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A Study of the Effectiveness of Lidocaine to Treat Severe Pulmonary Vascular Constriction induced by Protamine

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ABSTRACT

Background: Protamine neutralises heparin after separation from cardiopulmonary bypass. This study aimed to evaluate the effects of lidocaine on protamine induced pulmonary vascular constriction in paediatric cardiothoracic surgery. **Methods:** This was a single-centre, prospective, double-blind and randomised study conducted among eighty pediatric patients with acyanotic congenital cardiac disease, scheduled for elective on-pump cardiac surgery under general anaesthesia. In the study, the participants were divided into four groups: Group NPHL- nonpulmonary hypertension with lidocaine preconditioning, group NPHS- nonpulmonary hypertension with normal saline (as placebo), group PHL- pulmonary hypertension with lidocaine preconditioning, and group PHS- pulmonary hypertension with normal saline (as placebo). **Results:** Pulmonary vasoconstriction occurred in 11.25% of cases after protamine administration. Both the NPHS and PHS groups exhibited an increase in mean airway pressure (Paw), Respiratory index (RI), alveolar-arterial oxygen difference (A-aDO2), pulmonary artery pressure (PAP) and decreased dynamic pulmonary compliance (Cydn) and oxygen index (OI) after protamine administration. However, these changes were not observed in the NPHL and PHL groups with lidocaine preconditioning. Plasma levels of TXB2 in the NPHS and PHS groups were higher than the NPHL and PHL groups, but 6-keto-PGF1 alpha levels were lower in the NPHS and PHS groups than in the NPHL and PHL groups. **Conclusion:** In congenital heart disease, repair without cardiopulmonary bypass is not possible in most cases. Prior to reversing heparin with protamine, preconditioning lidocaine reverses protamine-induced pulmonary vasoconstriction and improves lung function.

KEYWORDS: Cardiopulmonary bypass, lidocaine, protamine, pulmonary hypertension

INTRODUCTION

To neutralise systemic anticoagulation induced by unfractionated heparin in cardiac surgery after separation from cardiopulmonary bypass (CPB) requires protamine administration and is a Food and Drug Administration (FDA) approved drug [1]. Protamines are small, low molecular weight (5.5-13.0 kDa), alkaline, rich in arginine, polycationic amine, mainly isolated from Clupeidae or salmon fish sperm, but now are being produced increasingly by recombinant biotechnology [2].

Protamine is commercially available in sulphate and chloride form for intravenous use. Strongly anionic anticoagulant heparin forms a salt aggregate when exposed to the cationic peptide of protamine within seconds [3]. This salt aggregate is inactive and has no anticoagulant properties of heparin and later in a few minutes leads to the recovery of the original anti-thrombin activity . Platelet factor 4 (PF4) also influences the neutralisation of heparin by protamine by stabilising the protamine-heparin complex [4].

The proper dose of protamine is essential if administered protamine is excessive then shown to possess anti coagulation properties and may lead to bleeding [5, 6]. However, little is known about the metabolism of the heparin-protamine salt aggregate. Some studies described metabolism in the liver, while others reported that salt is metabolised and excreted by the kidneys [5].

With protamine administration, immunological and inflammatory alterations lead to an anaphylactic response ranging from 0.06% to 10.6%. The most common side effects of protamine use include hypotension, bradycardia, pulmonary vascular constriction, pulmonary hypertension, and broncho-constriction [2, 7, 8]. Furthermore, if protamine is administered in excess, it can interfere with coagulation factors, negatively impact platelet function, and stimulate clot breakdown [2]. Despite associated complications and a narrow therapeutic index, still, protamine is the mainstay drug for heparin neutralisation in cardiothoracic surgeries.

In 2018, Guan Z et al. reported in their study 1 per 832 cases of severe pulmonary vascular constriction (PVC) induced by protamine [9]. Dilation of pulmonary artery pressure (PAP) is also used to decrease PAP. In addition, a few case reports described the successful use of nitric oxide [10] or prostaglandin E1 [11] to decrease PAP in cases of severe PVC induced by protamine. However, there is a paucity of literature on protamine-induced PVC; systemic

research is needed to reveal evidence-based knowledge regarding protamine-induced PVC and its clinical impact.

