EFFECTS OF PHENYLEPHRINE VS NORADRENALINE ON LACTATE LEVEL DURING CARDIOPULMONARY BYPASS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT

Objective: To evaluate effects of phenylephrine vs noradrenaline on lactate level during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Department of Anesthesia, Armed Forces Institute of Cardiology Rawalpindi Pakistan, from Jan to Jun 2019.

Methodology: A total of 200 patients, divided in two groups, group A and B, each consisting of 100 patients. Group A received phenylephrine and group B received noradrenaline, keeping mean arterial pressure between 65-90 mmHg. Serum lactate level was measured before induction, before initiation of cardiopulmonary bypass, after cooling, after rewarming and before shifting to ICU by collecting ABGs blood sample. Lac, Bicarbonate, PH, Hb and Base excess in patients at different time Points was measured. Data was stratified for age, gender, BMI and ASA class (II/III) to deal with effect modifiers. Post stratification T-test was applied taking p-value ≤ 0.05 as significant.

Results: Lactate levels before induction were 1.30 ± 0.05 and 1.40 ± 0.04 in phenylephrine and noradrenaline groups with no statistically significant difference (p= 0.134). Lactate levels before cardiopulmonary bypass were 02.77 ± 1.82 and 03.83 ± 1.17 in phenylephrine and noradrenaline groups with no statistically significant difference (p=0.229). Lactate levels after cooling were 04.98 ± 01.67 in phenylephrine group and 06.11 ± 1.35 in noradrenaline group, with statistically significant difference (p= 0.003). Lactate levels after rewarming were 05.72 ± 01.85 in phenylephrine group and 07.17 ± 02.11 in noradrenaline group, with statistically significant difference (p=0.044). Lactate levels before shifting to ICU were 06.17 ± 02.43 in phenylephrine group and 07.52 ± 02.82 in noradrenaline group, with statistically significant difference (p=0.041).

Conclusion: Nor-adrenaline was associated with increase in the serum lactate levels more significantly as compared to phenylephrine in patients undergoing coronary artery bypass grafting via cardiopulmonary bypass.

Keywords: Bypass, Cardiopulmonary bypass, Cardiopulmonary epinephrine, Lactate, Nor-adrenaline, Nor-epinephrine, Phenylephrine, vasopressor.

INTRODUCTION

Conventionally vast majority CABG procedure is performed on CPB. CPB is nonphysiological, in which patient's pulsatile perfusion is replaced with nonpulsatile flow and is sometimes associated with organ dysfunction, metabolic derangements, haemodilution, coagulopathies and the severity of postoperative organ dysfunction with increased intensive care unit (ICU) length of stay and mortality[1]. The mechanisms leading to organ dysfunction may include global hemodynamic alterations, regional blood flow alterations, mitochondrial dysfunction, and microcirculatory alterations. Cardiopulmonary bypass is associated with release of mediators[2], that seem to be involved in the alterations in tissue permeability[3], leading to microcirculatory changes associated with hypoperfusion, shunting and ischaemia that temporally last well into the post-surgical recovery period, and are paralleled by serum lactate levels[4]. An increase in lactate concentration may be the result of diminished tissue perfusion and oxygen delivery, decreased oxygen extraction, and decreased hepatic lactate clearance. The adequacy of perfusion during hypothermic CPB is generally monitored by means of indirect or global indices of perfusion. The flow rate and perfusion pressure during CPB varies according to the level of hypothermia. A fall in mixed venous oxygen saturation during CPB may occur even though flow rate and perfusion pressure appear adequate. Optimal perfusion pressure on CPB is undecided[5]. Originally, mean arterial pressure (MAP) on CPB was chosen based on cerebral autoregulation limits thought to be in the range of 50-150 mmHg. The studies showing the benefit of higher mean pressures on CPB have used varying protocols with phenylephrine, noradrenaline, adrenaline or vasopressin. Techniques recognising patients benefiting from higher

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perfusion pressures are in their infancy. As a result, there are no head-to-head comparisons of the various vasopressor options. Current consensus guidelines recognise the need for tailored pressure management, but do not distinguish between the pharmacological agents[5]. Vasoplegic shock has an incidence between 5-25% in the peri-CPB period[6,7]. The goal of maintaining vital organ perfusion by returning vascular tone to acceptable levels seems prudent. Phenylephrine is effective in increasing MAP in this setting. This increase has been found to be accompanied by no change in pulmonary capillary wedge pressure (PCWP), heart rate (HR), central venous pressure (CVP) and cardiac index[8]. However effects of phenylephrine on serum lactate level, that is indirect measure of oxygen delivery and perfusion, is lacking. No head-to-head studies with noradrenaline are available at present. The primary goal of our study is to compare the effects of phenylephrine vs noradrenaline on lactate level during bypass period. The objective of this study is to evaluate effects of phenylephrine vs noradrenaline on lactate level during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting.

