THE USE OF PREOPERATIVE PROSTACYCLIN FOR THE TREATMENT OF RIGHT VENTRICULAR FAILURE AND ACUTE PULMONARY HYPERTENSION AFTER PROTAMINE USE

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The efficiency of preoperative prostacyclin application for the treatment of acute pulmonary hypertension which can be seen after protamine infusion [given to neutralize heparin after cardiopulmonary bypass (CPB)] and for the treatment of right ventricular failure due to the increase in afterload, is investigated in comparison to a control group.
The aim of the treatment is to decrease pulmonary pressure while maintaining both systemic arterial pressure and right ventricular contractions. Especially in right coronary graft application cases, developing distension exerts pressure on the coronary graft causing myocardial ischemia which can be followed by a vicious circle.
It is important to decrease right ventricular afterload by effective vasodilatation therapy.

Key words: Pulmonary hypertension, prostacyclin, right ventricular failure, protamine

Protamine infusion is used for the neutralization of heparin after CPB. Side effects of protamine have a wide spectrum ranging from minimal cardiovascular deterioration to grave cardiovascular collapse which can be life-threatening (1-4).

One of the most serious complications is acute pulmonary hypertension which occurs as a result of pulmonary arteriolar vasoconstriction and right ventricular dysfunction due to the distension after sudden increase in afterload. The reasons of myocardial ischemia which can cause a vicious circle are increasing wall stress, right ventricular end systolic volume (RVESV) and right ventricular end systolic volume index (RVESVI), and especially pressure on the RCA and stretching of the right coronary artery (RCA). In such a case, the most safe known treatment method is to stop protamine infusion, re-heparinize the patient and begin CPB again. The aims of CPB are to relieve the distension in the right compartments and give enough time to the right ventricle to recover. Pulmonary hypertension (PHT) is temporary most of the time and supporting the right ventricle by a combination of inotropic and vasodilator agents is the appropriate therapy.

A true anaphylactic or allergic reaction caused by immunospecific antibodies developing against protamine is under investigation (5-7). A life-threatening protamine reaction is mostly seen in NPH insuline dependent Diabetes Mellitus (DM) patients (1-8). To investigate the efficiency of prostacyclin (PGI_2) infusion in such cases we used two groups with similar patient characteristics. In the first group, we used preoperative PGI_2 + norepinephrine + dopamine infusion in 12 patients to whom we applied isolated coronary bypass (CABG) and in whom we have observed pulmonary hypertension and right ventricular failure due to protamine infusion. In the control group of 10 patients with similar preoperative, operative characteristics and with the same reactions against protamine infusion, we used nitroglycerin + dopamine infusion preoperatively. We compared hemodynamic parameters, the need for secondary CPB, duration of operation and intensive care unit stay. The cases with concomitant valve lesion which can cause pulmonary hypertension were excluded.

MATERIALS AND METHOD

Between 1991-1998 in two different centers, we chose 22 cases out of 1800 isolated CABG cases, in whom pulmonary hypertension (PHT) and right ventricular failure developed secondary to protamine infusion. The first group including 12 patients was named as group A, and the other group including 10 patients was group B. Patients with valve disease PHT or patients concomitant CABG procedures were excluded in this study.

The preoperative characteristics of groups A and B are shown in Table 1. As it can be seen

Table 1. Preoperative profiles Group A and Group B.

	Group A (n=12)	Group B (n=10)
Age	54±38	51±2.8
Sex	7M/5F	7M/4F
Previous MI	60%	50%
Performance score	18±2.4	16±3.2
Diseased vessel number		
3 V	8	5
2 V	2	2
1 V	1	1
LMC	1	1
Hypertension	40%	50%
DM	60%	50%
Oral antidiabetic+diet	40%	25%
İnsulin+diet	20%	25%
Obesity	40%	37.5%
NYHA class		
II	20%	25%
III	70%	62.5%
IV	10%	12.5%
EF %	56±2.4	58±2.8

MI: myocardial infarction, LMC: left main coronary, DM: diabetes mellitus, NYHA: NewYork Heart Association

in the table, preoperative characteristics were similar in both groups.