Lidocaine is a commonly used local anaesthetic in clinical practice. It acts by inhibiting sodium influx in the voltage-gated sodium channels. When the influx of sodium is interrupted, the signal conduction is inhibited. lidocaine has significant anti-inflammatory characteristics; lidocaine can alleviate acute lung injuries caused by protamine and CPB. [10, 11]

There is a paucity of literature on lidocaine's effectiveness in treating severe pulmonary vascular constriction induced by protamine administration after separation from cardiopulmonary bypass in pediatric congenital heart disease repair surgery.

MATERIALS AND METHODS:

This study was carried out from May 2020 to January 2021 after obtaining ethical approval from the Committee on Human Research Ethics (CHRE) SAMSRI as per the Helsinki Declaration and revised guidelines of 2000. The nature of the study was explained to the participants and the parents/ guardians included in the study. Written informed consent was obtained from the parents/guardians. The study population consisted of the physical status II and III of the American Society of Anesthesiologists (ASA), pediatric patients of either sex at the age of 1 to 12 years with acyanotic congenital heart disease scheduled for elective open-heart surgery that requires CPB. They all received heparin anti coagulation on CPB and reversed with protamine while going off the pump.

I. Study Design: This study was a prospective, randomised, single-centre, and double-blinded clinical comparison study.The study's sample size was calculated using an online sample size calculator and was eighty. Participants were randomly divided into four groups, using a computer-generated randomisation table, meeting the study criteria. Person' 1' prepared the study drugs and managed the patient, and Person' 2' was responsible for the patient's records in the intensive care unit (ICU), while Person' 3' participated in the randomisation process. Person 2, 3 and the patient were kept unaware of the study drug to enable double-blinding.

II. Inclusion Criteria and Exclusion Criteria: In this study, patients of both sexes, between the ages of 1 to 12 years, ASA grade II and III, who underwent elective acyanotic congenital heart disease surgery that required cardiopulmonary bypass (CPB) under general anaesthesia were included.

Patients with cyanotic heart disease, less than one year or more than 12 years, refusal to provide guardians for the patient, history of protamine allergy, infection, preoperative hemodynamic instability, preoperative respiratory disease, emergency surgery, and abnormalities found in the lung, liver, kidney or coagulation function were excluded from this study.

III. Preoperative Preparation: All patients underwent a pre-anaesthetic evaluation a day before surgery, with particular consideration to elicit any new complication and review previous anaesthetic history and drug sensitivity. All routine investigations were re-checked, and procedures were explained to the guardians. The patients fasted according to hospital protocol before elective surgery.

IV. Anesthetic Protocol: Identification of the patient in the operating room (OT), a short preoperative history was taken along with the clinical examination, and routine investigations were re-checked. Oxygen saturation in 4 limbs was checked without oxygen and with oxygen. Children below five years were premedicated by oral route with midazolam 0.5 mg/kg and ketamine 5 mg/kg along with glycopyrrolate in OT. Non-cooperative children or over five years of age received inj. midazolam 0.03 mg /kg and inj. ketamine 0.5 mg/kg by intravenous (IV) route. The patient's vital signs were monitored, including blood pressure, electrocardiogram (ECG), and oxygen saturation. Induction of anaesthesia was performed with IV opioids (inj. fentanyl 10 ug/kg) and benzodiazepines (inj. midazolam 0.1mg/kg). For muscle relaxation Inj. pancuronium (0.1mg /kg) was used. Intubation was performed after adequate muscle relaxation. Additional monitoring included invasive blood pressure, central venous pressure, rectal and nasal temperature were performed after intubation. Anaesthesia was maintained with an infusion of inj. midazolam 0.02mg/kg/h and inj. fentanyl 2ug/kg/hr as per patient requirement.

After sternotomy, the patient's vena cava and ascending aorta were cannulated for venous drainage and arterial perfusion. The patients were heparinated with 3 mg/kg and taken on the pump after ACT>480 seconds. The CPB technique was standardised for all patients. Supplemental heparin was administered into the CPB circuit from time to maintain ACT>480 seconds. The CPB flow was maintained at 2liter/minute/meter^{2,} and the pressure was >30 mm Hg. Core cooling was used in all patients, rectal and esophageal probes monitored temperature.

