Original Article

Effects of Dexmedetomidine on Clinical Outcomes and Renal Function after CABG

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Abstract

Background: This study was carried out to determine the effects of dexmedetomidine on clinical outcomes and renal function after coronary artery bypass grafting (CABG) to address the increased rate of CABG? and the importance of modification in stress responses and control of adverse effects on renal function and with the aim of cost reduction.

Materials and Methods: This double-blind randomized clinical trial was carried out with the participation of 129 subjects under elective CABG in Rajaei Heart Center, Tehran, Iran in 2017. Patients were randomly assigned to four groups with simple randomization including one placebo (normal saline infusion) group and three dexmedetomidine groups; 0.5 µg/kg/h on CPB, 0.5 µg/kg/h in 24 hours, and 0.75 µg/kg/h in 24 hours. The blood pressure, blood urea nitrogen (BUN), serum creatinine, transfused blood volume, urine volume, and hemofiltration on pump and lactate were assessed at different time intervals.

Results: Results showed more stability especially in central venous pressure (CVP) (p=0.001) and systolic blood pressure (p=0.006) in the groups receiving dexmedetomidine 0.75 µg/kg/h per 24 hours. But diastolic blood pressure and heart rate were the same across the groups (p>0.05). All other variables including hepatic and renal function tests were the same across the groups (P>0.05).

Conclusion: Overall, according to the obtained results in the current study, it may be concluded that dexmedetomidine would have some promising effects on hemodynamic stability but there are no obvious renoprotective effects for this medication.

Keywords: Coronary Artery Bypass Graft, Dexmedetomidine, Renal Function

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Introduction

Cardiovascular disease is a common cause of morbidity and mortality is seen in approximately 17 million subjects in the United States (1). Acute kidney disorders in subjects undergoing cardiac surgery are a common postoperative problem in subjects undergoing coronary artery bypass graft (CABG). The prevalence rate of acute kidney injury varies from 3 to 30 percent

(2-4) and nearly 0.5 to 3 percent in cases that would require dialysis (5-8). Known risk factors include age, BMI, lipid-lowering agents, hypertension, peripheral vascular diseases, chronic lung diseases, hemoglobin concentration, previous cardiac surgery, emergency heart surgery, and any type of operation which may increase the risk of acute kidney injury (8-9). It is also related to ward stay in patients undergoing coronary artery bypass grafting (CABG) (5). Furthermore, in cases with dialysis requirements, it may result in a high (60%) mortality rate (4, 5).

In this research, with regards to the increased rate of CABG and the importance of modification in stress responses and control of adverse effects on renal function, and with the aim of cost reduction we carried out this study to determine the effects of dexmedetomidine on clinical outcomes and renal function after CABG.

Methods

This double-blind randomized clinical trial was done with the participation of 129 subjects under elective CABG in Rajaei Heart Center, Tehran, Iran in 2017. Inclusion criteria were the signing of informed consent forms, lack of previous renal disorder, and no diuretic use, lack of peripheral vascular disease or chronic lung disorders, and lack of any previous cardiac surgery. The IRCT code was IRCT20170912036157N1.

In all patients monitoring for venous and arterial blood pressure was done at the entry to the operation room. Anesthesia induction was performed using the same method and drugs. Patients were randomly assigned into four groups with block randomization including one placebo (normal saline infusion) group (A) and three dexmedetomidine groups; 0.5 µg/Kg/h from induction of anesthesia till the end of CPB (B), 0.5 µg/Kg/h from induction of anesthesia for 24 hours (C), and 0.75 µg/Kg/h from induction of anesthesia for 24 hours (D). When the mean arterial pressure reached lessthan 50 mmHg and the heart rate decreased to less than 60 per minute the drug was discontinued for 30 minutes and fluid administration was done. After normalization of blood pressure and heart rate, the infusion was initiated again.

The tidal volume was set at 10 ml/kg with the optimal respiratory rate for age by anesthesia machine to maintain PaCO2 between 30 and 35 mmHg under mechanical ventilation. The priming solution of the bypass machine includes ringer-lactate 800 ml, mannitol 20% 100 ml, and heparin 5000 units for all patients. The mean arterial blood pressure was maintained between 40 and 70 mmHg. Total bypass time and aorta cross-clamp time were recorded. Hypotension and hypertension during pump state were treated with phenylephrine and Trinitroglycerine (TNG), respectively; besides, the used doses were recorded. The other variables including age, gender, blood pressure, blood urea nitrogen (BUN), serum creatinine, transfused blood volume, urine volume, and hemofiltration on pump and lactate were assessed at different time intervals according to lab data and medical documents. All assessments were done by a single-blinded trained nurse.

