

Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass

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We set out to determine if the heparinase-modified thrombelastogram using anticoagulated blood from patients during cardiac surgery could guide treatment with haemostatic components. In 60 patients a simple algorithm predicted a possible 60–80% decrease in the use of haemostatic components. In a second series, 30 patients were allocated to receive components using this intra-operative algorithm and 30 using clinical criteria and laboratory-based tests. Ten patients in the clinical group received a total of 16 units of fresh frozen plasma and nine platelet concentrates compared with five patients transfused with five units of fresh frozen plasma and one platelet concentrate in the algorithm group. Twelve-hour chest tube losses [algorithm group 470 (295–820) ml, clinically managed group 390 (240–820) ml (median, quartile values)] were not different between groups despite the threefold reduction in the use of haemostatic products, showing that intra-operative monitoring of coagulation in the anticoagulated patient can be used to guide treatment.

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Haemostatic blood components contribute significantly to the overall transfusion burden in patients having major surgery and especially cardiac surgery.

The thrombelastogram measures the rate and strength of clot formation.¹ Initiation of clot formation is defined as the reaction or r-time and the strength of the clot by the maximum amplitude of the trace. During cardiopulmonary bypass, the heparinase-modified thrombelastogram will develop despite anticoagulation with heparin in doses of 300 IU kg⁻¹ and gives the same results as those obtained using blood when heparin has been antagonized with protamine.²

Previous reports^{3,4} have described algorithms that reduce the need for haemostatic blood component therapy and re-

exploration. However, these studies waited until micro-vascular bleeding occurred before starting testing and intervention.

In this pilot study we investigated the predictive value and use of an algorithm using thrombelastogram measurements made during heart surgery using anticoagulated blood. The principal end-point for efficacy was reduced total exposure to haemostatic component therapies.

Methods and results

We studied two groups of 60 patients, who gave consent to the study. Ten per cent of the patients in each group had a heart transplantation and were taking aspirin and/or

Table 1 Decision tree for administration of haemostatic components based on the heparinase-modified Celite-activated thrombelastogram (TEG) at time 2. The range of normal values in Celite-activated blood for r is 10–14 mm and the maximum amplitude (MA) should be more than 56 mm. FFP=unit(s) of fresh frozen plasma. $Lys_{30} = (MA - \text{trace amplitude 30 min later}) \times 100$

Intra-operative TEG variable	Implication	Therapy
$r > 14 \text{ mm} < 21 \text{ mm}$	Clotting factors mildly reduced	1 FFP
$r > 21 \text{ mm} < 28 \text{ mm}$	Clotting factors moderately reduced	2 FFP
$r > 28 \text{ mm}$	Clotting factors severely reduced	4 FFP
MA <48 mm	Moderate in platelet number/function	1 platelet pool
MA <40 mm	Severe decrease in platelet number/function	2 platelet pools
$lys_{30} > 7.5\%$	Increased lysis (this was not observed)	Aprotinin

warfarin immediately before surgery. About 50% of the patients in each group had revascularization and were also taking aspirin, and required multiple grafts with a bypass time estimated to be greater than 100 min. The remaining 40% of the patients were having the Ross procedure, multiple valve or valve and revascularization surgery. No patients were having repeat operations and none received prophylactic aprotinin, epsilon aminocaproic or tranexamic acid.

The study plan allowed data from patients who returned to theatre for the control of surgical bleeding or who died within 48 h of the surgery to be discarded and replaced by measurements from an additional patient allocated to the same group. Three patients in the first series of patients and two in the second series (one each in the algorithm and control groups) returned to theatre. All these patients had drain losses of $>400 \text{ ml h}^{-1}$ and a thrombelastogram result within the normal range. No patient died during the first 48 h after operation.

Patient details were not significantly different between groups but showed a wide distribution of values for age (21–83 yr) and bypass time (48–167 min).

We made standard thrombelastogram measurements (TEG[®]; Haemoscope Corporation, Niles, IL, USA) in 360 μl of whole blood activated with 1% Celite. Samples were taken and analysed at the following times. (i) Baseline, after induction of anaesthesia. This sample was to exclude any pre-operative coagulopathy. (ii) Bypass. This sample was taken during rewarming when the bypass system venous blood temperature was $\geq 35^\circ\text{C}$, or within 30 min of separation from bypass in patients when tepid bypass was used (nasopharyngeal temperature $\approx 34^\circ\text{C}$). The sample was developed in a cuvette containing heparinase. The result was used to define the need for haemostatic components using the algorithm shown in Table 1. (iii) Ten to fifteen minutes after protamine. The thrombelastogram was developed with and without heparinase, to detect any residual heparin effect. Some of this blood was sent for laboratory measurement of prothrombin time, activated partial thromboplastin time (APTT), platelet count and fibrinogen concentration.

No patient had an abnormal thrombelastogram before surgery (sample 1) and there was no difference between measurements made at sample times 2 and 3, confirming

previous data.² No patient showed a residual heparin effect in paired samples at time point 3. The results were available within 20 min. Laboratory tests of coagulation, fibrinogen and platelet count typically took 70–90 min to perform and report.

Statistical and power analysis was performed using GB-Stat[™] version 6.5 for Macintosh (Dynamic Microsystems, Silver Spring, MD, USA) on a PowerMac. Statistical differences between groups were defined using the χ^2 test.