The cardiac surgeon directly measured PAP in the PA. All patients were divided into four groups by a computer-generated randomisation table, with 20 patients in each group: NPHL group (non pulmonary hypertension with lidocaine preconditioning), NPHS group (non pulmonary hypertension with normal saline as a placebo), PHL group (pulmonary hypertension with lidocaine preconditioning), and group PHS (pulmonary hypertension with normal saline as a placebo drug). The volume of the preconditioning study drug or placebo (normal saline — NS) was kept at 5 ml in patients. A pulmonary/systemic circulatory pressure ratio of $\leq$0.3 was considered normal, while the ratio >0.3 was considered as pulmonary hypertension [12].

V. Diagnostic criteria: After successfully weaning from the CPB, adequate volume loading from the pump and stable haemodynamics. The NPHL and PHL groups received

lignocaine (2 mg/kg in 5ml syringe), and the NPHS and PHS groups received NS as a placebo (5 ml in 5ml syringe) one minute before neutralisation of heparin with protamine. After CPB, the patients reversed with Protamine sulfate (1.3 mg/1 mg of heparin) slowly in five minutes. Protamine mediated PAC is considered when constriction occurs within 30 minutes of the protamine administration and meets one or more of the criteria [5, 7, 13, 14] from the following:

(i) PAP increase at least 25%, require inotropic drugs or re institution of CPB after administration of protamine, $\geq$25% decrease from the baseline or $\geq$10% decrease in systemic arterial pressure.

(ii) PO2 decrease requiring ventilatory support, indicating non-cardiogenic pulmonary oedema.

(iv)Peak inspiratory airway pressure elevation more than 5 mm Hg indicates bronchospasm

These events lead to pulmonary hypertension, which may be clinically insignificant if haemodynamic instability does not occur.

VI. Measurement of outcomes: PAP continuously measured through a needle of 22G placed into the PA by a surgeon at (M0) baseline, 1minute before CPB, (M1) 1minute before protamine start, (M2) 1minute after-protamine start, (M3) 3minutes after-protamine start; (M4) 5minutes after-protamine start. Blood pressure (BP), heart rate (HR), mean arterial pressure (MAP), airway pressure (Paw) and dynamic lung compliance (Cdyn) were recorded at 6 points: M1, M2, M3, M4, M5, (10 minutes after-protamine ends), and M6 (20 minutes after-protamine ends).

In the analysis of arterial blood gas (ABG), the alveolar-arterial oxygen gradient (A-aDO2), the respiratory index (RI), which is the relationship between P (A-a) DO2 and the PaO2, and oxygenation index [(OI) = (mean airway pressure $\times$ FiO2 $\times$ 100)/PaO2)] were documented at 3-time points: M0, M1, and M6.

The sample collection and cryopreservation of radial artery blood and right ventricular blood were performed at the M1 and M6 time points. Thromboxane B_2 (TXB_2) and 6-keto-prostaglandin 1 alpha (6-keto-F1a) in plasma were detected by enzyme-linked immunosorbent assay (ELISA). In addition, the data of protamine adverse reactions was recorded.

Routine perioperative data were collected, including age, sex, weight, height, types of operation, preoperative EF value, ACT value after protamine neutralisation, CPB time, aortic cross-clamp time and operation time.

VIII. Parameters and Statistical Analysis: A structured questionnaire was used to collate prespecified demographic, anthropometric and clinical data from each participant. The data collection tool sought to ascertain 41 variables covering demographic and anthropometric characteristics, anaesthesia and surgery information in addition to measured laboratory parameters assayed from collected blood and urine samples. In addition, routine perioperative data were collected and analysed. The Shapiro-Wilk test was used for normally distributed data. Continuous variables were expressed as mean $\pm$ SD and compared across groups using one-way analysis of variance (ANOVA). Categorical variables were expressed as the number and percentage of the total group and analysed using the chi-square tests or Fisher's exact test. Hemodynamic indicators, pulmonary inflammatory factors, and pulmonary function indexes assessment and changes over time across groups were performed using repeated-measures ANOVA in all groups. Spearman's correlation analysis was performed to evaluate the relationship between pulmonary haemodynamic indicators and inflammatory factors. The SPSS 14.0 statistical package was used, and a P-value <0.05 was considered statistically significant.

RESULTS:

Eighty patients with congenital acyanotic heart disease were recruited, scheduled for elective on-pump cardiac surgery under general anaesthesia. The patients were randomly assigned to each group (n=20). The demographic and clinical profiles in the groups NPHL, NPHS, PHL and PHS, were comparable (p>0.05), shown in theTables 1 and 2. In group NPHL no pulmonary vasoconstriction case was noticed. There was no statistically significant difference in the incidence of protamine adverse reactions between the four study groups (P>0.05). However, there was a statistically significant difference in the incidence of protamine adverse reactions between NPHL & PHL groups used lidocaine and NPHS & PHS groups used normal saline, as shown X^2=6.135 with Fisher's exact test p=0.029.

