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DOES CONCOMITANT ADMINISTRATION OF DEXMEDETOMIDINE AND PROPOFOL PROVIDE MYOCARDIAL PROTECTION AND RENAL FUNCTION PRESERVATION IN COMPARISON TO PROPOFOL ALONE; A RANDOMIZED PROSPECTIVE STUDY

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Contribution
MFAR conceived the idea and designed the study. Data collection and manuscript writing was done by MFAR, SF, SUH, HMSY, HSMIY, and MARB. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To ascertain the safety and efficacy of concomitant administration of dexmedetomidine and propofol in maintaining myocardial protection and renal function integrity in comparison to propofol alone in adult cardiac surgical patients.

Methodology: A randomized clinical trial was conducted at cardiac center Bahawalpur from June 2018 to January 2020. Study included 64 patients who underwent coronary artery bypass grafting (CABG). Two groups, DP (DEXMEDETOMIDINE (DEX) +Propofol) and P (Propofol alone) were made by allocating 32 patients in each group. Hemodynamic parameters (Heart rate, Diastolic blood pressure (DBP), systolic blood pressure (SBP) and mean arterial pressure (MAP) at different time intervals throughout the surgery were measured, pre and post-operative CKMB, any arrhythmias, events of tachycardia and bradycardia were recorded and renal parameters (urine output immediate post pump and 4 hours post pump, creatinine clearance of day 1 and day 2) were measured.

Results: DP group showed stable hemodynamics with values of hemodynamic parameters were lesser and statistically significant than patients in group P (Heart rate ($p<.05$), DBP ($P<.05$), SBP ($P<.05$) and MAP ($p<.05$). Both groups showed insignificant difference in terms of incidence of arrhythmias ($p=0.325$), Post-operative CKMB ($P=0.512$), events of tachycardia ($p=0.6$) and bradycardia ($p=0.5$).Immediate post pump urine was statistically significant ($p<.05$), however, 4-hour post pump urine ($p = 0.45$), creatinine clearance of day 1 ($p = 0.8$) and day 2 ($p =.092$) were comparable.

Conclusion: Concomitant administration of dexmedetomidine and propofol provide adequate cardioprotection by maintaining stable hemodynamics in comparison to propofol alone, however they did not prove to be effective renoprotective agents.

Keywords: Dexmedetomidine, Cardiac Surgery, myocardial Protection

INTRODUCTION

Myocardium is extremely vulnerable to injury during cardiac surgery owing to multitude of factors resulting in varying degrees of morbidity and mortality. Abrupt perturbations in hemodynamics in the form of arrhythmias, extremes of arterial pressures and heart rate , global ischemia during cross clamping in already hypoxic and hypertrophied cardiac muscles, inflammatory cascades erupted during cardiopulmonary bypass, inefficient surgeries i.e., incomplete revascularization during CABG ,and ,ultimately, reperfusion at the end of surgery (by aortic de clamping and resumption of coronary flow through coronary conduits) leading to re-oxidation of multiple cellular components resulting in cellular necrosis ,are some of notable factors hampering smooth proceeding of a proficient cardiac surgical procedure.[1]

Diverse myocardial protective strategies have been presented for the last three decades with varying degree of success.[1] They can be broadly segregated in various varieties depending upon methods of cardioprotection, their time of utilization and their specific targets.[2]

Among the various methods of cardioprotection are, Ischemic conditioning (further classified into local ischemic preconditioning, post conditioning and remote ischemic preconditioning.[3] Various pharmacological substances i.e, cardioplegias, metoprolol etc, hypothermia and electrical stimulation of heart resulting in fibrillatory arrest for CABG during on pump surgery.[4]

Cardioprotective techniques can be classified according to time of application i.e. During and after ischemia. Examples of methods used during ischemia are, use of cardioplegia, hypothermia and glucose-insulin-potassium solution etc. during aortic cross clamping. Ischemic post conditioning and administration of some drugs,i.e,adenosine immediately after declamping are examples of protective techniques applied after ischemia.[5] Finally, protective modalities can be divided on the basis of weather they are acting on cardiomyocites or cells other than cardiomyocites like platelets or white blood cells that play an important role in ischemic reperfusion injury.[4]

Use of multiple rather than sole myocardial protective modality is required for good myocardial preservation.[6] Abrupt changes in hemodynamics during cardiac surgery induced by pain, shallowness of anesthesia and myocardial depressant effects of anesthetic agents puts enormous strains on myocardium resulting in poor performance. The pressure changes also are the major risk factors leading to acute kidney injury in patients with normal pre-operative kidney function. Therefore, use of a myocardial friendly anesthetic agent along with various other cardioprotective techniques is warranted for these tender and vulnerable procedures.

