Is there evidence that fresh frozen plasma is superior to antithrombin administration to treat heparin resistance in cardiac surgery?

Gwyn W. Beattie* and Robert R. Jeffrey

Department of Cardiothoracic Surgery, Aberdeen Royal Infirmary, Aberdeen, UK

* Corresponding author. Department of Cardiothoracic Surgery, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK. Tel: +44-1224552295; e-mail: gwynbeattie@doctors.org.uk (G. Beattie).

Received 22 March 2013; received in revised form 11 June 2013; accepted 8 July 2013

Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was, ‘in [patients with heparin resistance] is [treatment with FFP] superior [to antithrombin administration] in [achieving adequate anticoagulation to facilitate safe cardiopulmonary bypass]?’ More than 29 papers were found using the reported search, of which six represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Antithrombin (AT) binds to heparin and increases the rate at which it binds to thrombin. The levels of antithrombin in the blood are an important aspect of the heparin dose–response curve. When the activated clotting time (ACT) fails to reach a target >480, this is commonly defined as heparin resistance (HR). Heparin resistance is usually treated with a combination of supplementary heparin, fresh frozen plasma (FFP) or antithrombin III concentrate. There is a paucity of evidence on the treatment of heparin resistance with FFP, with only five studies identified, including one retrospective study, one in vitro trial and three case reports. AT has been studied more extensively with multiple studies, including a crossover trial comparing AT to supplemental heparin and a multicentre, randomized, double blind, placebo-controlled trial. Antithrombin (AT) concentrate is a safe and efficient treatment for heparin resistance to elevate the activated clotting time (ACT). It avoids the risk of transfusion-related acute lung injury (TRALI), volume overload, intraoperative time delay and viral or vCJD transmission. Antithrombin concentrates are more expensive than fresh frozen plasma and may put patients at risk of heparin rebound in the early postoperative period. Patients treated with AT have a lower risk of further FFP transfusions during their stay in hospital. We conclude that the treatment of HR with FFP may not restore the ACT to therapeutic levels with adequate heparinization, but AT is efficient with benefits including lower volume administration, less risk of TRALI and lower risk of transfusion-related infections.

Keywords: Review • Cardiopulmonary bypass • Heparin resistance • Antithrombin • Plasma

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients with heparin resistance] is [treatment with FFP] superior [to antithrombin administration] in [achieving adequate anticoagulation to facilitate safe cardiopulmonary bypass]?

CLINICAL SCENARIO

A 63-year old man presented with a non-ST elevation myocardial infarction and remained as an inpatient for 24 days for an operation. Prior to cannulation the perfusionist informs you that the activated clotting time (ACT) is only 281. The anaesthetist has already given a second dose of heparin to bring the total dose to 500 IU per kg. Your consultant arrives and demands two units of fresh frozen plasma (FFP). After 40 min awaiting delivery of the FFP, the repeat ACT is 347, so it is again below 480. Antithrombin (AT) concentrate is given and the ACT rises to over 600. Given the length of the waiting period and the ineffectiveness of FFP, you check the literature for the evidence surrounding heparin resistance (HR) and FFP administration.

SEARCH STRATEGY

MEDLINE 1950 to March 2013 using OVID interface MESH Categories.

[*Cardiopulmonary Bypass/AND Heparin Resistance.mp AND exp Antithrombin/] OR [*Cardiopulmonary Bypass/AND Heparin Resistance.mp AND *Plasma/]

SEARCH OUTCOME

Twenty-nine papers were found using the reported search. From these, six papers were identified that provided the best evidence to answer the question. These are presented in Table 1.
<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiess et al. (2008), Ann Thorac Surg, USA [2]</td>
<td>Systematic review of the literature</td>
<td>ACT</td>
<td>Paucity of evidence for FFP in managing HR during cardiac surgery, one retrospective study, one in vitro study and three case reports</td>
<td>FFP may not resolve all cases of HR</td>
</tr>
<tr>
<td></td>
<td>Search was performed using MEDLINE and PubMed databases between 1975 and 2006</td>
<td>Mean heparin dose</td>
<td>Significant time delay for FFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keywords used: HR, AT, recombinant human AT and FFP. Additional studies were identified from references cited in publications found using the search terms and also in published review articles</td>
<td>Time to achieve bypass ACT</td>
<td>Transfusion related injuries more likely with FFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No prospective clinical trials to date have evaluated the use of FFP in treating heparin resistant patients</td>
<td>Safety</td>
<td>Risk of viral transmission or vCJD with FFP</td>
<td></td>
</tr>
<tr>
<td>Sabbagh et al. (1984), Ann Thorac Surg, USA [3]</td>
<td>44 patients for cardiopulmonary bypass</td>
<td>ACT</td>
<td>FFP restored heparin ACT response curve</td>
<td>Initial cohort report showing rise in ACT following FFP administration</td>
</tr>
<tr>
<td></td>
<td>20 patients ACT &lt; 300 after first dose of Heparin</td>
<td></td>
<td>2 FFP increased ACT from 417 [±60] to 644 [±71]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 patients extra heparin to 600 units/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 patients 2 FFP and supplemental heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams et al. (2000), Ann Thorac Surg, USA [4]</td>
<td>85 patients ACT &lt; 480 after 450 U/kg of heparin</td>
<td>Failure of therapy</td>
<td>Heparin dose: AT GP 638 ± 173</td>
<td>Patient who required one additional dose of heparin, then FFP followed by an ACT minimum extra time is 40 min</td>
</tr>
<tr>
<td></td>
<td>Randomized to receive either 1000 IU AT or additional heparin</td>
<td>ACT</td>
<td>Heparin GP 869 ± 188 P &lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients crossed over groups if ACT not satisfactory</td>
<td>Total heparin used</td>
<td>Failure of therapy: AT 2/44 (5%) Heparin 13/41 (32%) P = 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing cycles (marker for time to acceptable ACT)</td>
<td>Dosing cycles: AT 1.09 ± 0.42 Heparin 1.95 ± 0.83 P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
RESULTS

