A retrospective audit of the use of Prothrombinex-HT for refractory bleeding following adult cardiac surgery

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ABSTRACT

Objective: To review the frequency of use, possible efficacy and safety profile of Prothrombinex-HT (CSL Bioplasma, Melbourne, VIC) in treatment of patients with microvascular bleeding refractory to standard measures after cardiothoracic surgery.

Methods: A retrospective chart review was performed of 60 consecutive cardiothoracic surgical patients who received Prothrombinex-HT between February and August 2003. Data collected included baseline demographic information, nature and complexity of surgery, preoperative medications, baseline haematological parameters and evidence of clinically significant prothrombotic complications. Consumption of blood products, haematological parameters and mediastinal bleeding rates before and after administration of Prothrombinex-HT were documented in 22 patients who received Prothrombinex-HT in the ICU.

Results: No major prothrombotic complications were noted in the series of 60 patients. Two patients had superficial thrombophlebitis. Blood product consumption and haematological parameters were markedly reduced after administering Prothrombinex-HT.

Conclusions: Use of Prothrombinex-HT was not associated with significant prothrombotic complications. Limited evidence of its efficacy suggests that it should be further evaluated in the setting of cardiothoracic surgery.

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Major bleeding in the early postoperative period is a well-recognised complication after cardiac surgery.[1] In some cases, the cause may be surgically correctable. However, many patients have a functional coagulopathy which, unless corrected, precipitates further bleeding, and may expose the patient to unnecessary blood transfusion or further surgery.

There is no universally accepted procedure for correcting this coagulopathy, and there are few randomised controlled trials to guide protocol development. Management is therefore commonly based on local experience and preference. Therapy is often started empirically because of prolonged turn-around times for laboratory coagulation assays. Point-of-care testing, including thromboelastography and heparinase-activated clotting time, may provide earlier information to guide management.

A standard approach to early postoperative bleeding includes reversal of heparin with protamine, use of blood products such as fresh frozen plasma and cryoprecipitate to restore clotting factor levels, platelet transfusion, and maintenance of normothermia and normal calcium levels. Bleeding refractory to these measures has been treated with aprotinin and recombinant factor VIIa.[2]

Prothrombinex-HT (CSL Bioplasma, Melbourne, VIC) is a factor concentrate, which comprises factors II (prothrombin), IX and X and has been used primarily in haemophilia B and to reverse the anticoagulant effects of warfarin. Its use in patients with refractory bleeding after cardiac surgery has theoretical benefits, such as reducing the volume of infusion required and the risk of blood-borne virus transmission. However, its place in this setting remains undefined, and concerns persist about potential prothrombotic complications.[3]

This study aimed to review the current practice of Prothrombinex-HT use in patients with refractory early postoperative bleeding after adult cardiac surgery in our institution.

Methods

A retrospective chart review was performed of all cardiothoracic surgery patients issued with Prothrombinex-HT between February and August 2003.

Patients undergoing cardiac surgery during this period received blood products according to a hospital protocol based on recommendations of the National Health and Medical Research Council. This protocol included the use of Prothrombinex-HT when heavy mediastinal bleeding persisted despite the use of fresh frozen plasma, cryoprecipitate and platelets to correct specific coagulation defects (Figure 1). Residual heparin effect was assessed using a heparinase-activated clotting time system and, if present, corrected with additional protamine. Laboratory screening was repeated when clinically indicated to monitor response.

The following information was collected for all patients who received Prothrombinex-HT during the period:

- age and sex;

- preoperative medications;
- type of surgery;
- antifibrinolytic therapy administered;
- complexity of surgery (with complex procedures defined as urgent or emergency cases, combined grafts and valve replacements, procedures involving more than one valve, aortic root procedures, and procedures requiring a repeat median sternotomy); and
- when available, preoperative haemoglobin level, platelet count, international normalised ratio (INR) and activated partial thromboplastin time (APTT).

We sought evidence of prothrombotic complications detected during inpatient stay (deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, graft thrombosis, recurrent myocardial ischaemia, cerebrovascular accident, and acute peripheral vascular occlusion) from discharge summaries and history review.

