The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-0-5815

https://doi.org/10.29309/TPMJ/2021.28.04.5815

A prospective randomized study to see the effects of dexmedetomidine plus propofol versus propofol alone in cardiac surgery patients.

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Article received on:
25/07/2020
Accepted for publication:
22/09/2020

ABSTRACT… Objective: To compare the hemodynamics changes, intraoperative awareness and postoperative delirium after combined administration of dexmedetomidine plus propofol versus propofol alone in cardiac surgical patients. **Study Design:** Randomized Clinical Trial. **Setting:** Cardiac Center, Bahawal Victoria Hospital, Bahawalpur. **Period:** 1st December 2018 to January 2020. **Material & Methods:** Sixty-two (62) patients who underwent different cardiac surgical procedures were included in the study. Patients were randomly divided in group 1 {Dexmedetomidine (DEX) +Propofol} and group 2 {propofol alone}. Induction in group 1 was done by loading dose of DEX (0.7 microgram/kg) while induction in group 2 was done by Lignocaine 1.5 mg/kg. Heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were recorded at different time intervals. Intraoperative awareness and post-operative delirium was also assessed. **Results:** All hemodynamic parameters (HR, SAP, DAP, MAP) were statistically significant lower in group 1 in comparison to group 2 at different intervals indicating a more stable hemodynamic profile in group 1. End tidal CO_2, pH, and peak airway pressures were not statistically significant between both groups. Intra-operative awareness was diagnosed in 1 (3.2%) patients in group 1 and in 5 (16.1%) patients in group 2 (p-value 0.08). Delirium was diagnosed in 3 (9.6%) patients in group 1 and in only 1 (3.2%) patients in group 2 (p-value 0.30). **Conclusion:** Combined administration of DEX and propofol produces more stable hemodynamics, less intraoperative awareness but more incidence of delirium as compared to propofol alone in cardiac surgical patients.

Key words: Cardiac Surgery, Dexmedetomidine, Propofol, Hemodynamics.

Article Citation: Farooq S, Rizvi MFA, Hashmi SU, Baig MAR, Yousaf HSMI, Munir T. A prospective randomized study to see the effects of dexmedetomidine plus propofol versus propofol alone in cardiac surgery patients. Professional Med J 2021; 28(4):447-454. https://doi.org/10.29309/TPMJ/2021.28.04.5815

INTRODUCTION

Hemodynamic perturbation is an integral part of cardiac surgery as heart being hub of all reflexes of vascular dynamics is itself diseased. Vanquishing even the subtle alteration in normal vascular tone and heart rate should be the least goal of a shrewd team involved in cardiac surgical case, failing to which may result in catastrophic events resulting high rate of morbidity and mortality. In the constellation of cardiac surgical pharmacologic agents, sedative agents play pivotal role in maintenance of hemodynamics by relieving the anxiety, providing adequate hypnosis and analgesia and ameliorating devastating effects of sympathetic nervous system stimulation.[1]

The search of an ideal sedative agent, i.e. nontoxic, non-accumulative, quickly active and with no abnormal effects on any organ system of body is still going on.[2] Two most commonly used sedative agents in perioperative cardiac surgery are propofol and dexmedetomidine.

Propofol, like many other GABA receptor agonistic agents, is one of the most commonly used sedative agents for patients requiring mechanical ventilation and cardiac surgery.[3,4] Hasty onset of action and nimble recovery, possession of antiemetic and anti-pruritic properties, relative safety in cirrhosis and renal failure patients[5], cardio protective effects including decrease in oxidative stress, decrease in ischemia reperfusion injury and decrease in cardiac troponin release and only dose dependent myocardial depressant effects

make it a sober choice for cardiac surgery.[6] While peripheral vasodilation, lack of analgesic effects, respiratory depression, apnea, pain during injection and a fatal propofol infusion syndrome (PRIS) are some cumbersome complications that require vigilance by the cardiac surgical team.[7]