Heparin binds to AT III and increases the rate at which it can bind to thrombin by a factor of several thousand, creating its anticoagulant effect [7]. AT III is commonly referred to in the literature as AT and is a circulating plasma protein that inhibits thrombin, factor Xa and other circulating coagulation factors. AT levels and activity are important to defining the heparin dose–response curve [5]. HR is usually defined as the failure to achieve an ACT of 480 s after 450 IU of heparin per kg bodyweight. HR can be treated with further heparin, FFP or AT concentrate.

Spiess [2], in 2008, performed a detailed systematic review and identified only five papers relating to FFP. Only one was a retrospective study, one was an _in vitro_ study and three were case reports. Five prospective clinical trials investigated AT. Two of the trials were placebo controlled [7, 8] and one was a crossover trial [4]. Spiess identified the risks of transmission of viral infections from FFP as 1 in 10 million donations for HIV, 1 in 1.2 million donations for Hepatitis B and 1 in 50 million donations for Hepatitis C. The risk of prion transfer is mentioned for FFP, but there have been no documented cases. No cases of viral transmissions from AT have been reported in patients who were not transfused with other blood products.

AT is a smaller volume to transfuse than FFP. One IU of AT is defined as the activity of endogenous AT in 1 ml of plasma. 500 IU of AT concentrate is made up in 10 ml, but FFP requires 500 ml of volume to equate to 500 IU, and this may not be suitable for patients with congestive heart failure [2]. Transfusion related acute lung injury (TRALI) from FFP is a major concern. In a retrospective review of 58 TRALI-related deaths by the US Food and Drug Administration, FFP was implicated in 50% of the deaths and suspected or possible cases of TRALI increased the mortality rate by 47% [2].

AT costs approximately eight times more than the price of two units of FFP; however, the delay in theatre can be significant and frustrating. The minimum time to defrost FFP is 20 min, followed
by at least another 8 min to reach therapeutic ACT, not factoring transport times.

Sabbagh et al. [3] was the first to suggest FFP as a treatment for HR after a retrospective analysis of 44 patients who underwent cardiopulmonary bypass. Twenty patients had an ACT <300 after 600 IU/kg of heparin was given. Eleven patients had supplemental heparin and 9 had two units of FFP followed by heparin. The transfusion of FFP increased the ACT from 417 s [±60] to 644 s [±71].

In a prospective randomized crossover trial Williams et al. [4] identified that AT was quicker and more effective, and patients had a lower total dose of heparin. HR patients were randomized to receive either 100 IU of AT or additional heparin. Any patients not achieving an ACT above 480 crossed into the other group. To analyse the time required to reach target ACT, they used the surrogate of dosing cycles. Each dosing cycle was ~12 min. The AT group had half the number of dosing cycles of the heparin group 1.09 ± 0.42 vs 1.95 ± 0.83 P < 0.0001. The total heparin dose was 638 IU ± 173 vs 869 IU ± 188 P < 0.00001. The number of patients who failed therapy and crossed groups was 2/44 [5%] vs 13/41 [32%] P = 0.001.

Avidan et al. [7] reports on a multicentre, randomized, double-blind, placebo-controlled trial with 54 patients. Administration of AT increased the ACT from 442 to 601 P < 0.001. The intraoperative transfusion rate for FFP was 19% in the AT group and 81% in the placebo group, P < 0.001. The in hospital FFP transfusion rate was 19% in the AT group and 81% in the placebo group, P = 0.009. Two units of FFP did not restore AT activity to the normal range. There were no differences in outcome measures, but patients receiving AT had a higher chest tube drainage and drainage rate in the early postoperative period. The authors conclude this was most likely due to heparin rebound.

**CLINICAL BOTTOM LINE**

AT concentrate is a safe and efficient treatment to elevate ACT. It avoids the risk of TRALI, volume overload, intraoperative time delay and viral or vCJD transmission. AT concentrates are more expensive than FFP and may put patients at risk of heparin rebound in the early postoperative period.

We conclude that the treatment of HR with FFP may not restore the ACT to therapeutic levels with adequate heparinization, but AT is efficient, with benefits including lower volume administration, less risk of TRALI and lower risk of transfusion-related infections.

**Conflict of interest:** none declared.

**REFERENCES**