MODESTUM
OPEN ACCESS
Eurasian Journal of Analytical Chemistry
ISSN: 1306-3057
2018 13(3):em15
DOI: 10.20933/ejac/85013

Comparison of Infusion and Bolus Injections of Phenylephrine on Hemodynamic Stability during Cardiopulmonary Bypass and their Effects on Bicarbonate and Lactate Blood Level

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Received 27 August 2017 ▪ Revised 8 December 2017 ▪ Accepted 25 December 2017

ABSTRACT

During open cardiac surgery that the heart should be suspended, for preventing damage of other tissues and organs, vasopressors drugs have been used for maintenance of blood pressure. The aim of this study was the comparison of infusion and bolus injections of phenylephrine on hemodynamic stability during cardiopulmonary bypass and their effects on bicarbonate and lactate blood level. In this randomized double-blind clinical trail, 88 patients who were candidate for on-pump coronary artery bypass grafting, were considered and then divided into the infusion and bolus groups. In the beginning and at the end of study, the blood pressure and laboratorial variables was recorded and finally analyzed by SPSS software. According to the obtained information, out of 88 examined patients, 52.2% of them were received phenylephrine in bolus regimen while 47.8% were received phenylephrine in infusion regimen. The mean age of patients in the bolus and infusion groups was 56.59 ± 19.5 and 59.2 ± 10.16 years, respectively. The results show that there were not statistically significant differences in mean values of the MAP, PH, HCO_3 and lactate between two groups. The results show that the infusion injection of phenylephrine has no advantage than bolus injection on hemodynamic stability during cardiac pulmonary bypass, and on the bicarbonate and lactate blood level.

Keywords: phenylephrine, hemodynamic stability, cardiac pulmonary bypass

INTRODUCTION

Cardiovascular diseases are the main cause of mortality in the United States. Despite significant advances in preventive measures and early medical interventions, the extent of these diseases often necessitates invasive procedures such as angioplasty, stenting and cardiac surgery [1]. The interest in surgically addressing cardiac dysfunction dates back to the late 1800s. The introduction of cardiopulmonary bypass machine in 1950 enabled surgeons to perform a heart procedure in a motionless organ while ensuring adequate protection to other tissues and organs [1]. Technological advance in 1990 allowed surgeons to avoid the complications of cardiopulmonary bypass. For providing adequate perfusion pressure immediately after cardiopulmonary bypass, the vasoconstricting drugs are usually used. To receive this purpose, phenylephrine that is a synthetic sympathomimetic drug chemically related to epinephrine and ephedrine, is usually applied [2]. Phenylephrine administration methods could have effect on baroreceptor sensitivity [3]. Phenylephrine is a selective α 1 receptor agonist at clinically relevant doses, and at much higher doses β agonist action can only be seen. An intravenous dose of phenylephrine has rapid onset and duration of action of 5-10 min. Tachyphylaxis accompanied with