Dexmedetomidine (DEX) relatively newer drug for anesthesia induction and sedation is a highly selective alpha 2 receptor agonist. Its ability to spare significantly additional sedative and analgesic drugs[8], relative preservation of blood pressure and heart rate during induction and maintenance when given in slow bolus dose[9], its central sympatholytic effects[10], and minimal respiratory depression makes it a new choice.[11]

Various studies have compared the effects of dexmedetomidine versus propofol for various effects including, sedation, ICU stay, respiratory complications and hemodynamic changes. Some consider dexmedetomidine a clear winner[12], while others consider propofol advantageous.[13,14] Some of studies have even considered them having similar effects.[15,16]

In this study we have designed to compare and contrast the cumulative effects of dexmedetomidine and propofol versus propofol alone in cardiac surgery patients, to see if they are having synergistic effect or have an antagonistic and counterproductive effect on hemodynamic response of body during and after cardiac surgery, intra operative awareness and occurrence of delirium after recovery.

MATERIAL & METHODS

The research Ethics committee of QAMC/CCB approved this study protocol, which is a single blinded, randomized clinical trial. The research was carried out at Department of Cardiac Surgery during the period of 1st December 2018 to January 2020.

Patients of age between 20 years to 70 years undergoing open heart surgeries were included.

Patients having bradycardia (HR≤ 60 beats/min bpm), conduction abnormalities, continuously low systolic arterial blood pressure (≤ 80 mmHg), recent MI, NYHA heart failure of Class III and IV, obese, having severe respiratory derangements and known allergies to propofol and DEX were excluded from the study.

The size of sample was measured from the standard dose used for anesthesia maintenance with the administration of automated dual-loop of propofol 4.70 + 1.60 mg/kg/h. Utilizing a power of 90% to establishing a 30% reduction of propofol dose in patients who will receive propofol along with DEX and with an alpha of 0.05 by utilizing a 2 tailed t test, this research should be required 62 patients.[17]

Patients admitted for open heart surgery were divided randomly into group 1 (propofol +DEX) and group 2 (propofol only) with the help of computer produced randomization codes in sealed envelopes. Informed, written consent has been taken from all the patients.

All patients were pre-medicated with ranitidine 40 mg, metoclopramide and Inj. nalbuphine 0.3 mg, in the preoperative area. Baseline values of heart rate, systolic, diastolic, mean arterial pressure and SpO_2 were recorded before starting the drugs studied by using Avance C/S_2 monitor. After establishing arterial line in the left radial artery, patients in group 1 were given loading dose of dexmedetomidine 0.7 microgram/kg in 10 minutes and continued after with a dose of 0.3 microgram/kg/h until the recovery of patient, in group 2 Inj. lignocaine was given in a dose of 1.5 mg/ kg over a period of five minutes. Later on all the patients in each group were given Inj. propofol 1 $mg.kg^{-1}$ on induction along with Inj. atracurium 0.6 mg/kg and intubated with endotracheal tube of number 7F in female and 7.5F in male patients. Anesthesia was maintained in group 1 with maintenance dose of DEX and in group 2, maintenance was carried out with injection propofol alone 0.2 to 0.3 mg/kg/h till the recovery from anesthesia. HR, SAP, DBP, MAP, $PaCO_2$, pH and Peak airway pressures were recorded just after induction, at 15 min, 30 min, 45 min, 60 minutes and every 15 minutes after returning from cardiopulmonary bypass pump till the patient shifting to ICU. Propofol infusion

dose of 0.15 – 0.3 mg/kg/h was taken equivalent to the infusion of 0.10 – 0.70 microgram/kg/h of DEX. Inj. nalbuphine (0.2 mg/ kg) was given once after 15 minutes of induction to every patient of both groups. If severe bradycardia, hypotension or prolonged pump and tracheal intubation time observed in any patient, he or she was withdrawn from study. Ventilator adjustments of controlled mechanical ventilation and standard breathing circuit were selected for all the patients. Both study drugs (propofol and DEX were administered via syringe pump in a 50 ml syringe at a rate set in the study plan for the patients in respective groups. Air-O_2 mixture (FiO_2 50%) was standardized for preoperative ventilation. DEX was withheld immediately after the case of severe bradycardia or an acute sustained decrease in MAP (20% decrease from pre-induction) for 5 minutes which was not responsive to standard medication including adrenaline bolus of 50 μg and injection atropine 0.1 mg/ kg for low heart rate. Conversely, episodic "hemodynamic activation" resulting in 20% increase in blood pressure from the baseline was treated with boluses of isosorbide dinitrate and labetalol (2 mg) accordingly. The use of total dose of inotropic and vasopressor drugs was recorded.

