Effect of Site of Venous Protamine Administration, Previously Alleged Risk Factors, and Preoperative Use of Aspirin on Acute Protamine-Induced Pulmonary Vasoconstriction

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Objective: To determine whether the incidence of protamine-induced pulmonary vasoconstriction (PIPV) is influenced by central venous versus peripheral venous infusion of protamine and whether aspirin ingestion within a week of surgery would decrease the incidence of PIPV.

Design: Single-institution, prospective, observational, randomized trial.

Setting: University teaching hospital.

Participants: One thousand four hundred ninety-seven consecutive patients undergoing cardiopulmonary bypass procedures.

Intervention: Protamine neutralization of heparin by infusion pump via either central venous or peripheral venous route.

Measurements and Main Results: Five previously suspected risk factors (valve surgery, prior protamine exposure, history of pulmonary hypertension, fish allergy, and vasectomy), aspirin ingestion within 7 days of surgery, and demographic information were recorded. PIPV was defined as an abrupt increase in mean PA pressure of 7 mmHg or more with associated right ventricular dysfunction as assessed by observation of the right ventricle in the field and regional wall motion abnormality by transesophageal echocardiogram and hypotension (systolic blood pressure ≤ 90 mmHg). Data were collected via continuous strip chart recording. A total of 10 patients (0.6%) developed PIPV during protamine infusion. The incidents were similar with respect to the site of venous administration. Prior exposure to protamine was associated with a greater incidence of PIPV (odds ratio 6.9; $p < 0.01$). Other previously suspected risk factors did not achieve statistical significance. None of the 766 patients who ingested aspirin experienced PIPV as opposed to 10 of the 731 patients who did not ingest aspirin (odds ratio 0.08; $p < 0.001$).

Conclusions: Although the site of venous protamine administration does not influence incidence of PIPV, aspirin ingestion within 1 week of surgery may decrease it. These data also confirmed other studies suggesting that previous protamine administration predisposes to this protamine reaction.

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KEY WORDS: heparin, protamine, aspirin, pulmonary vasoconstriction, thromboxane

CATASTROPHIC ACUTE PULMONARY hypertension associated with protamine administration or acute protamine-induced pulmonary vasoconstriction (PIPV) was described in 1983.[1] Pulmonary vasoconstriction[2] occurs only when protamine is administered in the presence of heparin.[1,3] Studies in experimental animals and humans have suggested a major role for thromboxane as a mediator of these life-threatening reactions.[4-7] The effect of the site of administration on incidence of protamine reactions has been examined previously with conflicting results.[8-14]

The authors conducted a large, single-institution, prospective, randomized trial to determine whether the incidence of PIPV is influenced by central venous versus peripheral venous infusion of protamine. It was hypothesized that the incidence of PIPV would be decreased with peripheral venous infusion. Dilution of peripheral blood containing heparin-protamine complexes with central venous blood containing only heparin would thereby drive the heparin, protamine, and heparin-protamine complex equilibrium reaction toward the left.[2,15] The rate of protamine administration was standardized to avoid any effect of speed of administration.[14] Data were also collected on patients to determine whether previously suspected risk factors were valid and to test the hypothesis that aspirin (ASA) ingestion within a week of surgery would decrease the incidence of PIPV. It was reasoned that the irreversible inhibition of the enzyme cyclooxygenase by aspirin would impair the generation of the pulmonary vasoconstrictor thromboxane A_2, the responsible mediator.[4-6]

METHODS

After review and approval by the institution's investigational review board, and after informed consent, 1,497 consecutive patients undergoing full heparinization for cardiopulmonary bypass procedures from 1992 to 1995 were randomized via random number table to receive protamine neutralization of heparin via either the central venous route through the side port of a pulmonary artery catheter introducer (ie, right atrium) or peripheral venous route via a hand or antecubital intravenous catheter. In addition, data were recorded for 5 other alleged predictor variables that included the following: valve surgery, fish allergy, vasectomy, preexisting pulmonary hypertension (mean PA pressure > 25 mmHg at catheterization), and prior protamine exposure. The last category is comprised of diabetics who had received insulin preparations containing protamine and/or patients who experienced protamine exposure at cardiac catheterization. Additionally, because of its effect on thromboxane generation,[4-6] ingestion of aspirin (325 mg or more per day) within 7 days of surgery was also recorded. Demographic data included age, sex, and surgical procedure. Patients with a known history of allergy to protamine were excluded from study.