Protamine-induced pulmonary vasoconstriction occurred in 9 cases of 80 study participants in the three groups, representing 11.25% in our study as in Table 3. Catastrophic pulmonary vasoconstriction occurred at 3minutes of protamine infusion in one patient from the PHL group.Pulmonary vasoconstriction followed by an abrupt and significant increase in pulmonary artery pressure, elevation in airway pressure, decrease in blood pressure, further bradycardia, and right ventricular distension. The patient was immediately hyperventilated with 100% oxygen, multiple doses of adrenaline were used to support the heart rate. In addition, dopamine and milrinone were perfused. In the NPHS and PHS groups, protamine-induced pulmonary vasoconstriction occurred within 3 minutes after protamine infusion in three and five patients, respectively. The symptoms were bronchospasm, hypotension, bradycardia and pulmonary hypertension. One patient in group NPHS and two patients in group PHS were relieved after 30 seconds without any interventions, while other patients received calcium chloride for mild/moderate hypotension or adrenaline for severe hypotension and hyperventilated with 100% oxygen for hypoxia.

Compared to the NPHL group, the MAP in the PHS group at the M_3 point was significantly lower, while the PAP in

Variables	Group NPHS	Group NPHL	Group PHS	Group PHL	p-value
Age (yrs)	4.73±2.31	4.25±2.85	4.52±2.83	4.38±2.52	0.848
Weight(Kg)	15.96±7.35	15.73±6.41	15.67±8.13	15.41±8.51	0.764
Height (cm)	102.56±17.19	101.25±15.72	103.95±18.47	100.25±19.32	0.643
M & F % ratio	(45%:55%) 1:1.22	(35%:65%) 1:1.85	(40%:60%) 1:1.5	(30%:70%) 1:2.33	0.326

Data are presented as means ± standard deviation (SD), percentages and ratio. Group NPHS-non-pulmonary hypertension with normal saline, group NPHL- non pulmonary hypertension with lidocaine preconditioning, group PHS- pulmonary hypertension with the normal saline, group PHL- pulmonary hypertension with lidocaine preconditioning. Not significant $p > 0.05$. Cm-centimetre, F-Female, Kg-Kilogram, M-Male, Yrs-Years.

Table 1: Comparison of the demographic profile of the patient:

Pulmonary vasoconstriction in each group	PAP baseline→max (mmHg)	Paw baseline →max (mmHg)	Cydn baseline→min (ml/cmH20)	BP base-line→mini (mmHg)	HR baseline →mini (beats/min)
Group NPHS Cases-1	17→30	14→25	16→5	105/56(83)→ 80/40(56)	116→94
Group NPHS Cases-2	13→34	13→30	28→8	96/59(71)→ 66/36(48)	94→83
Group NPHS Cases-3	17→44	9→28	10→7	132/76(99)→ 89/46(65)	117→113
Group PHS Cases-1	16→24	14→18	16→11	100/64(77)→ 91/51(65)	144→131
Group PHS Cases-2	22→38	16→22	15→3	72/39(50)→ 69/37(49)	120→119
Group PHS Cases-3	23→35	13→17	19→11	78/48(58)→ 47/34(40)	112→87
Group PHS Cases-4	35→48	17→26	13→4	82/53(68)→ 66/40(51)	138→135
Group PHL Case-1	139→88	12→17	11→9	112/69(85)→ 50/34(4)	117→ 103

Group NPHS- nonpulmonary hypertension with normal saline preconditioning, group PHS- pulmonary hypertension with normal saline preconditioning, PHL- pulmonary hypertension with lidocaine preconditioning, mini-minimum, PAP- pulmonary artery pressure, Paw- airway pressure, Cydn- dynamic pulmonary compliance, BP-blood pressure, HR-heart rate.