After surgery patients were shifted to the ICU and monitoring of parameters included in study continued. When patients started breathing spontaneously and opening eyes, the patients were extubated after fulfilling modified aldrerte score criteria. Total time from induction to extubation, any awareness and delirium were recorded in the Performa. Intraoperative awareness were analyzed with Modified Brice Questionnaire and delirium which the help of confusion assessment method (CAM-ICU) in the postoperative period.

Statistical Analysis

SPSS, version 20 (Chicago IL) was used to perform statistical analysis between group 1 and group 2. Mean ± standard deviation were used to present continuous variables. Ordinarily dispersed continuous data were analyzed using the student t test while categorical variables were compared using either fisher exact test or chi-square test. A p-value of 0.01 for primary outcome and 0.05 for secondary outcome were taken to display a statistically significant difference.

RESULTS

A gross number of 69 patients were found eligible for the study and 62 patients were enrolled and 7 patients were barred as a result of defiance, not fulfilling the criteria and sedative protocol violation from study. Demographic characteristics of study patients were similar and no statistically significant difference were observed (Table-I).

Baseline values of hemodynamics in terms of SAP, DAP and MAP were observed and no difference has been found (Table-II and III). The incidences of bradycardia and hypotension were not statistically significant before induction and after administering DEX loading dose of 0.7microgram/kg in 10 minutes in group 1 and lignocaine bolus of 1.5mg/kg in group 2. All the hemodynamics (HR, SAP, DAP and MAP) showed statistically significant difference (P 0.05) between two groups and these were lower in group 1 as compared to group 2, after intubation of trachea. Statistically significant trends in terms of heart rate as well as in systolic, diastolic and mean arterial pressure were followed during whole study period (before bypass and after bypass period) where these values showed more stable dynamics in group 1 as compared to group 2 where these were on the higher side. See Figure-1.

Occurrences of bradycardia, hypotension, hypertension and tachycardia in each of two groups were not detected (<0.05), thereby no need of administrating the drugs to counteract these effects. Quantitative difference in the use of drugs such as dobutamine, norepinephrine and isosorbide dinitrate have not found any statistical significant value (0.05) in each of group 1 and group 2. After shifting in ICU, the heart rate, SAP, DAP and MAP readings were found lower in group 1 as compared to group 2 till the recovery of the patient (0.05) which could be seen in Table-II and III and Figure-1.

Intra-operative awareness was diagnosed in

1 (3.2%) patients in group 1 and in 5 (16.1%) patients in group 2 (p-value 0.08). Delirium was diagnosed in 3 (9.6%) patients in group 1 and in only 1 (3.2%) patients in group 2 (p-value 0.30).

Furthermore, no statistically significant differences were detected in pH, End tidal CO_2, and peak airway pressures at different time intervals after immediate endotracheal intubation and after bypass till the patients recovered. Time from induction of anesthesia to end of surgery was the same in both study groups (p value .2).