METHODOLOGY

This is a comparative cross sectional study which was conducted in Department of Anesthesia, Armed forces Institute of Cardiology, from January to June 2019. A total of 200 patients, divided in two groups, group A and B, each consisting of 100 patients. Non probability consecutive sampling was used to collect the sample. Patients with, age 18-65 years, elective CABG, either gender and patients of (ASA) grade II and III were included in this study. Patients with present or suspected acute mesenteric ischemia, Patient's with (Hb<10) before CPB, CKD/ Liver dysfunction, uncontrolled diabetes, Emergency procedure, poor LV functions (EF<30%), Low cardiac output state before CPB leading to high lactate level were be excluded from this study. Study was conducted after approval of hospital ethics committee. Two hundred patients fulfilling inclusion criteria with age between 18-65 years, elective CABG will be included in study. Patients will be divided in two groups A & B comprising of 100 each by lottery method. Group A received phenylephrine and group B received noradrenaline, keeping mean arterial pressure between 65-90 mmHg. Serum lactate level was measured before induction, before initiation of CPB, after cooling, after rewarming and before shifting to icu by collecting ABGs blood sample. 1mL of arterial blood was collected into a heparinized blood gas syringe and immediately analyzed on the Ultra C analyzer (Nova Biomedical, Waltham, Mass) for blood gas, lactate, hematocrit, electrolytes, magnesium, Ca2+, and glucose. Quality controls will be performed on the analyzer before laboratory determinations.

All patients received similar technique of induction with midazolam, morphine, propopol, cisatracurium, and ventilation. Patients with Hb<10 g/dl, CKD, Liver dysfunction, Poor LV functions and hemodynamically unstable were not included in study. All the above-mentioned information was analyzed with SPSS 21 program. Lac, Bicarbonate, PH, Hb and Base excess in Patients at Different Time Points was measured. Data was stratified for age, gender, BMI and ASA class (II/III) to deal with effect modifiers. Post stratification t-test was applied taking *p*-value ≤0.05 as significant.

RESULTS

Mean age of the patients was 52.15 ± 8.02 years and 52.59 ± 7.56 years in phenylephrine and noradrenaline groups, respectively (*p*=0.690). Phenylephrine group included 61 males and 39 females while noradrenaline group included 55 males and 45 females (*p*=0.390). Mean BMI was 29.5 ± 3.81kg/m^2 in phenylephrine group and 29.78 ± 4.40kg/m^2 in nora-drenaline group (*p*=0.631). Phenylephrine included 54 ASA-II and 46 ASA-III patients while noradrenaline group included 51 ASA-II and 49 ASA-III patients (*p*=0.671) table-I.

Table-I: Demographic data.

Variable	Phenylephrine (n=100)	Noradrenaline (n=100)	*p*-value
Age, years	52.15 ± 8.02	52.59 ± 7.56	0.690
Gender, M/F	61 / 39	55 / 45	0.390
BMI, kg/m^2	29.50 ± 3.81	29.78 ± 4.40	0.631
ASA status, II/III	54 / 46	51 / 49	0.671

Lactate levels before induction were 1.30 ± 0.05 and 1.40 ± 0.04 in phenylephrine and noradrenaline groups with no statistically significant difference (*p*= 0.134). Lactate levels before CPB were 02.77 ± 1.82 and 3.83 ± 1.17 in phenylephrine and noradrenaline groups with no statistically significant difference (*p*=0.229). Lactate levels after cooling were 4.98 ± 01.67 in phenylephrine group and 6.11 ± 01.35 in noradrenaline group, with statistically significant difference (*p*=0.003). Lactate levels after rewarming were 05.72 ± 1.85 in phenylephrine group and 7.17 ± 02.11 in noradrenaline

group, with statistically significant difference (p= 0.044). Lactate levels before shifting to ICU were 6.17 ± 2.43 in phenylephrine group and 7.52 ± 2.82 in noradrenaline group, with statistically significant difference (p=0.041) table-II.

cardiac index remained similar i.e. 4.3 vs 4.3 L/min/m^2.

