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Heparin and Protamine Use in Peripheral Vascular Surgery: A Comparison Between Surgeons of the Society for Vascular Surgery and the European Society for Vascular Surgery

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It was the intent of this study to document, in general, the patterns and complications of heparin and protamine usage during carotid endarterectomy, aortic and femoral-popliteal-tibial reconstructions for occlusive disease, elective and emergent abdominal aortic aneurysmectomy, thromboembolectomy, and dialysis arteriovenous (AV) fistula placement by surgeons from North America and Europe. All vascular surgeons from the Society for Vascular Surgery (SVS) and the European Society for Vascular Surgery (ESVS) were surveyed by a voluntary, self-reported questionnaire. Six hundred and forty-six completed questionnaires (284 from SVS and 362 from ESVS), representing a 62% response rate, were returned for evaluation. Systemic and regional administration of heparin was common during vascular procedures performed by both SVS and ESVS surgeons. Use of protamine to reverse heparin anticoagulation varied among SVS and ESVS surgeons, respectively, during: carotid endarterectomy (54% vs. 26%, $p < 0.01$), elective aortic reconstruction for occlusive disease (58% vs. 23%, $p < 0.001$), elective aortic reconstruction for abdominal aortic aneurysm (63% vs. 27%, $p < 0.001$), and femoral-popliteal-tibial reconstruction (44% vs. 15%, $p < 0.001$). Adverse reactions to protamine among the 25 219 and 12 902 cases reported from SVS and ESVS surgeons, respectively, included: hypotension (1209 and 495 cases), pulmonary artery hypertension (65 and eight cases), anaphylaxis (52 and 10 cases), and death (seven and two cases). These adverse responses accounted for 5.3% and 4.0% of the SVS and ESVS cases, respectively. Although this study is subject to the known limitations of a retrospective survey, it is clear that heparin use is common. Protamine reversal of heparin anticoagulation is more common in North America. Severe reactions to protamine occur often enough to support the tenet that a safer compound is needed for heparin anticoagulation reversal.

Key Words: Heparin; Protamine sulfate; Anticoagulation reversal; Adverse responses.

Introduction

Heparin is administered frequently during peripheral vascular surgical procedures. Protamine sulfate is currently the only agent available for reversal of heparin anticoagulation, and is known to be associated with adverse and potentially life-threatening complications including systemic arterial hypotension, pulmonary artery hypertension, depressed cardiac output, bradycardia, and marked declines in oxygen consumption. Despite the frequent use of both heparin and protamine, there are little data to document the actual frequency of heparin administration and its reversal with protamine, as well as the incidence of associated side effects during peripheral vascular surgical procedures. In addition, it has been generally believed, but never documented, that differences exist in the use of these agents in different locations. This communication reports on the general practice patterns and complications associated with heparin and protamine usage by North American and European Vascular Society surgeons.

Materials and Methods

All members of the Society for Vascular Surgery (SVS) and the European Society for Vascular Surgery (ESVS) were sent survey questionnaires regarding heparin and protamine use. A total of 646 of the 1045

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questionnaires sent were returned with a response rate of 62%. Questionnaires were received from 284 SVS surgeons and 362 ESVS surgeons.

A self-reported, voluntary, retrospective survey was developed to assess the use of heparin anticoagulation and its reversal in common peripheral vascular surgical procedures, including: carotid endarterectomy; aortic reconstruction for occlusive disease; elective abdominal aortic aneurysmectomy; femoral-popliteal-tibial reconstruction for occlusive disease; emergent abdominal aortic aneurysmectomy, thromboembolectomy; and dialysis arteriovenous (AV) fistula placement (Fig. 1). Specific questionnaire items related to: the frequency of heparin and dextran use; the manner in which heparin dose was determined; the amounts of heparin and dextran used; the time between heparin administration and clamp application; preoperative coagulation tests performed; and the manner in which heparin anticoagulation was monitored intraoperatively. Questions regarding the frequency of protamine use, dosage, complications related specifically to protamine usage, and means to prevent these complications, along with a summary of the previous years operative experience completed the survey. The definitions of hypotension, pulmonary hypertension, and anaphylaxis were left to the discretion of the responding surgeon, but were assumed to be clinically important events recognised by those involved in the patient's care. Respondents were allowed to answer questions with multiple