Well documented efficacy data were available for the 22 patients who received an initial dose of Prothrombinex-HT in the ICU. The following information was also recorded before and after administration of Prothrombinex-HT, when available:

- volume of blood products used;
- laboratory measures of coagulation (INR, APTT); and
- documented blood loss in the 2 hours before and 2 hours immediately after Prothrombinex-HT administration.

Results

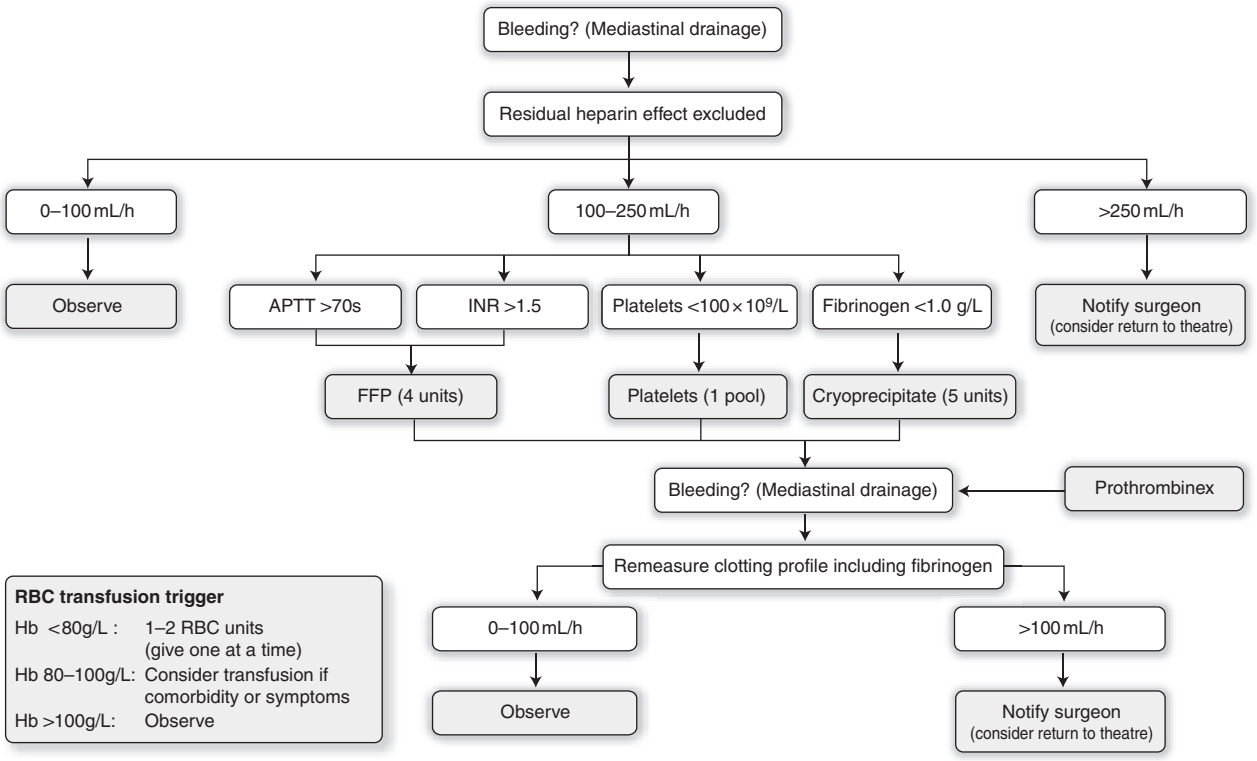
All patients who received Prothrombinex

During the study period, 203 patients underwent cardiothoracic surgery, and 60 of these (30%) received at least one dose of Prothrombinex-HT perioperatively.

Characteristics of these 60 patients are shown in Table 1. Their median age was 71 years (range, 42–81 years), and 75% were men. None were known to suffer a bleeding disorder preoperatively. Thirty-two patients (53%) underwent complex procedures. No patient underwent deep hypothermic circulatory arrest. Eight (13%) received cell saver blood.