Propofol is extensively used anesthesia drug in cardiac surgery. An effective sedative agent with additive anti emetic and cardio protective properties makes it a good choice. Nevertheless, peripheral vasodilation, respiratory depression and propofol infusion syndrome are some of its complications.[7] Dexmedetomidine is a highly specific alpha -2 receptor agonist having high quality sedative and analgesic properties. Minimal respiratory depression and cardio protective effects are additional features.[8] However, dose dependent changes in heart rate and blood pressure because of its sympatholytic properties is a known complication. Various studies have compared both drugs declaring one drug advantageous over the other,[9] but very few have combined both drugs in cardiac surgery.

We have combined propofol and DEX together hypothesizing that combination of duo will result in greater efficacy in myocardial protection and renal protection in comparison to use of propofol alone.

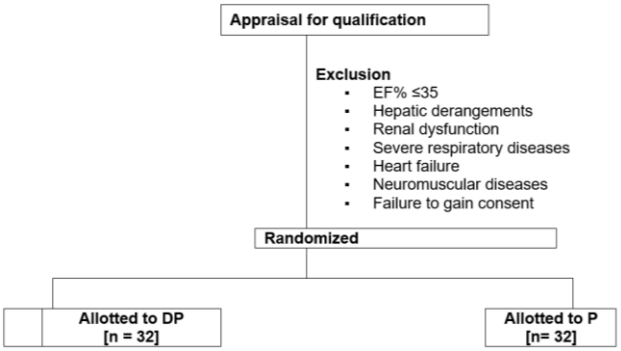
METHODOLOGY

This single blinded study was carried out at CCB/QAMC Bahawalpur after mandated by ethical review committee (ERC) from June 2018 to January 2020. Sample size of thirty two patients in each group was calculated online by using standard calculator from Open-epi. The randomized clinical trial encompassed a total of sixty four patients, who were ASA II and ASA III and undergoing CABG, after gaining informed written consent. The patients having acute cardiac problems in last four weeks,

uncontrolled diabetes mellitus, sufferers of any end organ diseases of kidney, liver and lungs, morbidly obese, those who underwent any previous cardiac operations, all patients with EF<35% and patients suffering from severe bleeding intra and post operatively were excluded from study. Thirty two patients (aged 20-70 years) were allocated randomly into each of group, DP (DEX+Propofol) and group P(propofol).

Before induction DEX was given as a bolus of 0.7 μgkg^{-1} in group DP and continued later at a rate of 0.2 – 0.4$\mu gkg^{-1}hour^{-1}$ till completion of surgery. In the same way, N/10 saline is injected at rate of 1 ml kg^{-1} h^{-1} in group-P along with propofol infusion at a rate of 0.3 – 0.5 mg kg^{-1} hr^{-1} in both groups. Injection nalbuphine was used for intraoperative analgesia with a single dose of 0.3 mg kg^{-1} after endotracheal intubation and muscle relaxation with intermittent injection of Cisatracurium. After intubation, anesthesia was maintained with O2 + air (50%) along with DEX +Propofol infusion in group DP and Propofol infusion alone in control group P and adequate tidal volume adjusted after getting muscle relaxation with Cisatracurium.

Figure 1: Graphical presentation of patients randomized for clinical trial



Monitors(Infinity C700) for heart rate, blood pressures from radial artery, ECG, O2 saturation and capnography were attached in OR and hemodynamic variables systolic pressures (SBP), diastolic, (DBP) and mean arterial pressure (MAP) and heart rate (HR) were written in Performa at different time intervals. The intraoperative variables comprise of urine output immediate post cardiopulmonary bypass (CPB) and 2 hours post CPB, crossclamp and CPB times, Creatinine clearance at three different intervals (table 2). Arrhythmias, events of tachycardia and events of Bradycardia, pre and postoperative CKMB levels measured. Total doses of drugs used (inotropic agents) were compared in each of 2 groups.