Monitoring included 5-lead, 3-channel electrocardiogram, intra-arterial blood pressure, pulmonary artery pressure, and central venous pressure recorded continuously with hard copy available for immediate and

Table 1. Patient Demographics

Patient Demographics (N = 1,497)		Patients With Protamine Reaction (n = 10)	
Males	1053 (70%)	Males	8 (.53%)
Females	444 (30%)	Females	2 (.13%)
Mean age	68	Mean age	68
Possible predictors		Possible Predictors	
History of pulmonary hypertension	429 (29%)	History of pulmonary hypertension	7
Allergy to fish	26 (1.7%)	Allergy to shell fish	0
Previous exposure to protamine#	553 (37%)	Previous exposure to protamine†	8 *$p < 0.01$
Aspirin prophylaxsis	766 (52%)	Aspirin prophylaxsis	0 *$p < 0.001$
Peripheral protamine infusion	748 (50%)	Peripheral protamine infusion	6
Central protamine infusion	749 (50%)	Central protamine infusion	4
History of vasectomy	21 (1.4%)	History of vasectomy	1
Procedure		Procedure	
CABG	1057 (70.5%)	CABG	6
Redo CABG	70 (4.7%)	Redo CABG	1
CABG/MVR	39 (2.6%)	CABG/MVR	0
CABG/AVR	78 (5.2%)	CABG/AVR	1
AVR	88 (5.9%)	AVR	2
MVR	40 (2.7%)	MVR	0
Multivalve	26 (1.7%)	Multivalve	0
Redo valve	18 (1.2%)	Redo valve	0
Other	83 (5.5%)	Other	0

Abbreviations: CABG, coronary artery bypass grafting; MVR, mitral valve replacement; AVR, aortic valve replacement.

*Fisher exact test (2-tail).

†Includes diabetics with exposure to protamine containing insulin preparations and/or exposure to protamine at cardiac catheterization.

retrospective analysis (Astromed Inc., West Warwick, RI). Anesthesia was induced using fentanyl (up to $50\mu g/kg$) and sodium thiopental (up to 4 mg/kg). Adequate muscle relaxation was achieved using pancuronium; after which, the trachea was intubated and patients were ventilated with 100% oxygen. Anesthesia was maintained using isoflurane. Blood pressure and heart rate were maintained within 20% of the preoperative baseline values using prescribed anesthetic changes and administration of prescribed cardiovascular agents. Patients received an initial dose of porcine heparin, 300 IU/kg, (Elkins-Sinn, Inc., Cherry Hill, NJ) with additional 100 IU/kg doses as needed to achieve an activated coagulation time (ACT) (International Technidyne Inc., Edison, NJ) of greater than 480 seconds before commencing cardiopulmonary bypass (CPB). After termination of CPB, neutralization of heparin was initiated at a dose of 4 mg/kg protamine (Elkins-Sinn Inc.) with additional 1-mg/kg doses if needed to return the ACT to preheparinization values. Protamine was initially infused at 10 mg/min for 5 minutes. After 50 mg, the rate of infusion was increased to 20 mg/min for another 5 minutes. The remainder of the protamine was then infused at 30 mg/min.

Baseline mean pulmonary artery pressure was determined after weaning from CPB and before protamine administration. PIPV, as defined previously,[1,14,16] was considered present when an acute rise in mean pulmonary artery pressure of 7 mmHg or greater occurred with right ventricular dysfunction and systemic hypotension during or within 10 minutes after the administration of protamine in the absence of other causes. Right ventricular dysfunction was determined by visualization of contractile function of the right ventricle in the surgical field, as well as by deterioration of regional wall motion as observed by transesophageal echocardiogram. Systemic hypotension was defined as a decrease in systolic blood pressure to less than or equal to 90 mmHg. When PIPV occurred, the protamine infusion rate, total amount of protamine infused at that time, and treatment undertaken were recorded, and the protamine infusion was stopped. Protamine infusion was reinstituted at 10 mg/min after resolution of the event.

Chi-square and power analysis were performed using SAS software (SAS Institute, Cary, NC). Power analysis indicated that a sample size

Table 2. Protamine Infusion Rates and Treatment of Patients Developing Protamine-Induced Pulmonary Hypertension

Patient	Infusion Rate at Time of Reaction	Amount of Drug Infused at Time of Reaction	Treatment
1 AVR	180 mL/h	*	Stop infusion
2 CABG	180 mL/h	130 mg	Stop infusion; NTG
3 CABG	180 mL/h	270 mg	Stop infusion; NTG
4 CABG	60 mL/h	40 mg	Stop infusion; NTG/DOBUTA
5 CABG/AVR	180 mL/h	175 mg	Stop infusion; NTG/EPI
6 CABG	60 mL/h	22 mg	Stop infusion; NTG/EPI
7 CABG	120 mL/h	90 mg	Stop infusion
8 AVR	*	*	Stop infusion; NTG
9 CABG	180 mL/h	160 mg	Stop infusion; NTG/EPI
10 REDO CABG	60 mL/h	20 mg	Stop infusion; NOREPI/DOBUTA

Abbreviations: CABG, coronary artery bypass grafting; NTG, nitroglycerin; EPI, epinephrine; NOREPI, norepinephrine; DOBUTA, dobutamine.