Series one

In the first 60 patients, haemostatic treatment (fresh frozen plasma and platelets) was determined using criteria obtained from conventional laboratory tests (prothrombin time and/or APTT ratio >1.5 times control, platelet count $<50\,000 \text{ dl}^{-1}$, fibrinogen concentration $\leq 0.8 \text{ mg dl}^{-1}$) in the presence of microvascular bleeding ($>400 \text{ ml}$ in the first hour after surgery or $>100 \text{ ml h}^{-1}$ for four consecutive hours). We noted the number of component units actually given, and the amount predicted from the thrombelastogram algorithm. This was done so that the method could be used to estimate the likely reduction in component transfusion, and to define the size of sample in the subsequent series after power analysis.

On the basis of clinical assessment and laboratory tests, 22 of 60 patients received blood components. If we had used the treatment algorithm, the number of patients receiving component therapy would have been seven ($P < 0.05$). The predicted number of components used (six units of fresh frozen plasma and two pools of platelets) would have been significantly less than the 38 units of fresh frozen plasma and 17 platelet pools actually transfused in these 60 patients ($P < 0.05$).

Power analysis suggested that 27 patients per group would be required to demonstrate a fourfold reduction in component use with an α of 0.05 and a power of $>90\%$.

Series two

In the second part of the study, 60 patients were randomly allocated to have products ordered and administered on the basis of either the algorithm (group T) or the wishes of the clinician (group C). Patients were allocated to groups by

means of a series of sealed envelopes. Haemostatic products were ordered and given as soon as test results were known, or as judged clinically by the surgeon or anaesthetist responsible for the case. The amounts of products given and volumes of chest drainage 6 and 12 h after surgery were recorded.

Ten of the 30 clinically managed patients received blood components according to clinical assessment and/or laboratory test results, compared with five of 30 managed by thrombelastogram data ($P < 0.05$). The amount of product use in group T (five units of fresh frozen plasma and one pool of platelets) was significantly ($P < 0.05$) less than the 16 units of fresh frozen plasma and nine platelet pools given to the 30 patients in group C.

Chest tube losses [median (lower and upper quartiles)] were not different between groups despite the fourfold difference in the use of haemostatic products. Twelve-hour losses were 470 (295, 820) in the group managed with the thrombelastogram and 390 (240, 820) in the group managed clinically.

Comment

The thrombelastogram has developed as a bedside monitor of the coagulation process over the past 15 yr. The device was first popularized by Dr Kang and the group in Pittsburgh for monitoring during hepatic transplantation,⁵ mainly because the device detects clot lysis, which is the principal haemostatic defect in this operation.

Others in the USA found the thrombelastogram useful for cardiac surgery, in which coagulopathy has different causes compared with hepatic surgery. In the presence of microvascular bleeding, thrombelastography was better than conventional tests of coagulation in defining the abnormality and in guiding treatment.⁶ Abnormal formation (principally r-time) implied reduced clotting factors, and reduced maximum amplitude deficiency implied reduced platelet numbers or function. A later study showed that this device reduced blood transfusions and also re-exploration for bleeding, which decreased fourfold during the study period.³ Other centres reported that the maximum amplitude, measured after protamine administration, was related to early losses from post-operative drains.^{4, 7} This device has also been used in obstetric,⁸ trauma⁹ and peripheral vascular¹⁰ practice. In all these reports the patients' blood was not anticoagulated at the time of the analysis and the test was being used to characterize rather than to predict and anticipate a coagulation abnormality.

The pilot study described here is the first to show that a heparinase-modified thrombelastogram in anticoagulated blood can predict, and reduce substantially, the need for haemostatic products without increasing post-operative bleeding in patients having heart surgery.

There are a number of potential concerns and weaknesses in the present study.

The first is related to the magnitude of the observed effect. We studied patients who were considered at high risk of requiring haemostatic products but in whom prophylactic drug therapies, such as aprotinin, would not be universally appropriate. Haemostatic components were given to about 30% of our control group patients, which is the same proportion reported from Montreal¹¹ and New York.⁴ The second of these reports showed the benefit of an algorithm when microvascular bleeding was established. The authors described a four- to fivefold reduction in the use of frozen plasma, and our study supports this finding. In contrast to this earlier report,⁴ the present study demonstrates a statistically significant, eightfold reduction in platelet transfusion, suggesting that assessment of coagulation before the observation of microvascular bleeding can be valuable.

Part of this improvement may be related to the time the components are given. The algorithm we used allowed treatment shortly after the antagonism of heparin action by protamine. In contrast, the delay in obtaining laboratory data meant that patients in the control group received their component therapy after transfer to the intensive care unit. It is obvious that the magnitude of any benefit would be less for operations in which there is less need for haemostatic components.

Secondly, we did not want to use prophylactic drug therapies such as aprotinin and tranexamic acid, as they have different effects on thrombelastography. In particular, the r-time is prolonged by aprotinin therapy and shortened by tranexamic acid.¹²

This leads to the third weakness of the present algorithm and other algorithms,⁴ which is that the numerical values for each thrombelastogram parameter are based on reference ranges found in a standard population. There are no current data to show that the values chosen, or the treatment these values indicate, are optimal for any particular patient group. This is highlighted by the difference in the predicted requirement for transfusion of haemostatic components between the first and second cohorts despite similar patient characteristics, the same team of anaesthetists and surgeons, and very similar actual transfusions using conventional clinical criteria.

Finally, if the algorithm predictions were wrong, then the patients in group T might have had increased bleeding after the bypass. However, the accuracy of the prediction is not known as in neither group did we completely withhold products to determine any association with increased bleeding and the need for re-exploration. The values used in this algorithm may need modification to allow additional benefits and improve their applicability. This would require a larger, appropriately powered, multicentre study.

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