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phenylephrine may be caused by the down-regulation of α adrenergic receptors and could be reversed by using hydrocortisone [4]. It was seen that cerebral oxygenation significantly decreased after phenylephrine bolus treatment but its mechanism is intriguing. It has been demonstrated that after using phenylephrine, the sympathetic nerve activity originating from the superior cervical ganglion increases promptly that caused rapid increase in arterial pressure [5]. Also after using phenylephrine, the peak changes in CO and MAP occurred significantly earlier than those of the ephedrine. SVR changes after the vasopressors suggested a marked rise in afterload after phenylephrine [6]. Recently, minimally invasive cardiac surgery has been performed on patients with specific types of lesions such as the left anterior descending (LAD) artery, which can be exposed and bypasses with a left internal mammary artery (LIMA) via a left thoracotomy without the support of bypass pump and sternotomy. The major cardiac surgery methods in England are coronary artery bypass grafting (CABG) and heart valve repair or replacement surgery [7]. In this surgery, a piece of vein or artery is used to bypass blocked artery. It is nowadays one of the most common surgical procedures. Almost 30,000 CABG surgeries are done in England per year [8]. Although, the CABG significantly decreases the signs and symptoms of the disease such as angina, it is not a treatment for a coronary heart disease (CHD). This operation has a long-term effect of almost 20 years [9]. Nevertheless, rapid mortality following CABG has increased over the last 10 years, indicating the high intensity of the disease. Fortunately, the CABG has shown the longer survival in a specific group of such patients. Although, the chance of mortality after CAGB is high, this risk would be higher if the operation has not been performed. Annual mortality after medical treatment is almost 2%, which will decrease through surgery. Moreover, the quality of life and functionality are improved after easing pain from angina and shortness of breath. The CABG is influenced by different factors including the age, site of blood vessel to be used for the graft, access to the duct, and surgeon's opinion (9). In a normal cardiac surgery, the heart is suspended and CPB takes over the function of the blood circulation. Although, this method has been successful for three decades, physiological disorders after CPB and the need for long hospital stay have made it a disadvantageous technique. Different types of CABG techniques are as follows: minimally invasive cardiac surgery including CABG with standard sternotomy without CPB (off-pump or OPCAB), off-pump CABG through left anterior small thoracotomy (LAST), minimally invasive direct coronary artery bypass (MIDCAB), on-pump valve surgery with mini-sternotomy, and computerized robotic system techniques that allow on-pump CABG and heart valve surgeries through the use of smaller incision with the help of a videoscope and femoral bypass [9].

This study was performed to compare the effect of phenylephrine infusion regimen and phenylephrine bolus regimen on hemodynamic status of patients during cardiopulmonary bypass and its effects on the bicarbonate and lactate levels of blood**.**

MATERIALS AND METHODS

This study was approved by ethics committee of Zanjan University of Medical Sciences (ZUMS.REC.1392.21). The clinical trials were also registered and approved by research council of the Zanjan University of Medical Sciences.

This randomized double-blind clinical trial included 88 patients with ASAII, III (aged 50-70 years), who were candidate for on-pump coronary artery bypass grafting during 2012-2014 in Mousavi Hospital, Zanjan, Iran. Inclusion criteria were: pumping time and extracorporeal circulation of less than 120 minutes, need for phenylephrine administration, maximum average ventricular systolic dysfunction, no acute liver failure, no carotid stenosis of above 50%, no addiction to opioid substances, and no addition to drugs with effect on the central nervous system, no use of psychotropic drugs, and no history of uncontrolled hypertension. The patients underwent general anesthesia after receiving premedication, using the same method. Anesthetic induction was done with the administration of fentanyl (10 mic kg^{-1}), etomidate (2.0mg kg^{-1}), midazolam (30 mic kg^{-1}), and cisatracurium (0.2 mg kg^{-1}). General anesthetia was maintained with administration of ayzuflurn (0.6%), nitroglycerin (5-10 mic min^{-1}), fentanyl (10 mic kg^{-1}), midazolam (30 mic kg^{-1}), and atrakuryum (0.2 mg kg^{-1}). During the extracorporeal blood circulation, perfusion pressure was maintained in the range 60-90. Blood pressure was controlled with administration of higher dose of phenylephrine in case of hypotension, lower dose of phenylephrine in case of hypertension to higher than 100, and intravenous nitroglycerine (0.025-1 mic kg^{-1} per minute) in case of antihypertensive failure. Half an hour after bypass pumping, the ratio of lactate and bicarbonate levels to pumping time was measured via arterial blood gas (ABG) technique. Patients were then divided into the intervention (infusion) and control (bolus) groups through randomized method with blocks of size 4. In case of pump-induced hypotension during extracorporeal blood circulation, bolus and infusion patients received 10 mg ml^{-1} and 3 mg h^{-1} doses of phenyephrine 100 mic (Sandoz, Canada), respectively. The aim was to maintain the average arterial blood pressure in the range 60-90. To prevent the confounding effect of CO_2, its level was controlled every 30 minutes, and all CO_2 levels higher than 35 and lower than 30 mm Hg^{-1} were treated aggressively. The ABG was re-performed immediately after the surgery, 30-minute after the end of pumping, and at admission to the ICU to control blood lactate and bicarbonate levels. If blood pressure was higher or lower than the target range (60-90) for more than 3