*Data not available.

of 691 per group was necessary to attain an 80% chance of achieving a significant difference with a p of 0.05. The Fischer exact test was performed when the expected number of observations per cell was less than 5. Exact permutational logistic regression analysis was also performed (LogXact 2.1 for Windows, Cytel Software Corp., Cambridge, MA) on the following variables: previous exposure to protamine, previous history of pulmonary hypertension, valve surgery, gender, and ingestion of aspirin within 7 days of surgery.

RESULTS

One thousand four hundred ninety-seven consecutive patients were enrolled in this study. Demographic data are presented in Table 1. There were 1,053 (70%) men and 444 (30%) women enrolled, with a mean age of 68 years (range 42-90 years). Seven hundred forty-nine (50%) patients were randomized to central administration, and 748 (50%) were randomized to peripheral venous administration of protamine. One thousand fifty-seven (70.5%) patients underwent coronary artery bypass grafting, and 172 (11%) underwent isolated valve replacement. The remaining 268 (18%) operations consisted of combined valve and CABG procedures or other procedures requiring CPB. Ten patients (0.6%) developed PIPV.

Prior exposure to protamine was associated with PIPV reactions (odds ratio: 6.9; 95% confidence interval: 1.46-32.6; $p <$ 0.01). No patient who had received aspirin within 7 days of surgery developed PIPV (odds ratio: 0.078; 95% confidence interval: 0.003-0.766; $p < 0.001$). The site of protamine administration did not affect frequency of PIPV. Valvular heart disease and preexisting pulmonary hypertension were not related to frequency of PIPV. All episodes of PIPV occurred during protamine infusion (Table 2). Four patients experienced PIPV at the lowest infusion rate of 10 mg/min and 6 at higher infusion rates. All patients experiencing PIPV had acute elevations of PA pressures (mean elevation = 18.5 ± 5.5 mmHg, range: 12-28 mmHg); right ventricular dysfunction, as witnessed by inspecting the surgical field and/or by transesophageal echocardiography; and systemic hypotension. No patient required reinstitution of CPB.

Protamine infusion was restarted in all patients after resolution of PIPV. No patient experienced recurrence of pulmonary hypertension. Heparin neutralization was complete in all patients as indicated by return of postbypass celite ACT to preheparin control values.

DISCUSSION

The authors did not confirm their hypothesis that peripheral venous administration of protamine would decrease the incidence of PIPV reactions in comparison with central venous injection at similar infusion rates. Although the study confirmed the increased incidence in patients with previous protamine exposure, the data do not support the other suspected risk factors studied.

Heparin, protamine, and the heparin-protamine complex exist in a dynamic equilibrium governed by the laws of mass action: heparin $-$ antithrombin III $+$ protamine $\rightarrow$ heparin-protamine complex $+$ antithrombin III.[2,17] Rapid administration of protamine results in its local excess, driving the reaction to the right, with formation of heparin-protamine complexes. It is thought that heparin-protamine complexes initiate cellular events causing potentially life-threatening adverse hemodynamic sequelae.[2]

Others have investigated the hemodynamic effects of injecting protamine by various routes. Katz et al[9] found no difference in the hemodynamic changes associated with protamine administration when comparing right atrial, left atrial, and aortic injections. Procachini et al[10] and Milne et al[12] could not confirm the superior safety of intra-aortic injection of protamine over central venous administration. However, Ovrum and colleagues[11] showed significant increases in pulmonary artery pressures in patients receiving central venous administration versus intra-aortic administration of protamine. Unfortunately, these studies suffer from small sample size, lack of controls, lack of continuous hemodynamic recording, or dosing differences between groups.

This study, although only observational with respect to ASA ingestion, suggests that ingestion of ASA within a week of surgery may markedly decrease the incidence of PIPV. Whereas 10 of 733 patients who had not taken aspirin within a week of operation had an episode of PIPV, not a single episode was observed in the 766 patients who had taken ASA ($p <$ 0.001). Although prior protamine exposure was associated with an odds ratio of 6.9 ($p < 0.01$), ASA appears to protect against PIPV even in patients who had previously been exposed to protamine.