SPSS software, variant 20 (IBM Inc) was used to analyze the data and outcomes were computed as means±tandard deviation. The correlations of inputs were prepared by means of the student t test and chi-square and somewhere with ANOVA. Statistically significance was taken if p value would be $\leq$ 0.05.

RESULTS

The demographic characteristics were not dissimilar between both groups (Table 1.). The total dose of Propofol given in group DP was 110 mg ± 6.0369 and 126 mg ± 6.465 in group P, respectively. The total amount of fluid given in each of two groups were not statistically significant (1178 ± 406 versus 1200 ± 398 ml p = 0.281). Patients in each group did not differ in respect to medication and surgical particulars (Table 1). In both groups, pre -operative ejection fraction, number of grafts, dose of nalbuphine, inotropic and vasopressor drugs as well as extubation and cross clamp times were not statistically significant against control (p > 0.05).

Table 1: Comparison of Baseline Variables

Parameters	Group DP (N-32)	Group P (N-32)	P-Value
Age	40.43±8.23	39.79±9.35	0.30
Gender (Male/Female)	22/10	21/11	0.29
BMI	27.73±2.01	28.01±1.93	0.21
Ejection Fraction (%)	57.09±10.85	59.68±10.10	0.34
Pre-Operative Urea	29.84±7.92	31.71 ±12.01	0.491
Pre-Op Creatinine clearance(ml/ min)	87.51±26.54	96.89±37.56	0.219

Baseline dynamics comprise of (HR, SBP, MAP and DBP) were similar in both groups (p > 0.05). HR was raised statistically in control group as compared to group DP (p < 0.05) after induction, during maintenance and in post pump periods (Table 3).

Table 2. Comparison of Operative Variables

Parameters	Group DP (N-32)	Group P (N-32)	P-Value
X-Clamp Time (mins)	69.62±25.14	66.28±25.53	0.54
Duration of Operation (mins)	161.26±30.01	159.89±31.12	0.15
Total number of Grafts	1.96± 1.49	1.96±1.59	0.9
Post Pump Urine (ml)	278.43±255.92	168.28±123.47	0.032
Urine after 4 hour(ml)	577.93±414.61	638.96±446.89	0.485
CPB Time(min)	108.34±38.74	100.71±35.99	0.433
Post-Operative Urea	52.87±16.85	43.87±14.20	0.038
Postop Creatinine Clearance[day-1]	92.45±27.02	93.93±31.30	0.832
Postop Creatinine Clearance[day-2]	74.01±23.52	88.44±37.44	0.092
Arrhythmias	0.031±0.17	0.093±0.29	0.325
Events of tachycardia	0.56±1.045	0.43±0.66	0.601
Events of Bradycardia	0.031±0.176	0.062±0.245	0.572
Pre op CKMB (mg/dl)	20.53±17.37	30.34±23.95	0.081
Post op CKMB (mg/dl)	42.5±35.01	50.68±53.83	0.512

DBP was significantly contrasting between both study groups with lower mean values in DP group after induction, before commencement of CPB ($p < 0.05$), and after CPB (Table 4), at 10 min ($p < 0.000$), at 40 min. ($p= 0.023$), at 80 min ($p = 0.047$) and at 100 min ($p = 0.001$) against control.

Table 3: Comparison of Mean Heart Rate

Parameters	Group DP (N-32)	Group P (N-32)	P-Value
Before induction	75.34±9.30	77.78±9.95	.014
After induction	76.06±11.19	84.78±9.61	.000
At 10 minutes	74±10.74	83.12±11.69	.000
At 20 minutes	75.84±8.56	85.5±7.39	.000
At 35 minutes	78.34±10.05	85.84±8.04	.000
Post pump 10 Minutes	73.31±6.46	85.31±10.16	.000
Post pump 20 Minutes	75.15±4.69	86.40±5.64	.000
Post pump 40 Minutes	77.87±7.29	87.53±7.39	.005
Post pump 60 Minutes	85.62±6.83	90.90±9.62	.000
Post pump 80 Minutes	83.93±5.14	89.62±8.74	.001
Post pump 100 Minutes	76.87±7.39	86.45±7.48	.005

According to t-test statistics, SBP and MAP during study at different intervals permutated between each groups. The pressure values of SBP and MAP were lessened in group DP and statistically significant at induction of anesthesia, before pump and post pump against group P (Table 5).