Table 1. Abundances of measured variables between bolus and infusion groups

Variables		Bolus group		Infusion group		Total		P-Value
		Number	Percentage	Number	Percentage	Number	Percentage	
Diabete history	Yes	14	48/3	15	51/7	29	100	0/389
	No	32	54/2	27	45/8	59	100	
Hypertention history	Yes	19	41/3	27	58/7	46	100	0/035
	No	27	64/3	15	35/7	42	100	
Renal disease history	Yes	0	0	1	100	1	100	0/477
	No	46	52/9	41	47/1	87	100	
Right carotidartery involvement	0	42	50/6	41	49/4	83	100	0/538
	15	1	100	0	0	1	100	
	30	1	100	0	0	1	100	
	50	2	66/7	1	33/3	3	100	
Left carotidatery involvement	0	45	53/6	39	46/4	84	100	0/235
	15	1	100	0	0	1	100	
	40	0	0	2	100	2	100	
	45	0	0	1	100	1	100	
Common carotidatery involvement	0	43	51/8	40	48/2	83	100	0/294
	15	2	100	0	0	2	100	
	30	0	0	2	100	2	100	
	49	0	0	1	100	1	100	

Table 2. Average and standard deviation of measured variables between bolus and infusion group

Variables	Bolus group	Infusion group	P-Value
Cardiovascular bypass duration (min)	113.5±33.54	98.75±28.68	0/03
Clamping time (min)	58.57±20.39	53.07±16.13	0/167
Ejection fraction (EF)	50.87±8.18	44.92±12.04	0/008
Total dose of phenylephrine	23.02±8.71	26.61±13.61	0/143

minutes, the patient would be excluded from the study. Since increase or decrease of blood pressure can cause ischemic changes in tissues, patients with such problems were excluded to avoid research bias.

The obtained information was statistically analyzed with SPSS software. In terms of quantitative variables, the scope of changes, mean, standard deviation and other factors required for obtaining p-value were extracted. P-value less than or equal to 0.05 was considered significant.

RESULTS

According to the results, information of 88 examined patients (52.2% in phenylephrine bolus regimen group and 47.8% in phenylephrine infusion regimen group) were completely gathered. The mean age of patients in the bolus and infusion groups was 56.59 ± 19.5 years and 59.29 ± 10.16 years, respectively, indicating no significant between-groups difference ($p = 0.202$). In terms of surgical procedure, 95.7% and 4.3% of bolus subjects received the CABG and MVR operations, respectively ($p = 0.077$). The frequency of hypertension was significantly higher in the infusion group ($p = 0.035$); whereas, there was no significant between-groups difference in frequency of diabetes, right and left common carotid artery involvement, and history of renal disease [**Table 1**].

According to [**Table 2**], there was a significant between-groups difference in cardiovascular bypass duration and ejection fraction; whereas, there was no statistically significant between-groups difference in the total dose of phenylephrine and clamping time ($p > 0.05$).

Analyses showed no significant between-groups difference in mean values of HCO_3, PH, MAP, and lactate in the activated clotting time (ACT), the first cardioplegia, or the off-pump procedures ($p > 0.05$) [**Table 3**].

Comparison showed a significant difference between the means of mentioned variables in the bolus group in the ACT and the first cardioplegia ($p < 0.05$). All mean values, except for bicarbonate, were significantly different between the first cardioplegia and off-pump surgery ($p < 0.05$). According to [**Table 4**], there was no significant difference between the measured variables among the bolus group in the ACT and off-pump surgery ($p < 0.05$). Moreover, there was a significant difference between the means of the measured variables among the infusion group in the ACT and the first cardioplegia ($p < 0.05$); whereas, means of these variables, except for lactate, were not significantly different in the cardioplegia and off-pump operation ($p < 0.05$) [**Table 4**]**.** According to [**Table 4**], there was no significant difference between the measured variables the infusion group during the ACT and off-pump operation ($p < 0.05$).