	Group 1 (N=31)	Group 2 (N=31)	P-Value
Age (Years)	44.36±9.03	39.01±8.26	0.59
Gender (Male/Female)	23 (74.2%)/8 (25.8%)	21 (67.7%)/10 (32.3%)	0.36
Weight (Kg)	54.73±6.01	53.91±7.03	0.47
Duration of Surgery (mins)	165±11.34	166.23±10.51	0.57

Table-I. Demographic characteristics and baseline variables

HEART RATE			
Group1		**Group2**	
Time	**Mean±SD**	**Mean±SD**	**P-Value**
Before induction	63.8947±5.82041	73.1579±9.00779	0.329
After induction	75.6316±10.15552	78.1579±10.69404	0.009
At 15 minutes	75.7895±11.26242	84.2105±9.81257	0.000
At 30 minutes	72.8947±10.88778	82.1053±12.24697	0.000
At 45 minutes	74.6842±9.01266	84.3158±7.9166	0.000
Post pump 15 Minutes	79.1053±9.76897	86.2105±8.04556	0.000
Post pump 30 Minutes	73.4211± 6.41453	85.4211±9.97394	0.000
Post pump 45 Minutes	75.4737±4.53834	86.5263±5.47082	0.000
Post pump 60 Minutes	78.1053±7.29455	87.6316±8.19356	0.000
Post pump 75 Minutes	85.8421±6.94633	90.8947±9.067	0.031
Post pump 90 Minutes	84.1579±5.01402	89.4211±9.63394	0.008
SYSTOLIC ARTERIAL BLOOD PRESSURE			
Before induction	106.0523±10.34625	116.7858±11.24504	0.150
After induction	141.3158±25.02899	141.7895±20.72191	0.001
At 15 minutes	109.6316±18.43671	120.4211±13.94161	0.000
At 30 minutes	104.5263±12.56259	119.5789±17.83354	0.013
At 45 minutes	107.0000±10.45626	117.8947±12.25604	0.140
Post pump 15 Minutes	101.7368±9.27267	108.8947±12.77104	0.060
Post pump 30 Minutes	74.8421±10.97605	75.7895±13.19334	0.000
Post pump 45 Minutes	80.4737±10.69459	90.1053±12.36884	0.009
Post pump 60 Minutes	85.3684±11.79082	96.6316±15.12617	0.000
Post pump 75 Minutes	86.0526±9.06442	97.8421±12.85934	0.001
Post pump 90 Minutes	93.5263±10.65295	103.2105±13.83867	0.000

Table-II. Heart rate and systolic pressure variations.

DIASTOLIC ARTERIAL PRESSURE			
	Group – 1 (n=31)	Group – 2 (n=31)	
	Mean±SD	Mean±SD	P-Value
Before induction	55.5263±6.3014	61.6316±6.0664	0.339
After induction	71.3684±10.20463	76.0526±10.26577	0.000
At 15 minutes	67.7895±12.8607	76.4211±10.35114	0.002
At 30 minutes	62.2105±11.6599	71.1579±12.2214	0.006
At 45 minutes	64.7368±10.95872	73.9474±13.93028	0.001
Post pump 15 Minutes	58.4737±9.66304	68.5263±10.91568	0.005
Post pump 30 Minutes	39.5263±6.44091	50.4737±5.60127	0.012
Post pump 45 Minutes	57.3837±8.58524	64.6358±6.72112	0.002
Post pump 60 Minutes	45.1579±7.08099	56.0000±8.28654	0.050
Post pump 75 Minutes	45.5789±5.56093	53.0000±5.56776	0.36
Post pump 90 Minutes	48.2105±4.27628	57.5789±8.46769	0.053
MEAN ARTERIAL BLOOD PRESSURE			
Before induction	76.5215±10.26652	77.2578±11.58513	0.059
After induction	90.0526±12.46093	92.8421±9.49423	0.000
At 15 minutes	84.2632±13.40333	89.6842±10.65652	0.000
At 30 minutes	75.9474±11.19759	82.2105±9.75579	0.026
At 45 minutes	78.3158±8.83209	82.8421±7.69028	0.001
Post pump 15 Minutes	73.1579±9.00779	63.8947±5.82041	0.329
Post pump 30 Minutes	52.2632±7.32456	59.0000±5.52771	0.000
Post pump 45 Minutes	54.6316±7.00167	60.4211±7.01836	0.001
Post pump 60 Minutes	58.4737±8.49424	63.7368±6.83002	0.001
Post pump 75 Minutes	58.5789±6.44908	63.8421±6.44863	0.009
Post pump 90 Minutes	65.1053±8.83739	70.7895±6.07892	0.025
Post pump 120 Minutes	62.1053±6.27955	67.2105±5.65272	0.000