Table 2: Comparison of the clinical manifestation of pulmonary vasoconstriction

the NPHS and PHS groups at the M_3 point was significantly higher. Paw in the NPHS and PHS groups at the M_4point was significantly higher. Compared to the NPHS group, the Paw in the PHS group at the M_4 point was significantly higher. Cydn in the PHS group at the M_4 point was significantly lower than the M_1 point. However, Cdyn in the NPHS and PHSgroups at the M_3 and M_4 points decreased significantly as shown inTable 4

Heart rate and mean arterial pressure before protamine started and 10 minutes after the end of protamine showed no significant difference in all the groups. However, three minutes after protamine, all groups showed reduced heart rate, and at five minutes, all groups showed a reduced mean arterial pressureFigures 1 and 2

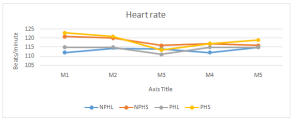

Figure 1: Intraoperative heart rate

Time point: M_1: 1 min before protamine start, M_2: 1 min after protamine start, M_3: 3 min after protamine start, M_4: 5

Group	M_1	M_2	M_3	M_4	M_5
Heart rate (HR) (beats/min)					
NPHS	121.50±14.65	119.75±14.29	116.70±15.60	117.40±9.96	116.00±11.83
NPHL	112.60±29.14	114.05±15.72	112.70±16.06	111.50±15.73	114.60±17.08
PHS	123.20±15.87	120.30±16.12	119.40±16.32	117.15±18.56	119.05±12.72
PHL	115.05±17.42	115.05±15.67	112.10±15.22	114.60±17.82	114.35±14.30
Mean Arterial Pressure(MAP) (mmg)					
NPHS	73.80±14.15	74.90±15.12	74.60±17.17	80.70±13.55	73.70±10.28
NPHL	73.65±12.80	77.15±12.85	81.00±14.23	81.95±13.19	75.20±7.91
PHS	71.70±16.59	74.10±15.33	69.70±15.99$^{\alpha}$	76.95±15.48	71.30±12.76
PHL	73.70±14.54	75.30±13.63	75.75±15.63	80.50±16.22	74.00±14.64
	Pulmonary Artery Pressure (PAP) (mmHg)				
NPHS	19.40±5.60	19.70±5.62	24.40±8.46$^{\alpha *}$	21.25±5.87	**NA**
NPHL	17.30±4.26	17.40±4.42	20.60±6.19	19.65±4.38	**NA**
PHS	27.40±8.31	27.80±7.98	32.35±11.24*	30.30±9.22	**NA**
PHL	27.75±7.25	27.05±6.95	31.40±15.25	30.45±9.85	**NA**
	Mean Airway Pressure (Paw) (mmHg)				
NPHS	13.75±3.18	14.00±3.08	16.80±7.67	18.25±6.54$^{\alpha *}$	13.85±3.82
NPHL	13.80±2.41	14.15±4.87	15.95±3.28	15.50±2.43	13.75±2.43
PHS	14.70±2.89	14.70±3.13	16.45±5.48	18.75±3.56$^{\beta}$	14.40±3.15
PHL	14.40±2.06	14.80±2.73	15.95±3.62	15.25±3.09	14.35±2.28
	Dynamic Pulmonary Compliance (Cdyn)(ml/cmH20)				
NPHS	13.65±5.69	13.30±5.55	11.45±4.9*	10.40±4.86*	14.50±5.17
NPHL	14.30±4.16	14.35±3.73	12.55±4.68	12.05±4.44	14.90±4.24
PHS	13.60±3.47	13.00±3.51	11.20±4.20$^{\alpha}$	9.55±4.07$^{\beta}$	13.45±5.92
PHL	13.10±4.94	13.05±4.89	12.85±4.79	12.05±5.45	12.95±4.05

Data are presented as mean ± SD. Significant differences are expressed as follows: Data compared with NPHL group — $^{\alpha}$, with PHL group- $^{\beta}$ and with M_1 time point- * if p<0.05. NA-not applicable time points-M_1-1 min before protamine start, M_2- 1 min after protamine start, M_3- 3 min after protamine start, M_4- 5 min after protamine start, M_5- 10 min after protamine end.

Table 3: Comparison of Intraoperative clinical variables

min after protamine start, M_5: 10 min after protamine end.

MAP:mean arterial pressure, time point: M_1: 1 min before protamine start, M_2: 1 min after protamine start, M_3: 3 min after protamine start, M_4: 5 min after protamine start, M_5: 10 min after protamine end.