In all cases, we used the same anesthesia and operation protocols. None of the patients had hemodynamic or arrhythmic problems during the induction. In all cases the left mammarian artery (LIMA) was anastomosed to the left descending coronary artery, saphenous grafts were used for the other bypasses. Myocardial protection was maintained first by using cold crystalloid then by cold blood and finally by warm blood cardioplegia according to the 'integrated cardioplegia protocol'. Mild systemic hypothermia (32°C) was applied as well. Single clamp technique was used for proximal anastomosis.

In all cases, the end of perfusion was uneventful. We observed a sudden increase in pulmonary pressure, right heart distension, distortion in the conjunctions and a tendency to bradycardia just at the beginning of protamine infusion. We did not observe any deterioration in left ventricular contractions in the early period.

All of the hemodynamic changes that developed are shown in Table 2. In all cases protamine infusion was stopped immediately, and heparin was given again. 200-250 cc of blood was taken from the heart to the pump to decrease distension.

In group A, infusion of PGI_2 (15 mg/kg/min) + norepinephrine (4 mg/kg/min) + dopamine (2.8 mg/kg/min) was used. In group B, nitroglycerin (5 mg/kg/min) + dopamine (2.8 mg/kg/min) was infused.

In group A, a decrease in pulmonary arterial pressure and right heart distension was achieved, and improvement in right ventricular contractions was observed as well. The need for a second CPB was less in group A, while in group B all the cases needed a second CPB.

Statistical Analysis

Data were analysed with Mann-Whitney U test to investigate significant differences between the groups. For non-parametric calculations Wilcoxon test was used. In all cases $p<0.005$ was considered significant.

RESULTS

The changes that developed after CPB as a result of protamine reaction are shown in Table 3. According these data, after protamine reaction significant differences ($p<0.005$) were found between the two groups. There were significant differences in tendency to bradycardia, atrial fibrillation, increase in

Table 2. Hemodynamic differences during CPB and after protamine reaction.

	Group A (n=12)		Group B (n=10)		
	After CPB	After protamine	After CPB	After protamine	p
BP					
Systolic (mmHg)	140±25	110±8.7	135±18.9	100±12.5	NS
Diastolic (mmHg)	80±14.5	70±11.3	85±13.6	65±6.8	
Heart rate(mean)	86	64	92	66	<0.05
Rhythm					
NSR	12	8	8	6	<0.05
AF	0	4	2	4	
CO (L/min)	3.8±0.9	3.1±0.4	3.6±0.85	3.2±0.38	NS
CI (L/min/m2)	2.3±0.2	2.01±0.18	2.28±0.3	1.98±0.2	NS
PAP					
Systolic	26±2.8	54±4.8	28±3.4	58±4.8	<0.05
Diastolic	12±2.4	22±3.6	12±2.6	26±2.8	
PCWP (mean)	12	26	11.28	28	<0.05
CVP (mean)	7	4	6	18	<0.05
EF % (mean)	54	38	48	34	<0.05
PVR	324±26.8	894±24.6	425±17.8	944±36.8	<0.05

CPB: cardiopulmonary bypass; BP: blood pressure; NSR: normal sinus rhythm; AF: atrial fibrillation; CO: cardiac output; CI: cardiac index; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CVP: central venous pressure; EF: ejection fraction; PVR: pulmonary vascular resplance; NS: nonsignificant.

Table 3. Hemodynamic differences between groups.

	Protamine reaction	PGI_2 + İnotrop infusion After CPB	6th hours	Protamine reaction	NTG + İnotrop infusion After CPB	PO 6th hours	p
BP							
Systolic (mmHg)	110±9.6	130±15.6	125±15.6	100±9.6	110±9.6	110±7.6	NS
Diastolic (mmHg)	70±5.9	80±17.6	75±14.8	65±6.4	70±8.7	70±6.7	
Heart rate /min	64	76	78	66	68	72	NS
Rhtym							
NSR	8	10	11	8	8	8	NS
AF	4	2	1	4	2	2	
CO(L/min)	3.1±1.1	3.8±1.2	4.2±1.2	3.2±0.6	3.6±1.1	3.8±1.4	NS
CI(L/min/m^2)	2.0±0.7	2.68±0.6	2.8±0.4	1.98±0.2	2.15±0.4	2.4±0.6	NS
PAP (mean)							
Systolic (mmHg)	54	28	24	58	48	42	<0.05
Diastolic (mmHg)	22	14	10	26	24	18	
PVR	894±34.7	894±36.8	224±18.6	944±44.5	684±33.6	568±44.5	<0.05
PCWP	26	22	16	28	24	22	<0.05
EF %	38	48	46	34	36	38	<0.05
CVP	14	10	8	18	26	14	<0.05
CPB necessition (case)	6			10			<0.01
CPB time (min)	17±7.8			38±12			<0.01
IABP	4			5			NS
ICU stay (day)	-	2.4		42			<0.01
Extubation time	-	104		16			<0.05