Data analysis was performed on 130 subjects including 42 patients in the control group and 87 subjects in the three intervention groups. Data analysis was performed by SPSS (version 13.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Chi-Square, ANOVA, and repeated-measure-ANOVA tests were used and were considered statistically significant at P values less than 0.05.

Results

The age and body mass index (BMI) were matched across the groups (Table 1). Previous medical history was also alike across the groups (Table 2). Except for operation time and intensive care unit (ICU) stay the other time intervals were matched across the groups (Table 3). As shown in Table 4 the utilized inotrope drugs in the operating room and ICU were alike across the groups ($P > 0.05$). As demonstrated in Table-5 all measured biochemical and arterial blood gas (ABG) and clinical results were matched across the groups ($p>0.05$). However, the heart rate and diastolic blood pressure had no significant alteration difference across the groups whereas the systolic blood pressure and central venous pressure (CVP) alteration differed significantly in the groups (Table 6) with better measures in dexmedetomidine 0.75 µg/kg/h for 24 hours.

Discussion

Table 1: The age and BMI distribution across the groups.

Group		Age	Body mass index
Placebo (A)	**Mean**	56.90	26.69
	Std. Deviation	13.36	4.82
0.5 micro on CPB (B)	**Mean**	61.56	26.74
	Std. Deviation	11.45	4.68
0.5 micro 24 h (C)	**Mean**	58.69	26.87
	Std. Deviation	11.66	4.49
0.75 micro 24 h (D)	**Mean**	57.00	26.95
	Std. Deviation	13.08	4.56

Table 2: Background diseases across the groups.

	Group							
	Placebo (A)		**0.5 micro on CPB (B)**		**0.5 micro 24 h (C)**		**0.75 micro 24 h (D)**	
	Count	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**
Hypertension	19	30.6%	21	33.9%	11	17.7%	11	17.7%
Diabetes	6	21.4%	0	.0%	11	39.3%	11	39.3%
Smoking	14	45.2%	8	25.8%	4	12.9%	5	16.1%
Thyroid Disease	0	.0%	0	.0%	0	.0%	2	100.0%
CVA	2	28.6%	0	.0%	1	14.3%	4	57.1%
Hyperlipidemia	10	34.5%	7	24.1%	7	24.1%	5	17.2%
Opiate/drug abuse	16	51.6%	8	25.8%	4	12.9%	3	9.7%

Table 3: Time intervals in the study groups.

Group		**CPB time**	**X clamp**	**operation Time**	**Mechanical Ventilation Time**	**ICU stay**	**Drainage 48hr**
Placebo (A)	Mean	81.80	44.04	188.18	14.89	36.02	790.51
	Std. Deviation	32.40	18.20	113.56	4.84	18.10	438.72
0.5 micro on CPB (B)	Mean	87.96	44.81	264.09	17.87	51.54	689.58
	Std. Deviation	41.66	21.92	66.93	8.63	26.03	207.98
0.5 micro 24 h (C)	Mean	88.90	54.56	4.62	60.74	34.00	745.16
	Std. Deviation	38.19	23.74	1.02	249.53	27.94	310.20
0.75 micro 24 h (D)	Mean	83.87	50.08	28.20	77.15	36.73	776.08
	Std. Deviation	26.12	18.89	59.10	298.90	24.931	544.78

As can be seen, the results showed more stability especially in CVP and systolic blood pressure in the

Table 4: Utilized inotropic agents in the study groups.

	Group							
	Placebo (A)		0.5 micro on CPB (B)		0.5 micro 24 h (C)		0.75 micro 24 h (D)	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Epinephrine OR	11	31.4%	9	25.7%	10	28.6%	5	14.3%
Norepinephrine OR	1	50.0%	0	.0%	0	.0%	1	50.0%
Milrinone OR	0	.0%	1	50.0%	1	50.0%	0	.0%
Epinephrine CU	15	37.5%	7	17.5%	13	32.5%	5	12.5%
Norepinephrine ICU	1	33.3%	0	.0%	1	33.3%	1	33.3%
Dopamine ICU	0	.0%	0	.0%	1	100.0%	0	.0%
Dobutamine ICU	0	.0%	0	.0%	1	100.0%	0	.0%
Milrinone ICU	0	.0%	1	33.3%	2	66.7%	0	.0%

receiving Dexmedetomidine 0.75µg/kg/h for 24 hours. But diastolic blood pressure and heart rate were the same across the groups. All other variables including hepatic and renal function tests were the same across the groups.