Spearman's correlation analysis was performed to assess the relationship between the plasma TXB_2 level in the radial artery at the M_6 point and the PAP value at the M_3 point. The Paw value at the M_4 point revealed a weak correlation (correlation coefficient 0.44, P=0.000 and 0.25, P=0.027, respectfully). Furthermore, the plasma level of TXB2 in the right atrium at the M_6 point, the PAP value at the M_3 point, and the Paw value at the M_4 point revealed a weak correlation (correlation coefficient 0.41, P=0.000 and 0.30, P=0.007, respectfully). There was no correlation between the plasma 6-keto-PGF1alpha level in the radial artery and the right atrium at the M_6 point. The PAP value at the M_3 point correlation coefficient was 0.09, P=0.413 and 0.2, P=0.85, respectively. The Paw value at the M_4 point correlation coefficient was -0.20, P=0.079 and -0.14, P= 0.216, respectively Table 5.

Compounds	M_1 radial artery	M_1 right atrium	M_6 radial artery	M_6 right atrium
Level of thromboxaneB$_2$ TXB$_2$ (pg/ml)				
NPHS	4062.27±1297.22	3904.48±1087.11	2835.11±1536.47$^{\alpha ¥}$	2663.43±1786.04$^{\alpha *}$
NPHL	4046.07±1358.21	3800.72±1367.60	2015.98±1130.71*****	1806.45±669.26*****
PHS	4618.44±618.00	4307.31±1140.12	3532.93±1535.05$^{\beta *}$	3149.82±1446.41$^{\beta *}$
PHL	4906.03±1460.70	4563.12±1235.46	3085.53±2092.23*	2754.69±1400.07*
Level of 6-keto- Prostaglandin F1alpha (pg/ml)				
NPHS	1383.90±325.46	1327.80±443.21	480.55±148.62$^{\alpha *}$	473.30±145.81$^{\alpha *}$
NPHL	1402.50±355.61	1326.95±344.56	579.50±142.28*	568.95±133.61*
PHS	1882.45±303.66	1777.95±525.26	658.40±155.89$^{\beta *}$	548.60±143.73$^{\beta *}$
PHL	2042.55±384.75	1828.35±328.71	778.95±165.02*	667.35±158.82*

Data are presented as mean ± standard deviation (SD). In addition, data compared to the NPHL group- α, PHL group- β and with the M1 time point- * and (p<0.05) significant differences are expressed. M1- 1 min pre protamine start M6-20 min after protamine end.

Table 4: Comparison of inflammatory compounds

Group	M_0	M_1	M_6
Oxygen index (OI)(mmHg)			
NPHS	422.40±109.69	359.95±123.29	371.67±128.45
NPHL	423.85±129.91	369.01±115.22	403.60±126.53
PHS	426.68±115.65	340.85±121.22	358.12±139.08*
PHL	426.93±101.09	363.87±148.86	378.61±137.69
Respiratory index (RI)			
NPHS	0.40±0.31	1.03±0.92*	0.84±0.69*
NPHL	0.59±0.47	0.94±0.77	0.78±0.70
PHS	0.53±0.44	1.18±1.12*	1.08±0.93*
PHL	0.49±0.44	1.00±0.94	0.79±0.57
Alveolar-arterial oxygen difference (A-aDO$_2$) (mmHg)			
NPHS	74.40±40.66	175.40±95.38*	131.10±61.70
NPHL	88.15±48.10	143.10±77.57	109.80±62.49
PHS	102.15±75.91	186.47±112.13*	145.43±97.40*
PHL	97.25±92.04	163.65±73.04	128.50±35.31

Data are presented as mean ± SD. Significant differences are expressed as follows: Compared with M_0 group - * (p<0.05). M_0 -baseline (1 min before CPB), M_1 -1 min before protamine start M_6 -20 min after protamine end, Oxygen index is calculated as (mean airway pressure × FiO_2 × 100) / PaO_2, a respiratory index is the ratio of P (A-a) DO_2 and PaO_2.