In vivo studies in experimental animals and clinical studies in humans have shown elevated thromboxane B_2 plasma concentrations and pulmonary vasoconstriction in response to protamine neutralization of heparin.[4,6,14] Blockade of thromboxane receptors or cyclooxygenase inhibition[4-6] prevented both the increase in thromboxane levels and PIPV. ASA is a known inhibitor of the cyclooxygenase pathway.[18] With the demonstration that acute coronary syndromes are related to the coagulation system, ASA is now commonly used for prevention of coronary thromboembolic events.[18-23] At doses used in patients with coronary artery disease (325 mg/d),[19] there is a greater decrease in thromboxane formation and activity compared with prostacyclin.[23] Thromboxane is a potent pulmonary vasoconstrictor. The inhibition of thromboxane generation in patients receiving ASA would explain the absence of PIPV in patients who had received ASA within 7 days of surgery. Also, it might help explain the previously reported association of PIPV in patients undergoing isolated valve surgery because patients with valve disease and without coronary disease would not routinely be on ASA therapy. The inability to confirm this finding may be because of the power of the study, a true lack of a relationship, or the rate of protamine administration. The authors' previous study of incidence of PIPV adds further credence to the postulate that aspirin decreases the incidence of pulmonary vasoconstriction.[16] The authors formerly reported from a different hospital a similar incidence of PIPV (11 of 904 [1.2%] to that group of patients in this study who did not receive aspirin [10 of 731 (1.4%)]). Although data were not collected on the number of patients in the former study who had ingested aspirin, it is probable that the number was exceedingly small. The data were obtained in 1986 to 1987, a period when every effort was made to delay cardiac surgery using CPB for a minimum of 1 week after aspirin ingestion for fear of excessive hemorrhage.

The definition of PIPV as an acute rise in mean pulmonary artery pressure of 7 mmHg or more, as determined previously,[1,14,16] could be considered too small a change in PA pressure to be truly representative of acute PIPV. However, patients who experienced PIPV in this study had acute increases of mean PA pressures of 12 mmHg or more (mean increase 18.5 mmHg), with associated right ventricular dysfunction and hypotension, which is quite characteristic of, although not specific for, acute PIPV.

The limitations of this study include not separating patients receiving protamine at cardiac catheterization from those receiving protamine-insulin formulations. Previous work suggests an increased frequency of PIPV in patients taking protamine-insulin formulations.[24] The authors are therefore unable to comment on the risk of PIPV after protamine exposure at cardiac catheterization only. This study lacks sufficient power to determine the relationship between PIPV and preexisting pulmonary hypertension, fish allergy, or vasectomy. This study is observational with regard to the use of ASA and its possible effect on the incidence of PIPV. The strength of observational studies has been the focus of interest and controversy, and recent analyses suggest that estimates of treatment effects in well-designed observational studies are not qualitatively different from those obtained in randomized controlled trials.[25,26] Bailar et al[27] have defined characteristics that strengthen observational studies that do not contain internal controls. These are (1) intent by the investigator expressed before the study that the treatment will affect the outcome reported, (2) planning the analysis before the data are generated, (3) articulation of a plausible hypothesis before the results are observed, (4) a likelihood that the results would still have been of interest if they had been "opposite," and (5) reasonable grounds for generalizing the results. The authors' observational study of aspirin fulfills all these design requirements. It additionally includes internal controls, which were collected prospectively and simultaneously as an integral part of this randomized, prospective study, thus further strengthening the data. Thus, complying with the design features specified by Bailar et al,[27] including incorporating internal controls and documenting a similar incidence of PIPV of "nonaspirin" patients to that gathered by the same team approximately a decade apart from 2 different cardiac surgical programs, all add credence to the hypothesis that aspirin ingestion within a week of cardiac surgery is likely to decrease the incidence of PIPV when heparin is neutralized by protamine.

Although it might be useful to perform a prospective randomized control study to assess the protective effects of ASA, such a study is unlikely to be performed in humans undergoing coronary artery bypass operations in which heparin and protamine are to be used. This is because of the established role that aspirin plays in the prevention and treatment of acute coronary syndromes.

In summary, this study was unable to show that the site of venous protamine administration affects the occurrence of PIPV when the rate of protamine administration is similar. The data strongly suggest that ASA ingestion within 7 days of operation decreases the incidence of PIPV.

ACKNOWLEDGMENT

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