Table-III. Diastolic and mean arterial blood pressure variations

$EtCO_2$			
	Group – 1 (n=31)	Group – 2 (n=31)	
	Mean±SD	Mean±SD	P-Value
Before induction	31.9989±4.00581	32.0108±4.65266	0.059
After induction	32.3847±4.10680	32.4247±4.75267	0.061
At 15 minutes	29.7368±3.91354	32.3158±4.84255	0.853
At 30 minutes	29.7368±3.88504	31.4737±3.90681	0.222
At 45 minutes	30.7368±4.18784	32.3158±4.84255	0.767
Post pump 15 Minutes	35.0526±3.34122	31.4737±3.90681	0.13
Post pump 30 Minutes	36.1053±3.78439	31.6316±3.81824	0.109
Post pump 45 Minutes	35.0526±4.16965	32.8947±4.48324	0.047
Post pump 60 Minutes	35.3158±4.33401	35.1053±4.24126	0.977
Post pump 75 Minutes	35.7895±3.88128	35.0526±4.3394	0.838
Post pump 90 Minutes	36.2105±4.69727	35.4211±4.19412	0.400
Ph			
Before induction	7.2385±0.03148	7.4013±0.04051	0.811
After induction	7.4037±0.02712	7.4147±0.02913	0.620
At 15 minutes	7.41±0.03073	7.4068±0.02709	0.380
At 30 minutes	7.4153±0.03204	7.4137±0.0265	0.013
At 45 minutes	7.4126±0.026	7.4132±0.02605	0.055
Post pump 15 Minutes	7.4189±0.02558	7.4142±0.02479	0.327
Post pump 30 Minutes	7.2963±0.0481	7.3137±0.04821	0.903
Post pump 45 Minutes	7.3111±0.0463	7.3163±0.04487	0.796
Post pump 60 Minutes	7.3253±0.04777	7.3132±0.05089	0.286
Post pump 75 Minutes	7.3295±0.0454	7.3105±0.03951	0.910
Post pump 90 Minutes	7.2957±0.0508	7.4137±0.0265	0.630
Post pump 120 Minutes	7.31±0.04751	7.2963±0.0481	0.590

Table-IV. END TIDAL CO_2 ($ETCO_2$) AND PH VARIATIONS.

PEAK AIR WAY PRESSURES			
	Group – 1 (n=31)	Group – 2 (n=31)	P-Value
	Mean±S.D.	Mean±S.D.	
After induction	15.6317±4.85642	15.8912±4.90291	0.584
At 15 minutes	15.4322±5.15658	15.2547±4.47858	0.057
At 30 minutes	15.0000±5.03322	14.6842±4.06957	0.215
At 45 minutes	14.8421±4.25915	14.4211±5.04773	0.32
Post pump 15 Minutes	16.3158±4.44788	15.4211±4.01823	0.000
Post pump 30 Minutes	14.7368±4.99825	15.6316±4.41224	0.463
Post pump 45 Minutes	15.7368±4.74742	15.4211±4.36292	0.614
Post pump 60 Minutes	17.8421±4.33671	15.4211±4.5864	0.020
Post pump 75 Minutes	17.5263±3.27225	15.6316±3.91877	0.470
Post pump 90 Minutes	15.0000±4.77261	14.3158±4.26943	0.503
INOTROPIC DRUGS			
Total dose of Dobutamin	941.25±523.3022	970.5264±492.91660	0.671
Total dose of Noradrenaline	438.1578±346.06073	425.9474±301.16413	0.637
Total dose of Adrenaline	1148.3333±888.63784	1188.000±884.38009	0.222
Total dose of Isosorbide	408.1436±361.00732	435.9474±312.14527	0.565

Table-V. Peak air way pressures and inotropic drugs used.