Table 5: Comparison of intraoperative pulmonary function:

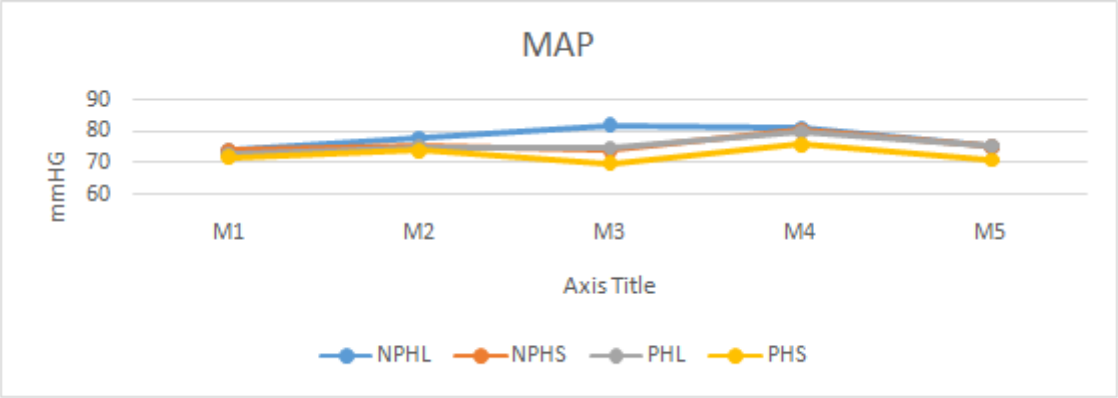

Figure 2: Intraoperative mean arterial pressure

The present study indicated that preconditioning with lidocaine before neutralisation of protamine improves respiratory function. Baseline values (M0) were compared with those at one minute before protamine (M_1) and 20 minutes after protamine administration (M_6). Intraoperative pulmonary function before neutralisation and after neutralisation with protamine is presented in Table 6. Compared to the PHS M_0 point, the OI in the group PHS at M_6 points significantly decreased, while the levels of RI and A-aDO_2 in the NPHS and PHSgroups at the M_1 point were significantly higher. RI levels in NPHS and PHS, as well as A-aDO2 levelsin PHS, were statistically significant. However, RI and A-aDO_2 in group PHL at the M_6 point recovered closer to the baseline M_0.

DISCUSSION:

Corrective cardiac surgery without cardiopulmonary bypass is not possible in most congenital heart disease repairs. Protamine is used in patients undergoing surgery to reverse the anticoagulant effects of heparin and restore coagulation. However, protamine administration may produce severe pulmonary vasoconstriction after administration. Protamine-induced pulmonary vasoconstriction occurred in 11.25% of our study population. Our findings were inconsistent with the previous studies that showed protamine-induced severe pulmonary vasoconstriction [3, 5, 12, 13]. We know about two mechanisms that cause pulmonary vasoconstriction induced by protamine infusion. First, local excess of the heparin-protamine complexes caused by rapid protamine infusion was thought to cause a lift-threatened adverse haemodynamic reaction [14]. Experimental studies showed that contact with the oxygenator surface causes activation of the complement system and causes the generation of complements C3a and C5a [15]. This leads to smooth muscle contraction, platelet accumulation, and leukocyte activation in the lungs. Subsequently, this induces the release of many proteolytic enzymes and causes lung injury [14]. Pulmonary vasoconstriction and lung injury mediated by complement C5a-induced TXB_2 generation. This results in various cardiovascular adverse effects, such as elevated pulmonary artery pressure and right atrial and right ventricular pressure, leading to systemic hypotension. Therefore, the treatment is to reduce PAP and inhibit inflammatory responses, which is achieved by reducing the generation of TXB_2 [14]. In our study, protamine-induced pulmonary vasoconstriction occurred in 20% of patients who were not preconditioned with lidocaine. The symptoms were fatal bronchospasm, hypotension, bradycardia, and pulmonary hypertension, as reported in other similar prospective studies [2, 3, 6].

After 20 minutes of protamine administration, plasma TXB_2 levels in the NPHS and PHS groups with normal saline (NS) as placebo were higher than that in the NPHL and PHL groups. The levels of 6-keto-PGF1a in the NPHS and PHS groups were lower than NPHL and PHL. The plasma TXB_2 level of patients receiving lidocaine preconditioningwas lower than that of patients receiving NS, while the 6-keto-PGF1a level of patients receiving lidocaine preconditioningwas higher in our study. Low level of 6-keto-PGF1a or high plasma TXB_2 level, a possible explanation for the increased PAP, hypotension and hypoxia shown by Petidis et al., Which were inconsistent with our findings [14].