PGI2: prostaglandin I2; NTG: nitroglycerine;CPB: cardiopulmonary bypass; BP: blood pressure; NSR: normal sinus rhythm; AF: atrial fibrillation; CO: cardiac output; CI: cardiac index; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CVP: central venous pressure; EF: ejection fraction; PVR: pulmonary vascular resplance; NS: nonsignificant; IABP: intraaortic balloon pump; ICU: intensive care unit

pulmonary arterial systolic and diastolic pressures, increase in wedge pressure, increase in pulmonary vascular resistance (PVR) and in central venous pressure (CVP), decrease in right ventricular ejection fraction (RVEP) ($p<0.005$).

Differences in arterial pressure (AP), cardiac output (CO), and index (CI) were not statistically significant ($p>0.005$). This shows that in the early period left ventricular functions were intact. But, a slight decrease in CO-CI values was also observed in both groups. In cases who have underwent second CPB, operational time was shorter ($p<0.005$).

DISCUSSION

Side effects of protamine have a wide spectrum ranging from minimal cardiovascular deterioration to grave cardiovascular collapse which can be life-threatening (1-4). Generally, IgG and IgM type of immunospecific reactions are considered (5-7). A life-threatening protamine reaction is usually seen in NPH dependent Diabetes Mellitus (DM) patients. In Levy's study (3), this ratio was 0.6-2% and 0.06% in non-dependent cases (4-8). We have found a high ratio in DM as well. Morel (11)

found increase in C5a and thromboxane A_2 (TXA_2) levels. He suggested that complement activation and increase of TXA_2 were responsible for acute PHT (8-11), and IgG is responsible for the increase in complement level (8-11).

The reason of pulmonary vasoconstriction is protamine's effect on the balance between PG/TXA_2 to the benefit of TXA.

In our study, the underlying cause of positive results we obtained especially in PAP, PVR, PCWP and CVP was prostacyclin which was the only effective agent to restore this balance again.

Therapeutic agents should not deteriorate contractions and should not decrease systemic arterial pressure while being effective (1-4). In addition to PGI_2, the use of an α-agonist did not create a serious hypotension problem. PGE_2, PGI_2 and an α-agonist -like norepinephrine- combination is the therapy of choice (1-6). Lock (12) reported that heparin reduced heparin-protamine complexes and stopped the release of TXA_2 from macrophages, and thus prevents PHT which is caused by protamine.

Acute PHT developed by protamine can be a significant reason of morbidity and mortality even after normal CABG.

Although it is a transient reaction, it is very important to begin the therapy as early as possible. In group A, PVR was resolved without the need for second perfusion in 50% of the cases and operational times were shorter in the second perfusion. These findings show that PGI_2 is an important treatment modality.

Because of such reactions due to protamine, recombinant platelet factor 4 (PF_4) is under investigation as an alternative to protamine. PF_4 is stored as dense granules in platelets and plays an important role in endothelial injuries in neutralization of vascular heparin. The least ratio must be 3/1. It has no effect on systemic arterial and pulmonary arterial pressures (4,12,13,15,22). Heparinase is obtained from flavobacterium heparinum and neutralizes heparin as effective as protamine (13,15,24-27).

As a result, we believe that PGI_2 is an important option in the treatment of acute pulmonary hypertension and right ventricular failure due to protamine reaction.

In our study, we found that PGI_2 restores hemodynamic status by directly reversing PGI_2/TXA_2 imbalance which is the main pathologic reason in such reactions.

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