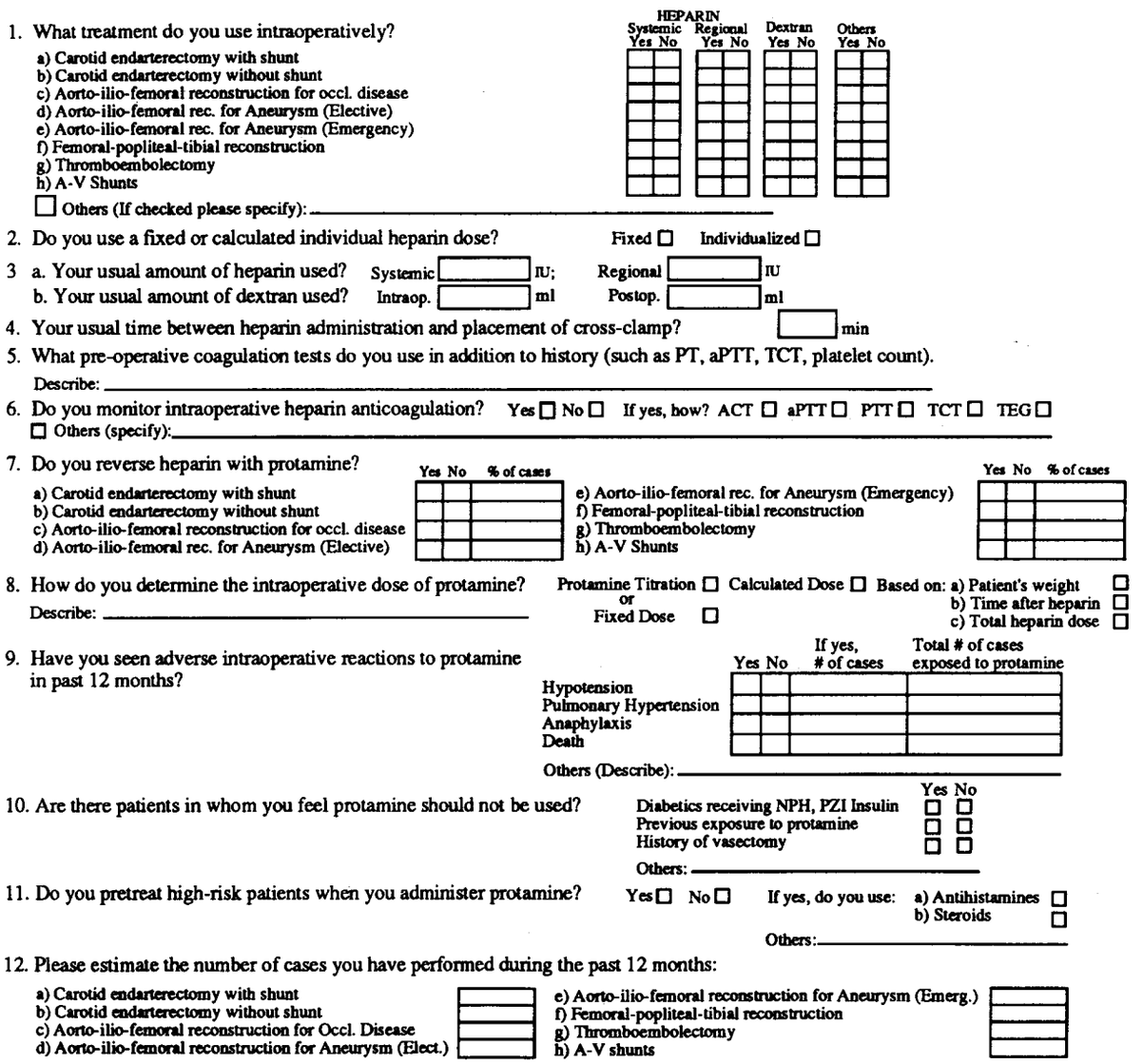

Fig. 1. Twelve items of a questionnaire sent to all members of the Society for Vascular Surgery and the European Society for Vascular Surgery. A 62% response was the basis for this report.