Two patients developed acute superficial thrombophlebitis at peripheral intravenous sites during their inpatient stay, neither requiring specific therapy. One patient had a cerebrovascular accident in the setting of combined carotid endarterectomy and coronary artery bypass grafting. Computed tomography of the brain demonstrated extension of a pre-existing stroke. There were three deaths, none of

Figure 1. Protocol for administration of blood products after cardiac surgery at the Geelong Hospital at the time of the study



APTT = activated partial thromboplastin time. FFP = fresh frozen plasma. Hb = haemoglobin. INR = international normalised ratio. RBC = red blood cells.

which were considered to be related to Prothrombinex-HT administration.

Patients who received Prothrombinex in the ICU

Twenty-two patients received their first dose of Prothrombinex-HT in the ICU. Average dose was 1.09 vials per patient (545 IU). In the 22 patients, an average of 3.4 units of packed cells was used before Prothrombinex-HT administration, decreasing to 1.5 units after its use (Table 2 and Figure 2). Administration of fresh frozen plasma (FFP) was reduced from an average of 6.5 to 2.5 units per patient, while administration of platelets was reduced from an average of 5.9 to 2.5 units per patient. Seven patients (30%) returned to theatre for control of persistent haemorrhage. Average blood loss was reduced from 253 mL/h in the 2 hours before Prothrombinex-HT administration to 144 mL/h afterwards. INR and APTT were also reduced (Table 2).

The five patients with the highest INR values were compared with the five with the lowest INR values. The former group had an average initial INR of 1.96 and an average reduction in bleeding of 188 mL/h, while the latter group had an average initial INR of 1.34 and an average reduction in bleeding of 35 mL/h.

Table 1. Baseline characteristics of 60 patients who received Prothrombinex-HT during the study period

Characteristic	Number (%)*
Sex	
Male	45 (75%)
Female	15 (25%)
Age (years): median (range)	71 (42–81)
Complex procedure†	32 (53%)
Preoperative anticoagulant medication	
Aspirin	46 (77%)
Heparin/fragmin	8 (13%)
Warfarin	7 (11%)
Tirofiban	2 (3%)
Clopidogrel	4 (7%)
Median haemoglobin concentration (g/L)	139
Median platelet count ($\times 10^9$ cells/L)	223
Median international normalised ratio (INR)	1.1
Median APTT (s)	31

* Unless otherwise indicated.
† Urgent or emergency cases, aortic root procedures, combined grafts and valve replacements, and procedures involving more than one valve or repeat median sternotomy.
APTT = activated partial thromboplastin time. ◆

Discussion

This study identified 60 cardiothoracic surgical patients who were administered Prothrombinex-HT in the early post-cardiopulmonary bypass period. None were found to have a serious prothrombotic complication. Use of Prothrombinex-HT was associated with a trend towards clinically significant reduction in the use of blood products, including packed cells, fresh frozen plasma and platelets. In addition, the rate of mediastinal bleeding decreased, and both INR and APTT were lower after Prothrombinex-HT administration. The reduction in mediastinal bleeding appeared to be greatest in the patients with the highest INR.

To our knowledge, this study is the largest published data collection on the use of Prothrombinex-HT in postoperative cardiothoracic patients. Our findings are consistent with those of a smaller audit of 20 patients in England, in which clotting times were improved by use of prothrombin complex concentrates, with no evidence of an increase in prothrombotic complications.[4] No randomised controlled trials of its use in cardiac surgery have been reported.