Pulmonary artery pressure (PAP) and mean airway pressure (Paw) increased significantly in NPHS versus NPHL (24.40±8.46 versus 20.60±6.19 mm Hg) at 3 minutes and (18.25±6.54 versus 15.50±2.43 mm Hg) 5 minutes after protamine administration. Paw was also significantly increased in PHS vs PHL were (18.75±3.56versus 15.25±3.09 mm Hg) after administration of protamine at 5 minutes. Statistically significant decreased dynamic pulmonary compliance (Cdyn) in PHS group 11.20±4.20 ml/cmH20at 3 min and 9.55±4.07ml/cmH20 at 5 min compared to NPHL and PHL groups. Our results indicate that the precondition of lidocaine prior to heparin neutralisation effectively prevents the protamine-induced pulmonary vascular reaction during the repair of coronary heart disease. PAP, Paw, and Cydn in patients who received lidocaine preconditioning before heparin neutralization experienced fewer fluctuations than patients who received NS placebo before heparin neutralisation.

NPHS and PHS exhibited a significantly increased respiratory index (RI) of 0.84 ± 0.69 and 1.08 ± 0.93, respectively, and the alveolar-arterial oxygen difference (A-aDO2) in the PHS group was 145.43 ± 97.40. Conversely, significantly decreased oxygen index (OI) in PHS was 358.12 ± 139.08 after 20 minutes of protamine administration. The protamine adverse reactions in the NPHL and PHL were lower than in groups NPHS and PHS, respectively. RI- the ratio of P(A-a) DO_2 and PaO_2, reflecting the function of pulmonary ventilation and oxygen exchange. OI reflects the effects of respirator pressure on oxygenation. Wood et al., in their study, confirmed a relationship between different pulmonary functions such as OI, RI, and A-aDO_2 and ventilation [16]. Post-protamine pulmonary function was unchanged compared to baseline in patients receiving lidocaine preconditioning, but this worsened in patients receiving NS placebo.

The anti-inflammatory effect of lidocaine is well known in the literature. It inhibits neutrophil function, including chemotaxis, superoxide anion release and inhibits granulocyte adhesion [17]. In addition, the inhibition of the release of proteolytic enzymes and cytokines had a protective effect on vascular endothelial cells [18]. Furthermore, lidocaine was known to inhibit platelet activation, aggregation and decrease TXB2 concentration [11].

Hamp et al. administered 1.5 mg/kg bolus of IV lidocaine, and their trials reported no haemodynamic effects or cardiovascular changes with lidocaine [19]. Weinberg et al. administered 2 mg/kg bolus of IV lidocaine and reported that IV lidocaine has a significant effect on haemodynamic and cardiovascular [20]. Unlike our study, neither of these trials reported any effects of lidocaine on pulmonary artery vasoconstriction and pulmonary functions [12, 21]. This study was designed to investigate the potential cardiopulmonary benefits of lidocaine preconditioning prior to the neutralisation of protamine. As per available clinical literature, lignocaine 2 mg/kg was considered haemodynamically safe and effective, so we decided on this dose of lidocaine [22]. Regarding haemodynamic function, the present study indicated that lidocaine preconditioning before protamine neutralisation effectively reduces pulmonary vasoconstriction. The anti-inflammatory effect of lidocaine reduces harmful stimulation of protamine by reducing stress responses and spasm reaction of pulmonary vascular and tracheal smooth muscle caused by direct stimulation of protamine by a reduced generation of TXB_2 or increased production of 6-keto-PGF1alpha [14]

CONCLUSION:

Severe pulmonary vasoconstriction induced by protamine in cardiac surgery is very commonly associated with hypotension shortly after protamine administration. It interacts with the peptides on the surfaces of the vasculature and blood cells, triggering the release of a wide variety of vasoactive compounds and inflammatory mediators. This leads to inflammatory responses in the lung and pulmonary vasoconstriction. The use of lidocaine before heparin neutralisation exerts its effect through inhibition of TXB2 release and the generation of 6-keto-PG-F1a. Lidocaine improves respiratory function by reducing pulmonary vascular adverse reactions induced by protamine and plays an important role in lung protection.

Limitations: As a single-centre study, the generalisation of study findings will be finite. To generalise the result, we need to conduct a multicentric trial with large sample size and measure the plasma level of lidocaine. In addition, we could extend this study with increased and decreased doses to compare the results of different doses.

CONFLICT OF INTEREST: NONE DECLEARED.

Data Availability: All data are available within the manuscript. The data sets used and analysed during the current study are available from the corresponding author on reasonable request.

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