Table 1. Per cent of SVS and ESVS surgeons responding that they used heparin during a given vascular procedure

	Systemic heparin		Regional heparin	
Procedure	SVS	ESVS	SVS	ESVS
Carotid endarterectomy	99%	93%	13%	35%**
Aortic reconstruction for occlusive disease	97%	91%	35%	63%**
Femoral-popliteal-tibial reconstruction	97%	89%	50%	77%**
Elective abdominal aortic aneurysmectomy	94%	87%	32%	58%**
Emergent abdominal aortic aneurysmectomy	53%	34%**	49%	53%
Thromboembolectomy	94%	87%	55%	83%**
A-V fistula placement	57%	44%*	54%	73%†

Comparison between geographic groups using Chi square analysis of absolute case numbers: * $p < 0.05$; † $p < <0.01$; ** $p < 0.001$.

answers if appropriate, such as regarding the use of both systemic and regional heparin administration (Fig. 1). Thus, the total percentage of use could exceed 100%. The responses should be applied only to a given procedure, not the total practice pattern of the respondent. All questionnaire responses were entered into a computerised database (4th Dimension, ACIUS, Inc., Cupertino, CA, U.S.A.), and subjected to statistical evaluation. Data in this report are presented as the mean ± 1 S.D.

Results

Systemic administration of heparin during vascular reconstructions was commonly undertaken by both SVS and ESVS surgeons (Table 1). Heparin use was similar among the various procedures except in the cases of emergent aortic aneurysmectomy and AV fistula placement, where SVS surgeons used heparin more often. SVS surgeons used systemic heparin more often than ESVS surgeons for all operative procedures. In contrast, ESVS surgeons reported regional administration of heparin more often than SVS surgeons, for all operative categories. Regional use of heparin was assumed to represent conventional proximal and/or distal vessel irrigation at the site of the vascular reconstruction. Use of dextran during carotid endarterectomy and femoral-popliteal-tibial reconstruction was reported more frequently by SVS surgeons than ESVS surgeons.

Calculated individual heparin dosages, rather than fixed doses, were used more often by SVS surgeons than ESVS surgeons (56% *vs.* 39%, $p < 0.001$). The mean amount of intraoperative heparin used by 219 responding SVS surgeons was 6124 ± 2918 IU (median 5000 IU), a figure similar to the 5395 ± 4292 IU used by 307 responding ESVS surgeons (median 5000 IU). The mean calculated heparin dose used by the 54 responding SVS surgeons was 153 ± 178 IU/kg compared to 136 ± 195 IU/kg by the 34 responding ESVS surgeons. When utilising regional heparin intraoperatively, the total dose reported was 2520 ± 2985 IU for 57 responding SVS surgeons and 2971 ± 2239 IU for 151 responding ESVS surgeons. Intraoperative dextran was used in greater amounts by ESVS surgeons and was reported as 537 ± 501 ml by 88 surgeons as compared to 251 ± 183 ml by 73 SVS surgeons.

The duration of elapsed time following heparin administration until vascular clamping during the operative procedure was similar between the SVS and ESVS surgeons, being 3.7 and 4.0 minutes, respectively. Intraoperative monitoring of heparin anticoagulation was employed by 41% of SVS surgeons and 19% of ESVS surgeons ($p < 0.001$). The activated clotting time was used to monitor heparin's effectiveness by 80% of SVS surgeons, but only 43% of ESVS surgeons ($p < 0.001$).

Reversal of heparin by protamine sulfate was much more likely to be undertaken by SVS surgeons compared to ESVS surgeons during all procedures (Table 2). Protamine dosage was calculated in relation to the amount of previously administered heparin by 67% and 82% of SVS and ESVS surgeons, respectively.

Adverse reactions to protamine (Table 3) as reported by SVS and ESVS surgeons, respectively, included: hypotension (1209 and 495 cases), pulmonary artery hypertension (65 and eight cases), anaphylaxis (52 and 10 cases), and death (seven and two cases). The mean numbers of vascular patients in a given individual surgeon's practice were 185 patients

Table 2. Per cent of SVS and ESVS surgeons responding that they used protamine during a given vascular procedure

Procedure	SVS	ESVS
Carotid endarterectomy	54%	26%*
Aortic reconstruction for occlusive disease	58%	23%†
Femoral-popliteal-tibial reconstruction	44%	15%†
Elective abdominal aortic aneurysmectomy	63%	27%†
Emergent abdominal aortic aneurysmectomy	48%	17%†
Thromboembolectomy	30%	5%†
A-V fistula placement	27%	4%†

Comparison between geographic groups using Chi square analysis of absolute case numbers: * $p < 001$, † $p < 0.001$.