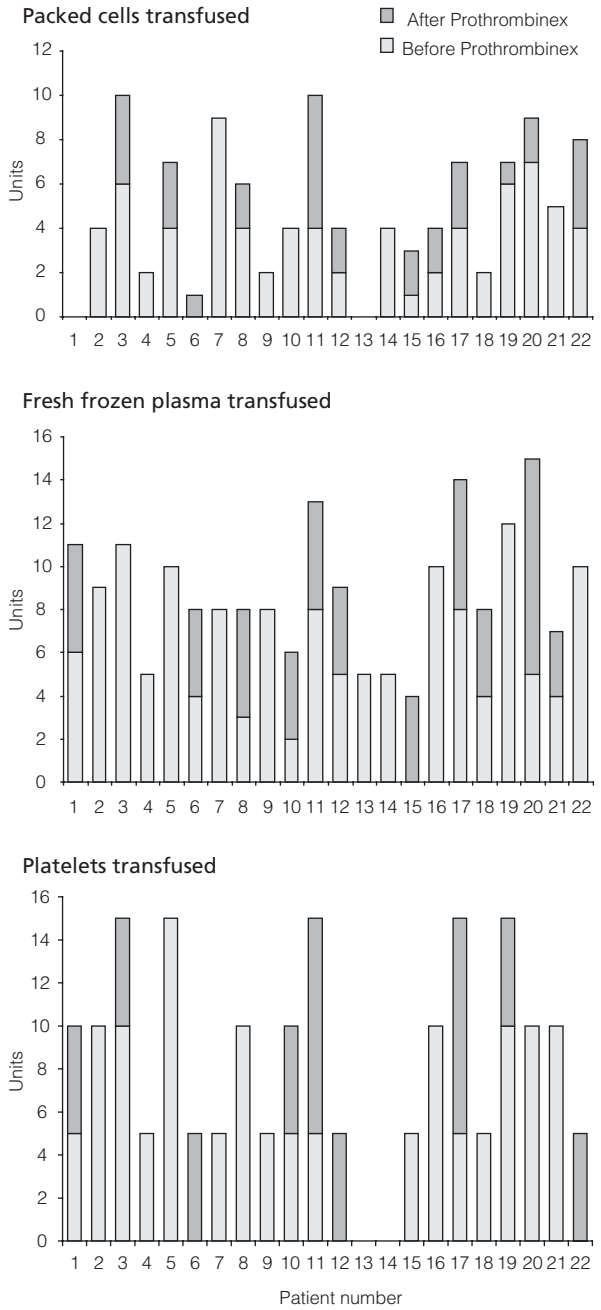
Our study had several limitations. As a retrospective review it relies on the accuracy of data recording in a non-study setting. Omission and incorrect documentation may

Table 2. Comparison of blood component therapy, coagulation profiles and bleeding rates before and after administration of Prothrombinex-HT to 22 patients in the ICU

	Before Prothrombinex-HT		After Prothrombinex-HT	
	Median (range)	Mean (95% CI)	Median (range)	Mean (95% CI)
Packed cells (units)	4 (0–9)	3.4 (2.4–4.4)	1 (0–6)	1.5 (0.8–2.2)
Fresh frozen plasma (units)	4 (0–12)	6.5 (5.2–7.8)	1 (0–10)	2.5 (1.3–3.7)
Platelets (units)	5 (0–15)	5.9 (4.1–7.7)	0 (0–10)	2.5 (1.1–3.9)
International normalised ratio (INR)	1.6 (1.2–2.2)	1.67 (1.55–1.79)	1.3 (1.2-1.8)	1.34 (1.28–1.40)
APTT (s)	59 (36–150)	75 (61–89)	46 (31–83)	49 (41–57)
Bleeding (mL/h)	230 (60–640)	253 (186–320)	140 (0–450)	144 (99–189)

APTT = activated partial thromboplastin time. CI = confidence interval.

Figure 2. Blood products used before and after Prothrombinex was administered to 22 patients in the ICU



lead to erroneous results. The effect of concurrent use of other interventions cannot be evaluated, and more subtle presentations of prothrombotic complications may have been missed.