Table 4: Comparison of Diastolic Blood Pressure

Parameters	Group DP (N-32)	Group P (N-32)	P-Value
Before induction	72.5±8.98	77.31±9.47	.000
After induction	68.87±11.88	77.53±9.87	.000
At 10 minutes	62.93±12.05	73±11.15	.000
At 20 minutes	64.53±10.23	73.71±13.78	.000
At 35 minutes	58.78±9.64	68.37±10.91	.001
Post pump 10 Minutes	40.06±6.67	51.06±5.35	.001
Post pump 20 Minutes	42.46±6.10	51.71±5.90	.068
Post pump 40 Minutes	45.56±6.88	56.90±7.87	.023
Post pump 60 Minutes	45.71±5.44	53.78±5.37	.269
Post pump 80 Minutes	48.03±4.09	57.78±8.32	.047
Post pump 100 Minutes	41.05±6.58	52.12±6.26	.001

Preoperative urea, creatinine clearance, urine four hours post CPB, CPB and cross clamp times, arrhythmias, tachycardia & bradycardia events and pre and postoperative CKMB did not show any significant trends but statistically obvious difference had been observed in immediate post pump urinary volume and blood urea ($p < 0.05$, [Table 2]).

Table 5: Comparison of Systolic Blood Pressure (SBP) and Mean Arterial Pressure (MAP)

Parameters	Group DP (N-32)	Group P (N-32)	P-Value
Systolic Blood Pressure (SBP)			
Before induction	142.5±25.03	143.90±19.93	0.673
After induction	111.43±18.26	122.06±13.14	.000
At 10 minutes	105.03±12.82	119.18±16.29	.000
At 20 minutes	106.96±9.61	118.71±11.96	.000
At 35 minutes	102.93±8.83	110.43±12.51	.002
Post pump 10 Minutes	75.68±11.25	76.65±12.99	.500
Post pump 20 Minutes	81.71±10.55	90.78±12.11	.000
Post pump 40 Minutes	86.37±11.073	98.03±13.74	.000
Post pump 60 Minutes	86.62±8.51	98.56±12.69	.000
Post pump 80 Minutes	93.96±10.11	103.84±13.06	.000
Post pump 100 Minutes	101.84±8.74	111.35±12.61	.001
Mean Arterial Pressure (MAP)			
Before induction	89.59±12.54	92.21±9.36	.055
After induction	83.28±13.51	89.78±10.43	.000
At 10 minutes	76.71±11.78	82.78±9.56	.003
At 20 minutes	78.15±7.62	82.84±6.76	.000
At 35 minutes	73.71±8.92	63.15±5.34	.000
Post pump 10 Minutes	53.06±7.49	59.53±5.64	.000
Post pump 20 Minutes	55.31±6.95	61.03±7.22	.000
Post pump 40 Minutes	58.5±8.17	63.84±6.66	.001
Post pump 60 Minutes	58.71±6.11	64.06±6.33	.001
Post pump 80 Minutes	65.18±9.05	71.78±5.75	.001
Post pump 100 Minutes	61.93±6.44	66.84±5.79	.000

DISCUSSION

We have done this randomized clinical trial to evaluate safety and efficacy of concomitant use of DEX and propofol versus propofol alone in adult cardiac surgery patients. Our study revealed that patients in combined group had more stable hemodynamics as compared to propofol alone group. This was evidenced by less values of heart rate, MAP, SBP and DBP (BUT WITHIN NORMAL RANGE) in study group than the control group. Albeit, incidence of arrhythmias, events of tachycardia and bradycardia and post-operative CKMB levels were not statistically significant. Urine output immediate post pump was significantly improved but creatinine clearance did not show any significant difference between both the groups.