The study by Zhai et al (24) revealed that dexmedetomidine infusion would result in renoprotective effects in patients undergoing CABG procedures leading to decreased rate of acute kidney injury due to decreased activity of super-oxide dismutase enzyme. But in our study, none of the factors of BUN and creatinine differed significantly in the different groups. This difference may be due to the

Table 5: Utilized inotrope agents across the groups.

	Group							
	Placebo (A)		0.5 micro on CPB (B)		0.5 micro 24 h (C)		0.75 micro 24 h (D)	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Preoperative ALT	24.38	13.29	26.71	16.13	36.11	65.43	21.22	7.15
Postoperative ALT	34.67	55.76	26.75	13.94	21.22	10.72	23.12	14.53
ALT24hr	29.26	25.81	51.33	114.18	23.22	20.16	20.33	11.17
ALT48hr	20.18	12.16	88.13	328.44	54.00	187.76	196.26	785.55
Preoperative AST	22.86	9.37	20.89	7.98	25.22	14.57	21.08	7.10
Postoperative AST	46.26	88.15	33.90	14.29	42.97	27.16	42.33	14.65
AST24hr	65.14	153.25	71.40	171.27	55.69	52.24	46.58	21.96
AST48hr	36.09	27.22	89.16	272.18	96.88	285.62	743.42	3084.35
Preoperative HGB	13.36	1.60	13.30	1.87	12.22	2.26	12.87	2.39

Postoperative HGB	10.25	1.34	10.35	1.24	9.97	1.45	68.19	284.11
HGB24hr	9.52	1.87	9.89	1.26	9.48	1.80	10.12	1.48
HGB48hr	9.47	1.20	10.04	1.36	9.23	1.05	9.75	2.43
Preoperative Cr	.96	.21	.98	.30	1.11	.24	1.23	.26
Postoperative Cr	.87	.23	1.52	2.50	1.00	.28	1.09	.27
Cr24hr	.90	.28	.93	.24	1.17	.31	1.17	.29
Cr48hr	.86	.31	.89	.35	1.03	.30	1.19	.64
Preoperative BUN	16.15	6.56	19.09	8.54	19.27	7.97	18.04	6.22
Postoperative BUN	18.88	8.06	17.84	5.66	21.31	6.87	21.63	11.26
bun24HR	20.31	6.52	26.22	28.76	24.41	8.24	23.92	9.35
BUN48hr	19.78	8.34	22.90	10.85	22.77	9.94	23.58	10.02
Preoperative Lactate	1.04	.44	.97	.37	.74	.44	.94	.26
Postoperative Lactate	7.53	33.30	5.10	18.60	2.36	2.02	2.14	1.31
lactat24hr	2.56	1.56	2.85	1.95	1.83	1.30	3.40	4.78
lactat48hr	1.40	.28	.	.	1.13	.44	4.50	7.60
Diuresis OR	662.50	511.88	785.31	660.55	1116.13	650.31	1333.91	1266.22
Diuresis First day	2102.57	749.77	2283.33	769.05	2385.00	824.63	2615.42	999.37
duresis2day	2369.12	735.69	2292.19	569.11	2720.31	590.91	2508.33	619.37
duresis3dat	.	.	.	.	1667.00	1526.98	2000.00	.
hemofiltration	1942.59	591.07	1645.65	603.95	1550.00	441.59	1783.33	567.16
Preoperative Hemoglobin	13.46	1.46	13.30	1.87	12.54	1.82	12.78	2.19
Hemoglobin ICU Entry	14.99	20.76	13.58	18.45	9.98	1.49	10.16	1.68
hemoglobin24hr	9.46	1.83	9.89	1.26	9.25	1.20	9.82	1.36
hemoglobin48hr	9.53	1.21	10.04	1.36	9.55	.99	10.08	1.67
Preoperative K	4.86	5.16	3.87	.61	3.88	.52	3.76	.57
K30min	5.55	5.15	5.36	1.22	4.35	.89	4.20	.93
Postoperative K	4.83	.83	5.03	.79	4.36	.71	4.12	.70
K ICU entry	4.74	.88	5.03	.79	5.29	5.49	4.16	.59
k12hr	4.32	.58	4.33	.47	4.33	.46	4.21	.51
k24hr	4.98	4.99	4.27	.53	4.11	.46	4.01	.44
Preoperative Na	144.30	4.22	144.03	4.61	136.21	23.39	144.46	5.36
Na30min	136.12	4.72	135.19	3.87	136.25	4.53	141.08	6.59
Postoperative Na	133.88	5.77	135.03	4.71	135.80	4.36	139.00	3.70
Na ICU entry	140.74	4.88	140.75	5.48	137.84	4.06	139.29	6.04
Na12hr	142.55	5.50	143.94	5.84	141.63	24.33	143.71	5.10
Na24hr	138.60	21.93	133.31	31.94	141.47	6.44	140.88	5.15
HCO3preop	23.34	3.47	22.59	3.38	22.77	2.67	21.74	2.30
HCO30min	21.15	2.25	20.03	3.20	20.97	2.68	20.83	2.58
HCO3postop	20.63	2.80	21.19	2.49	19.20	2.36	19.93	1.79
HCO3icuENTERANCE	19.48	2.18	20.09	2.22	22.50	17.98	19.25	1.89
HCO12hr	20.24	2.68	21.00	2.27	19.63	2.95	19.54	2.57
HCO24HR	21.55	3.19	21.88	3.05	22.06	2.95	22.04	3.34
Preoperative PCO	34.37	5.42	33.74	7.92	34.77	5.12	33.09	4.77
PCO30min	35.90	6.45	36.81	6.70	34.78	5.29	32.92	5.12
Postoperative PCO	33.90	6.01	35.69	4.37	34.68	7.86	35.38	6.13
PCO ICU entry	34.69	7.39	33.28	6.84	37.59	23.17	34.35	5.77
PCO22hr	33.48	6.10	36.47	5.46	34.84	5.73	33.71	4.72
PCO24hr	34.64	5.31	35.38	6.95	38.34	7.69	34.96	5.90