Post-bypass bleeding in cardiothoracic patients is a well-recognised multifactorial problem.[1] Decreased serum concentration of clotting factors due to dilution by pump prime and volume infusion, consumption associated with bypass membranes and loss in mediastinal drainage is well known, and occurs to a greater degree in patients who develop refractory microvascular bleeding.[5] Other factors, including hypothermia, severe anaemia, reinfusion of pericardial blood, qualitative platelet dysfunction and residual heparin effect, may all contribute to coagulopathy. Routine postoperative management of haemorrhage involves exclusion of a surgical cause, restoration of clotting factors, platelets and fibrinogen, correction of hypothermia, and reversal of the effect of heparin. Other measures which have been demonstrated or suggested to be effective include administration of desmopressin, rescue aprotinin and recombinant activated factor VII.[2]

Prothrombinex-HT is a plasma-derived concentrate of coagulation factors II, IX and X. It is prepared by absorption of coagulation factors from plasma onto an ion exchange medium, followed by selective elution. This solution is then sterilised by filtration, freeze-dried and heated in the dried state to 80° C for 72 hours. Each vial of Prothrombinex-HT contains 500 IU of factors II, IX and X, along with 25 IU of antithrombin III, low levels of factor VII, and 200 IU of heparin. Once reconstituted in water, Prothrombinex-HT forms a volume of 20 mL per vial. It is recommended that Prothrombinex-HT be given slowly (no faster than 3 mL/min) when used at this concentration, and used immediately after reconstitution.[3]

Prothrombin complex concentrates may be effective in restoring essential amounts of factors II, IX and X. Factor IX appears to be important for generation of the "thrombin burst", by combining with factor VIII on the phospholipid membrane to activate factor X in large amounts. Prothrombinex-HT was originally developed for use in patients with haemophilia B, but has also been used in management of liver failure, warfarin toxicity and other isolated factor deficiencies or inhibitors. Prothrombinex-HT is currently recommended by the Australasian Society of Thrombosis and Haemostasis for the management of warfarin toxicity.[6]

Prothrombin complex concentrates may have significant advantages in refractory bleeding after cardiac surgery. They are administered in significantly smaller volumes than FFP and cryoprecipitate, with the advantages of rapid administration and reduced volume load. They are able to deliver thrombin and factor IX, which are known to be deficient in patients with bleeding after bypass,[5] in higher amounts than are practical with FFP. Use of viral inactivation procedures during their preparation potentially reduces the risk of blood-borne infections when compared with FFP. These concentrates contain no leukocytes or agglutinins and may thus reduce the risk of many transfu-

sion-related immunomodulatory complications, such as transfusion-related acute lung injury.[3] Currently, Prothrombinex-HT is provided at no direct cost to hospitals.

Despite these possible benefits, concern remains regarding the potential for prothrombotic complications, such as pulmonary embolism, graft thrombosis and arterial thrombus formation.[7,8] Case reports of such complications have been published, and the product information warns of them.[3] The absence of prothrombotic complications in our series of 60 patients, together with 20 patients in an earlier audit,[4] suggests concerns regarding prothrombotic complications may be unfounded. However, as Prothrombinex-HT contains small amounts of heparin, there is potential for heparin-induced thrombosis thrombocytopenia syndrome. Constitutional symptoms, including vomiting, rash, dyspnoea and somnolence, have also been described.[3]

Doses of Prothrombinex-HT used in this study were relatively small. In specific factor deficiency states, such as haemophilia B and warfarin reversal, the recommended dose is 20–30 IU/kg, up to 50 IU/kg given for major haemorrhage. However, in the context of cardiac surgery, factors are depleted rather than absent. In our patient population, Prothrombinex-HT was prescribed in an ad hoc manner based on clinical response and laboratory data, the most common dose being 500 IU (one vial). Interestingly, the two patients in our series who received two vials required no further blood products after their administration.

Despite the study limitations, we believe that the efficacy and safety of Prothrombinex-HT warrants further investigation in a prospective trial looking clearly at its effect on blood parameters (INR, APTT and fibrinogen), factor levels (particularly factor IX) and bleeding rates.

Conclusion

Prothrombinex-HT offers significant advantages in the management of haemorrhage after cardiac surgery. Our data suggest that Prothrombinex-HT is potentially effective in slowing non-surgical bleeding, and that concerns over prothrombotic complications may be unfounded.

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