Various studies have evaluated hemodynamic effects of combined use of DEX and propofol. KIM et al, proved more stable heart rate and MAP in combined usage of DEX +Propofol group against propofol alone in surgical patients.[10] Khare A et al proved combined use of DEX +propofol resulted in significant control of hemodynamics than the control.[11] Soltani et al, also proved lesser heart rate and preservance of MAP in DEX group than the control.[12] Similarly PRODEX, largest clinical trial comparing DEX and propofol, found DEX non substandard to propofol in terms of incidence of hypotension and bradycardia in mechanically ventilated patients.[13] However SPICE III trial found more incidence of hypotension and bradycardia(although the incidence was merely 2.7% and 5.1% respectively) In critically ill patients receiving DEX in comparison to usual care group patients. Similarly, Buckley et al., proved evidence of adverse hemodynamic events in combined administration of DEX and propofol.[14] However, last two studies were done in critically ill patients of ICU which had much more co morbidities than our study population and duration of DEX therapy was also much prolonged than our study.

Propofol when used for anesthesia induction may result in peripheral vasodilation causing hypotension and resultant tachycardia through sympathetic nervous system surge. When given in combination with DEX which is a central sympatholytic agent(because of its strong stimulation of pre synaptic alpha 2 adrenoreceptors),the above mentioned effect is masked ,rather, strong peripheral vasoconstriction effect of DEX (through its alpha 1 and alpha 2b receptor stimulation)becomes evident thus resulting in preservation of heart rate

and systemic pressures.[15] Moreover, because of additional analgesic and hypnotic activity of DEX, it spares the administration of additional analgesic and hypnotic agents which have cardiop depressent and vasodilator effects thus proving it more effective sedative agent in cardiac surgery than the other available drugs.[16]

The incidence of arrhythmias during cardiac surgery is reported to be 15-50%.[17] However, our study found 8% incidence of arrhythmias. Administration of DEX is shown to reduce the arrhythmias in cardiac surgery patients by Liu et al.[18] and Soltani et al.[12] Our study did not found statistically different incidence of arrhythmias between both the groups .Shehabi et al.[19] and Herr et al.[20] also showed no correlation of administration of DEX and arrhythmias in cardiac surgery patients.

Guo et al.[21] and Okada et al.[22] reported that DEX prevents ischemic reperfusion induced left ventricular dysfunction in experimental rats.it exerted its effects by enhancing coronary flow in ischemic hearts by decreasing the norepinephrine levels and increasing the cyclic AMP (cAMP) levels. Similarly, propofol is known to exert its cardio protective effects by decreasing reactive oxygen species which are produced by ischemic reperfusion injury.[8] Our study showed decreased levels of CKMB in DP group than the P group, albeit,not statistically significant, but it does indicate that the combination therapy is at least not harmful for the ischemic hearts. Riha et al.[23] also reported decreased CKMB levels in cardiac surgery patients when they used DEX.

The incidence of Acute kidney injury (AKI) is 5-30% after cardiac surgery[24] We found 15% incidence of AKI (66% of KDIGO stage I AKI, 33% of KDIGO stage II AKI, though none of them progressed to KDIGO stage III and reversed back to normal RFTs). We calculated urine output immediate after bypass and 4 hours post bypass and it showed increased urinary output in DP group than in P group although it remained in normal limits in both groups. Creatinine clearance did not show any significant difference between both groups. DEX produces its diuretic effects through various mechanism. Increase in atrial natriuretic peptide level, decrease in norepinephrine and vasopressin levels and sympatholysis induced attenuation of sodium reabsorption are some proposed mechanisms.[24] Goksedef et al. also showed no significant rise of creatinine clearance with DEX administration.[25] Contrary to our results Rabie et al. showed DEX significantly improved creatinine clearance.[24]

There are few limitations of this study. Sample size of study is small. We could not compare our results with Off pump surgery patients in which hemodynamics changes are more frequent than the on pump surgery patients. Effects of longer duration of DEX+Propofol therapy could not be ascertained as cardiac surgery patients are extubated earlier. We did not include Valvular patients in our study group and could not see the differential effects of these drugs on that group of patients.

CONCLUSION

Concomitant administration of DEX + Propofol results in effective stability of cardiovascular hemodynamics than propofol alone. However the combination therapy has got no role in renal protection but may improve diuresis in cardiac surgery patients.

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