DISCUSSION

Cardiac surgery puts enormous strains on human body which is already compromised by the diminished cardiac reserves, hypoxemia, deranged and improper neurohormonal and hemodynamic responses. Improper sedation and analgesia during ventilation may produce sympathetic stimulation leading to unrestrained changes in heart rate and blood pressure thus resulting in excessive bleeding and ultimately significant morbidity and mortality. Our results showed that all hemodynamic parameters (HR, SAP, DAP, MAP) were not only lower in group 1 (DEX+PROPOFOL) but also lie in 95% CI of normal range. This indicates that combined effects of both drugs results in very stable hemodynamics than the propofol alone, the reason is as follows; propofol is a well-known vasodilating and myocardial depressant agent. This results in sympathetic stimulation because of increased baroreceptor activity resulting in increased heart rate, SAP, DAP and MAP thus may further compromising already strained hearts. DEX is a known sympatholytic agent, because of its strong central alpha 2 agonistic activity, this sympatholytic activity is masked when given in combination with propofol. This results in peripheral vasoconstrion effects of DEX (because of weak alpha 1 and alpha 2b agonistic activity and) thus preserving the SAP, DAP and avoiding the reactionary rise in heart rate.[18]

KIM et al, also proved that combined administration of DEX and propofol versus propofol alone results in greater cardiovascular stability and less adverse effects than using single drug.[19]

DEX produces a dose dependent blood pressure response ,with higher plasma concentration (produced by bolus) incites a hypertensive response and lower plasma concentration (produced by low maintenance dose as we used{0.3microgram/kg/hour}) results in a hypotensive response.[19] As evidenced by our results that, although SAP, MAP and DAP rose to maximum levels when bolus doses of DEX were given in group 1, but neither they dropped to dangerously low levels to produce hypotension (when maintenance dose of DEX and PROPOFOL were given)nor they became unstable thus indicating a synergistic response of both the drugs in comparison to propofol alone. This again can be explained by contrasting effects of propofol and DEX on sympathetic nervous system thus leading

to more stable hemodynamics in comparison to conditions when they are used alone. GUPTA et al, concluded that combined administration of DEX and propofol results in better hemodynamic profile and sedation even in children undergoing cardiac catheterization.[20]

An unwanted shortcoming of general anesthesia is awareness during surgical procedure, a common happening in cardiac surgery with reported incidence of 0.2%-2%.[21] Post-operative awareness was least experienced by group 1 (p value .015) as compared to group 2. Various studies have shown comparable results of DEX versus propofol in terms of awareness citing DEX as effective as propofol.[22,23] Thus when both the drugs were combined they produced far better result than the single drug.

Delirium is a fairly common occurrence in mechanically ventilated patients. It is a global abnormality of perception, cognisance and attentiveness posing significant challenge on treating physician. Various studies have described effects of DEX on delirium. A recent study proved that delirium may be more associated with DEX in comparison to other sedatives.[24] However, a large meta-analysis proved DEX more effective in reducing incidence of delirium in comparison to propofol or sevoflourane.[25] our study indicated more incidence of delirium in group 1 than in group 2 thus indicating that when DEX was combined with propofol the incidence of delirium became more as compared to propofol alone in group 1.

Both the groups showed same trends in terms of end tidal CO_2, peak airway pressure and ph. Duration of surgery and use of inotropic agents is also not statistically significant.

There are several limitations of this study, firstly it is a single center based study. Secondly, the patient population is relatively small but as ours was a new center so we could not enrolled higher number of patients. Moreover, we could not blind the anaesthesiologist about the methods of anesthesia delivery as the administration of DEX and propofol is clearly visible.

CONCLUSION

Combined administration of DEX and propofol produced a more stable hemodynamics than administering propofol alone during and after cardiac surgery. Intraoperative awareness was minimized when these two agents were given in combination but delirium was observed more in the combined group than in propofol alone patients.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Sajid Farooq	Conceived, designed the methodology and wrote manuscript.	
2	M. Farhan Ali Rizvi	Helped in writing and finalization.	
3	Sana Urooj Hashmi	Helped in data collection.	
4	Mirza Ahmad Raza Baig	Did review, did data analysis.	
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