Table 3. Comparison of average and standard deviation of measured variables between bolus and infusion groups

Time	Group	Mean Arterial Pressure		PH		HCO_3		Lactate	
		M±SD	P-Value	M±SD	P-Value	M±SD	P-Value	M±SD	P-Value
Accelerating clotting time	bolus	89.74±23.46	0.662[e]	7.44±0.04	0/812	21.3±2.11	0.835[e]	2.24±0.87	0/953
	infusion	91.83±21.16		7.44±0.04		21.39±2.02		2.23±0.77	
First cardioplegia	bolus	61.57±8.79	0/871	7.34±0.05	0/748	20.02±1.56	0/174	3.70±0.93	0/512
	infusion	61.85±6.73		7.34±0.05		19.58±1.40		3.85±0.88	
Off pump	bolus	94.39±25.74	0.237[e]	7.36±0.04	0.712[e]	5.24±2.26	0.129[e]	22.21±11.89	0.611[e]
	infusion	87.16±14.49		7.36±0.05		13.97±1.88		18.83±3.58	

Table 4. P-Values for the measured variables in different times between bolus and infusion

Group	Time	Mean Arterial Pressure	PH	Lactate	HCO_3
Bolus	Accelerating clotting time First cardioplegia	0/0001	0/0001	0/0001	0/003
	First cardioplegia Off pump	0/0001	0/002	0/0001	0/779
Infusion	Accelerating clotting time Off pump	0/663	0/719	0	0/135
	Accelerating clotting time First cardioplegia	0/0001	0/0001	0/0001	0/0001
	First cardioplegia Off pump	0/306	0/055	0/0001	0/407
	Accelerating clotting time Off pump	0/549	0/736	0/094	0

DISCUSSION

This randomized double-blind clinical trial was performed to compare the effect of phenylephrine infusion regimen and phenylephrine bolus regimen on hemodynamic status of patients during cardiopulmonary bypass and its effects on the bicarbonate and lactate levels of blood. According to the findings, although the total dose of phenylephrine in the infusion group was insignificantly higher than the bolus group, there was no significant between-groups difference in the mean values of HCO_3, PH, MAP, and lactate either during the ACT, cardioplegia, or off-pump operations. Comparison of the means of the given variables showed a significantly greater reduction in blood pressure, PH, and bicarbonate level in both group during the ACT as compared to the first cardioplegia; however, the lactate levels in both groups increased significantly. Moreover, the average blood pressure, PH, and Lactate level significantly increased during the first cardioplegia as compared to the off-pump procedure; whereas, no change was observed in bicarbonate level. There was also no significant difference between the measured variables in the bolus group during the ACT and off-pump operation. In the infusion group, only lactate level increased significantly. A study by Doherty et al. [10] compared the effect of phenylephrine bolus dose and phenylephrine infusion dose on hemodynamic status during cesarean section. Results showed no significant between-groups difference in cardiac output. Findings of this study are consistent with those of other studies except that the infusion group in the present study experienced significant decrease in blood pressure. Another study by Grubhofer et al. [7] in Australia show that the administration of phenylephrine during cardiopulmonary pump prevented post-operative complications induced by neural dysfunction through overperfusion and cerebral blood flow increase. Another study by Meng et al. [5] set out to investigate the effects of phenylephrine and ephedrine bolus regimens on cerebral oxygenation. This study was done on 29 patients with ASA I–III undergoing general anesthesia. Results showed that individuals receiving phenylephrine bolus dose 100–200 µg had significant reduction in CO pressure; whereas, no significant change was observed among those receiving phenylephrine bolus dose 5–20 µg. We hypothesized that the blood level of phenylephrine infusion regimen continuously increase the patient's hemodynamics balance and prevents hypertension and hypotension, and thus it is more effective than phenylephrine bolus regimen; however, no significant between-groups difference was observed. The small sample size, diversity of surgical procedures, and effect of other unknown confounding variables may be cause of these results.

CONCLUSION

We concluded from the study that the infusion injection of phenylephrine has no advantage than bolus injection on hemodynamic stability during cardiac pulmonary bypass, and on the bicarbonate and lactate blood level.

ACKNOWLEDGEMENTS

This study was financially supported by Zanjan University of Medical Sciences which this support is acknowledged.

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