On the other hand data collected from ICU patients with normal CO or increased CO proposed that use of nor-epinephrine while treating hypertension

Table-II: Comparison of various lactate levels between phenylephrine and noradrenaline group/;@~>.

Variable	Phenylephrine (n=100)	Noradrenaline (n=100)	*p*-value
Lactate levels before induction	1.30 ± 0.05	1.4 ± 0.04	0.134
Lactate levels before CPB	02.77 ± 1.82	03.83 ± 1.17	0.229
Lactate levels after cooling	04.98 ± 01.67	06.11 ± 01.35	0.003
Lactate levels after rewarming	05.72 ± 01.85	07.17 ± 02.11	0.044
Lactate levels before shifting to ICU	06.17 ± 02.43	07.52±02.82	0.041

DISCUSSION

No previous data has been found comparing the effectiveness of Nor-epinephrine and Phenylephrine during complex surgical procedures. Phenylephrine is mainly administered in the harmful cases of acute injury of kidney and the progression of lactic acidosis[9]. However, a study was conducted after the cardiac surgery, revealed the increase of lactic acidosis[10]. In a study done by Nygren *et al*[10], Nor-epinephrine and Phenylephrine were compared in that were infused to the patients, sedated with propofol, for enhancing the MAP up to 30%. They showed that Phenylephrine infusion was linked to enhancement of splanchnic oxygen extraction and mixed venous-hepatic vein oxygen saturation gradient significantly as compared to the Nor-epinephrine despite of having similar cardiovascular variables[10-13]. These findings proposed that Phenylephrine infusions cause more distinct global splanchnic vasoconstriction. It was demonstrated by the investigators that the Phenylephrine infusion was somehow linked to enhancement of concentration of lactate from baseline that is not demonstrated by NE.

In patients with septic shock initially infused with Nor-epinephrine infusion was replaced with Phenylephrine according to Morelli *et al*[11]. Phenylephrine was infused for 8 hours after replacement that lead to significant increases in concentrations of serum lactate, maintained MAP at 65-75mmHg after titration and also decreased creatinine clearance as well as indocyanine green clearance significantly.

Outcomes of a study by Reinelt *et al*[13], revealed that phenylephrine replacement in patients with septic shock caused 1.25 vs 0.85 L/min/m^2 decrease in the splanchnic blood flow rates 54-41% decrease in hepatic venous oxygen saturation and 690-248 µmol/min/m^2 decrease in the splanchnic lactate uptake rates, while

instead of Phenylephrine showed that there was no increase in the development of lactic acidosis and maintained hepatosplanchnic and renal perfusion effectively[14]. More research must be done in order to determine the effectiveness of Nor-epinephrine for prolonged intraoperative infusion during surgical procedure.

Results of our study suggest that with the use of nor-adrenaline the serum levels of lactic acids were higher peri and postoperatively as compared to phenylephrine which is in contrast to many previous studies. Phenylephrine enhances the vasoconstriction of microcirculation, decreases tissue blood flow and oxygen supply, augment anaerobic metabolism and lactic acid production. Many studies support these findings and documented that the using of phenyephrine during CPB resulted in an impairment of microcirculatory blood flow, peripheral arteriovenous shunting, deterioration in microvascular flow pattern of erythrocytes within capillaries, potentiating the anaerobic metabolism, more production of lactic acid and a rise in lactate levels in spite of an apparently adequate oxygen supply[15-19] and the same result was confirmed by another study that showed the using of catecholamines is responsible for splanchnic vasoconstriction thereby reducing perfusion to the gastrointestinal tract during and after surgery and leads to elevated lactate level[20].

The phenylephrine-induced increase in arterial lactate could be caused by increased global or regional (e.g., splanchnic) lactate production with or without combined decreased (splanchnic, renal, or muscular) lactate clearance[17].

CONCLUSION

Nor-adrenaline was associated with increase in the serum lactate levels more significantly as compared to phenylephrine in patients undergoing coronary artery bypass grafting.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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