (20m/kg), 30 minutes before induction had good efficacy in controlling hemodynamic changes at the time for endotracheal intubation but not as significant as compared with fentanyl. [16]

In our study, both groups T and M had a significant decrease in systolic and mean blood pressure compared with the control group. However, group M had performed significantly better than the other two groups. In a similar study conducted in cardiac surgical patients, paracetamol administered 15mins preoperatively decreased the systolic, diastolic and mean pressure. [17] In a study in healthy

volunteers, paracetamol caused a transient decrease in blood pressure immediately after infusion. [18] The physiological mechanism was consistent with vasodilatation. Although there are studies on the use of intravenous paracetamol in cardiac surgeries, ours is probably the only study involving paracetamol and adjuvants, that measured the hemodynamic response to intubation, opioid consumption and extubation time. The limitations are the failure to monitor other hemodynamic parameters such as SVRI, PAP and cardiac index. We have also not measured the pain scores postoperatively. Because our intervention was performed in the immediate preoperative period, a better measure would be to evaluate the hemodynamic response to intubation and total opioid consumption until the end of surgery.

Conclusion

Paracetamol along with the adjuvants magnesium and dexamethasone help in attenuating the hemodynamic response of intubation. The opioid consumption was also significantly lower in both the paracetamol groups T and M. However, there was no significant difference observed in the time to extubation between the groups. Further studies on the use of other adjuvants along with paracetamol can be attempted in cardiac surgery cases.

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