
Thomas W. Wakefield¹, Bengt Lindblad², Timothy J. Stanley¹, Brad J. Nichol¹, James C. Stanley¹, David Bergqvist², Lazar J. Greenfield¹ and Sven-Erik Bergentz²

¹ Section of Vascular Surgery, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A. and ² Department of Surgery, Malmo General Hospital, Malmo, Sweden

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
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 possibilities.

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

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

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

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 procedures. 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 ± 2918IU (median 5000IU), a figure similar to the 5395 ± 4292IU used by 307 responding ESVS surgeons (median 5000IU). The mean calculated heparin dose used by the 54 responding SVS surgeons was 153 ± 178IU/kg compared to 136 ± 195IU/kg by the 34 responding ESVS surgeons. When utilising regional heparin intraoperatively, the total dose reported was 2520 ± 2985IU for 57 responding SVS surgeons and 2971 ± 2239IU for 151 responding ESVS surgeons. Intraoperative dextran was used in greater amounts by ESVS surgeons and was reported as 537 ± 501ml by 88 surgeons as compared to 251 ± 183ml 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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>SVS</th>
<th>ESVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy</td>
<td>54%</td>
<td>26%</td>
</tr>
<tr>
<td>Aortic reconstruction for occlusive disease</td>
<td>58%</td>
<td>23%</td>
</tr>
<tr>
<td>Femoral-popliteal-tibial reconstruction</td>
<td>44%</td>
<td>15%</td>
</tr>
<tr>
<td>Elective abdominal aortic aneurysmectomy</td>
<td>63%</td>
<td>27%</td>
</tr>
<tr>
<td>Emergent abdominal aortic aneurysmectomy</td>
<td>48%</td>
<td>17%</td>
</tr>
<tr>
<td>Thromboembolectomy</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>A-V fistula placement</td>
<td>27%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Geographic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVS (25 220 reported cases exposed to protamine)</td>
</tr>
<tr>
<td>Systemic hypotension</td>
<td>1209 (4.79%)</td>
</tr>
<tr>
<td>Pulmonary artery hypertension</td>
<td>65 (0.26%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>52 (0.21%)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (0.03%)</td>
</tr>
<tr>
<td>Total reactions</td>
<td>1333 (5.3%)</td>
</tr>
</tbody>
</table>

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

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, thromboxane generation, histamine release, inhibition of plasma carboxypeptidase N, direct actions on the peripheral vasculature and the heart, and immunologic mechanisms including antibody-mediated and immediate anaphylactoid reactions without antibody involvement. Hypotension appears to result from elaboration of a vasodilator factor, such as nitric oxide, as well as depression of myocardial function, including bradycardia. Pulmonary artery hypertension, on the contrary, is thought to result from thromboxane release, primarily from non-platelet sources in the lung. Lastly, thrombocytopenia and leukopenia most likely result from direct toxic effects of protamine on phospholipid membranes of these elements.

Specific interventions may block one, but not another of such heterogenic responses to protamine. However, all of protamine’s recognised non-allergic side-effects are suspected to be due to its polycationic nature. 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, and pulmonary artery hypertension was noted in 4% to 5% of patients undergoing cardiopul-
monary bypass. 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 anesthesia 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.

References


15 KELLER R. Interrelationships between different types of cells. II. Histamine-release from the mast cells of various species by cationic polypeptides of polymorphonuclear leukocyte lysosomes and other cationic compounds. Int Arch Allergy Appl Immunol 1968; 34: 139–144.


30 PEARSON PJ, EVORA PR, AYRANCIOGLU K, SCHAFF HV. Protamine releases endothelium-derived relaxing factor from systemic ar-

Accepted 13 October 1993