O2SAT preop	95.26	3.19	93.03	10.33	94.26	4.02	93.48	12.69
o2sat30MIN	99.10	4.36	99.75	.44	100.00	.00	99.88	.45
O2SAT postop	99.03	1.97	100.28	5.50	98.56	1.45	98.69	1.30
o2satICUENTERANCE	95.43	3.97	93.72	15.67	97.69	1.71	97.87	1.49
O2SAT12hr	96.57	2.24	95.50	2.50	97.50	1.41	97.13	1.94
O2SAT24hr	94.43	7.24	91.22	9.88	92.91	9.24	94.33	8.66
po2PREOP	103.97	70.34	98.53	60.79	84.06	40.69	95.57	44.13
po230MIN	267.85	102.42	267.00	71.12	321.83	105.82	336.42	87.28
po2postop	225.20	112.38	198.79	63.34	181.28	72.56	181.40	85.86
po2icuENTERANCE	104.36	49.12	100.97	27.05	143.06	51.84	143.21	56.12
po212hr	98.75	31.88	89.91	27.07	120.16	43.62	118.63	39.67
po224hr	87.60	27.28	76.63	18.18	90.59	34.07	110.67	57.36
Preoperative pH	7.44	.04	7.43	.06	237.67	1281.95	10.79	16.18
PH30min	7.38	.06	7.35	.06	7.40	.05	19.85	60.95
Postoperative pH	7.40	.07	7.38	.05	7.34	.10	16.80	36.57
pH ICU entry	7.37	.07	7.39	.07	7.38	.08	12.26	24.01
PH12hr	7.38	.05	7.37	.05	30.14	128.81	12.15	23.40
PH24hr	7.40	.04	7.40	.05	30.37	130.04	8.64	6.04

dispersion of the data for kidney function tests in the three groups that received dexmedetomidine.

During CABG the non-pulsation blood flow, emboli, catecholamine release, inflammatory mediators, and hemoglobin released from destructed blood cells would result in increased renal vessel resistance and decreased glomerular filtration rate from 25 to 75 percent (9). Dexmedetomidine is a selective alpha-2-adrenergic agonist of sedation, analgesia, and anti-anxiety effects plus it has useful effects for reduction of anesthetics and increase of hemodynamic stability (6, 7). Regarding the high application of this drug in CABG procedures, considerable effects in the reduction of postoperative pulmonary and cerebral injuries are reported (8-10).