Table 3. Reported adverse reactions to protamine by SVS and ESVS surgeons

Reaction	Geographic group	
	SVS (25220 reported cases exposed to protamine	ESVS (12902 reported cases exposed to protamine
Systemic hypotension	1209 (4.79%)	495 (3.83%)
Pulmonary artery hypertension	65 (0.26%)	8 (0.06%)
Anaphylaxis	52 (0.21%)	10 (0.08%)
Death	7 (0.03%)	2 (0.02%)
Total reactions	1333 (5.3%)	515 (4.0%)*

Comparison between geographic groups using Chi square analysis: * $p < 0.05$. All other differences not significant.

for SVS members and 198 patients for ESVS members. Considering that the frequency of protamine use was 48% for SVS members and 18% for ESVS members, the overall complication rates were 5.3% and 4.0%, respectively. Although the difference in these rates was small, it was statistically significant ($p < 0.05$).

The frequency of serious protamine-related complications was high enough in certain patient subgroups that occasional surgeons stated that protamine should not be used in these situations. Identification of such patients by surgeons from the SVS and ESVS, respectively, included: diabetics previously exposed to protamine-containing NPH or PZI insulin (25% and 16%); patients previously exposed to salmine protamine, such as during cardiac catheterisation (13% and 15%); men having undergone prior vasectomy (7% and 6%); and patients with previously alleged allergic reactions to protamine (4% and 1%). SVS surgeons pretreated patients at high risk for protamine reactions with steroids and antihistamines more often than their ESVS counterparts (24% *vs.* 7%, $p < 0.001$).

Discussion

Protamine sulfate may cause severe side-effects when used to reverse the anticoagulant effect of heparin. A number of mechanisms have been suggested to cause protamine related toxicity. These include complement activation,[1–7] thromboxane generation,[8–13] histamine release,[14–16] inhibition of plasma carboxypeptidase N,[17] direct actions on the peripheral vasculature and the heart,[18] and immunologic mechanisms including antibody-mediated and immediate anaphylactoid reactions without antibody involvement.[19–27] Hypotension appears to result from elaboration of a vasodilator factor, such as nitric oxide,[28–30] as well as depression of myocardial function, including bradycardia.[31] Pulmonary artery hypertension, on the contrary, is thought to result from thromboxane release, primarily from non-platelet sources in the lung.[8,10,12,32–37] Lastly, thrombocytopenia and leukopenia most likely result from direct toxic effects of protamine on phospholipid membranes of these elements.[37–43]

Specific interventions may block one, but not another of such heterogenic responses to protamine.[44] However, all of protamine's recognised non-allergic side-effects are suspected to be due to its polycationic nature. Recently, it has been demonstrated that the efficacy of protamine's heparin reversal as well as its toxicity correlate closely with the total cationic charge of this agent.[45] Parenthetically, there has been no demonstration that the anaphylactoid responses to protamine are related to its cationic charge.

Few clinical studies have been published on the frequency of protamine usage and its adverse responses. This study does not answer the question of the indications for protamine reversal in vascular surgery patients based on heparin dosage, although it does indicate the frequency of protamine usage with various operative procedures. In two small series hypotension was observed in 3% to 5% of patients subjected to peripheral vascular surgical procedures,[46] and pulmonary artery hypertension was noted in 4% to 5% of patients undergoing cardiopul-

monary bypass.[8] The preponderance of systemic hypotension, rather than pulmonary hypertension, during peripheral vascular procedures was the reverse of that observed in cardiopulmonary bypass patients. This may reflect the generation of thromboxane-like products by the bypass circuit itself in these latter instances. However, this also may reflect the fact that many patients reported most likely did not have pulmonary artery pressure catheters placed, leading to an underestimation of pulmonary hypertensive responses by the questionnaire respondents.

The results of this survey document heparin use to be common by surgeons of the SVS and ESVS. Although this study is subject to the major limitations of a self-reported, voluntary, retrospective survey in that much of its data may have been based on the respondents' impressions rather than on the hard data from review of hospital charts and anaesthesia records, it is clear that protamine usage is more frequent among SVS surgeons than ESVS surgeons and the rate of adverse side-effects is significant worldwide. Data to support such a conclusion has heretofore not been reported. Furthermore, it is intuitive that this survey's data supports the tenet that a safer yet effective alternative to protamine is needed for reversing heparin anticoagulation.

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