It seems that stimulation of Alpha-2b receptor in locus coeruleus would result in a dose-dependent reduction of norepinephrine leading to increased renal blood flow (11). Also, it may decrease stress responses to surgery trauma with direct and indirect effects as an alpha agonist. Besides, dexmedetomidine may result in improvement in blood flow of the kidneys due to decreased pre-synaptic norepinephrine leading to vasodilatation (12-15). However, drug safety has not yet been established but there are some reports in animal models of decreased ischemia-reperfusion injury in kidneys in an increased urinary output (11-13). Väisänen et al (14) assessed the effect of dexmedetomidine on stress response in dogs. They found that premedication with dexmedetomidine would result in a reduction of preoperative stress hormones and also leads to decreased sympathetic activity by catecholamine stability. This is the main cause of a better hemodynamic status especially for systolic blood pressure in our study.

The study by Balkanay et al (15) demonstrated that dexmedetomidine would have a dose-dependent effect, especially for renoprotection. Such dose-dependent effects were seen in our study especially regarding CVP and systolic blood pressure. The study by Mukhtar and colleagues (16) showed that dexmedetomidine administration in children undergoing congenital heart surgery would result in a reduced rate of hemodynamic responses as well as systolic blood pressure in adults. Similar studies have been in favor of our findings (17-18).

Conclusion

Overall, according to the obtained results in the current study, it may be concluded that dexmedetomidine would have some promising effects on hemodynamic stability but there are no obvious renoprotective effects

Table 6: Measured hemodynamic variables across the groups.

	Group							
	placebo		0.5 micro on cpb		0.5 micro 24 hr		0.75 micro 24 hr	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
sysPREOP	108.55	21.78	113.81	16.48	124.69	18.49	129.26	24.86
sys30min	104.75	26.05	117.16	17.17	70.17	16.88	68.17	9.72
syspostop	112.26	18.95	109.28	12.34	112.63	12.90	107.91	12.94
sysICUenterance	115.83	18.55	113.59	11.21	103.00	21.86	100.79	20.52
sys12hr	117.67	16.06	113.59	11.21	111.22	13.60	112.46	13.39
sys24hr	118.19	18.31	119.50	20.65	111.94	10.15	110.04	12.07
sys36hr	116.68	14.08	112.47	13.81	113.67	13.26	115.88	13.34
sys48hr	116.92	13.23	119.47	13.64	118.80	13.25	115.94	18.81
diaPREOP	70.43	12.97	65.53	12.92	71.94	10.65	74.39	15.84
diaPOSTOP	55.64	12.32	57.47	13.20	62.88	8.08	57.30	10.52
diaICUenterance	64.55	11.89	63.88	11.88	57.88	13.04	63.71	13.06
dia12hr	63.81	9.80	64.56	10.88	62.06	9.03	62.17	8.42
dia24hr	65.00	9.67	65.72	12.81	61.78	14.12	60.92	7.29
dia36hr	64.98	9.01	63.19	11.00	64.00	8.03	66.75	9.98
dia48hr	63.73	12.99	68.38	13.30	68.20	11.80	63.41	8.97
cvpPREOP	10.68	3.50	10.81	3.20	9.72	2.23	7.88	2.97
cvppostop	9.54	4.30	10.28	3.00	9.50	3.35	10.32	3.73
cvpICUenterance	11.67	3.94	11.19	2.05	11.41	15.17	10.21	4.20
cvp12hr	15.79	5.20	17.25	3.86	11.50	3.62	12.75	3.94
cvp24hr	17.21	5.34	16.97	4.55	13.16	4.14	13.63	4.36
cvp36hr	18.08	5.81	18.81	3.97	12.83	4.27	14.38	4.26
cvp48hr	17.85	3.48	19.75	5.73	14.75	4.80	15.63	5.18
HRpreop	71.85	14.97	68.34	12.05	72.94	15.14	80.04	12.23
HRpostop	83.88	16.50	88.41	16.13	82.78	11.92	85.17	10.50
HRicuenterance	81.76	15.47	88.59	13.26	82.06	17.12	84.29	11.15
HR12hr	84.05	14.78	86.22	15.01	80.69	14.55	85.21	12.01
HR24hr	86.10	10.95	88.09	13.71	82.31	11.78	85.75	12.12
HR36hr	85.80	11.31	89.03	10.43	83.17	10.36	84.08	12.17
HR48hr	91.27	20.49	91.94	10.62	84.65	12.84	85.65	10.23

with this medication. However further studies with larger sample size and control for possible confounding factors would result in more pieces of evidence in this era in patients undergoing open-heart surgery.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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