Thrombelastogram reveals hypercoagulability after administration of gelatin solution

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We have compared the effects of gelatin, low molecular weight hydroxyethyl starch (HES) or albumin on tests of haemostasis and on the thrombelastogram in 42 ASA I patients undergoing total hip or knee replacement. Patients were allocated randomly to receive one of the three blood substitutes to obtain moderate intraoperative haemodilution. Blood loss and packed red cell infusion was the same in each group. A greater amount of gelatin was given (1.5 times the measured blood loss) because of its shorter half-life. There was a statistically significant but clinically negligible decrease in platelet count, prothrombin time and fibrinogen, and an increase in bleeding time in all groups. Platelets were slightly but significantly lower after HES. Haemodilution was comparable between groups. TEG showed a state of hypercoagulability in the gelatin group with a significant decrease in r, r+k and an increase in α angle.

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When perioperative blood loss is replaced partly with plasma expanders, impairment in haemostasis may be anticipated. High molecular weight hydroxyethyl starch is known to affect haemostasis.1,2 The effects of low molecular hydroxyethyl starch (HES) are still a subject of controversy. It has been found to decrease factor VIII procoagulant and von Willebrand factor antigen activity, and to increase bleeding time.3,4 Others authors have denied any effect of HES on blood clotting if doses remain within accepted guidelines.5–7 Dextran also affect coagulation, depending on their molecular weight.5,6 Little is known of the effects of gelatin plasma expanders on immediate postoperative haemostasis. This study was designed to compare the effects of HES, albumin and gelatin as blood substitutes on postoperative haemostasis. Standard tests of haemostasis and thrombelastograms were compared before and after volume replacement.

Patients and methods

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 42 ASA I I patients. Patients were undergoing total hip or knee replacement and were allocated randomly to receive a 3.5% modified gelatin solution (molecular weight 35 000 Da) (group GEL), 6% low molecular weight hydroxyethyl starch (molecular weight 200 000 Da and substitution ratio 0.62) (group HES) or 5% albumin solution (molecular weight 69 000 Da) (group ALB).

Patients with pre-existing coagulation disorders, abnormal preoperative platelet count (normal range 150–400 000 g litre–1), activated partial thromboplastin time (APTT) (normal range patient/reference 0.7–1.2) or prothrombin time (normal range 70–150%) were excluded. Patients with known renal failure (creatinine concentration >180 µmol litre–1; normal range 60–100 µmol litre–1), allergy to plasma substitutes or receiving haemostasis-impairing treatment in the 10 days before surgery were excluded.

Anaesthesia was standardized. Monitoring included ECG, SPO2, non-invasive arterial pressure, end-tidal carbon dioxide concentration, FIO2, isoflurane concentration and temperature in the auricular canal. Core temperature was maintained at >36°C using forced-air warming. All patients were included in a preoperative autologous blood donation programme (1–3 u.), with separation of packed red cells and fresh frozen plasma. When surgery necessitated removal of a previous prosthesis, intraoperative blood harvesting with a cell saver was used. Low molecular weight heparin (dalteparine 2500–5000 u.) was given from the day before surgery and continued after operation for prevention of deep vein thrombosis.

Intraoperative blood loss was estimated from the volume
Significance was considered at homogeneity of variance determined with the test of Bartlett.

of blood in the suction container and by weighing dressings and swabs. The volume of blood loss was replaced by the same amount of HES or albumin. The volume of administered gelatin solution was equivalent to 1.5 times blood loss to take account of its short half-life and to prevent postoperative hypovolaemia. Autologous packed red cells were given when the microhaematocrit decreased to less than 25%. Blood samples were obtained for standard coagulation tests and the thrombelastograph (TEG), after induction of anaesthesia, before surgery (T0) and after arrival in the recovery room (T1). The TEG was performed within 3 min of blood sampling, using a two-channel computerized thrombelastograph (CTEG #3000, Haemoscope, USA). A bleeding time was performed at T0 and T1 by the same investigator. Ionized calcium and blood pH were measured routinely before surgery in all patients. Autologous fresh frozen plasma was infused in the recovery room after T1.

Results

Fifteen patients received gelatin, 15 HES and 12 albumin. No patient had abnormal perioperative bleeding. Patients characteristics and surgery were comparable between groups (Table 1). Clinical and biological data other than haemostasis did not differ between groups. Preoperative doses of low molecular weight heparin used for prevention of deep vein thrombosis were similar in all groups when adjusted for patient weight.

Intraoperative blood loss did not differ between groups (Table 2). The volumes of lactated Ringer’s solution and packed red cells given were similar in all groups. According to the study design, the volume of gelatin was significantly greater than the amount of HES and albumin, although haemodilution, assessed by packed cell volume, was similar in each group. Doses of ephedrine given to treat hypotensive episodes were not different between groups (Table 2). Blood loss at 24 h was 739 (sd 96) ml in the gelatin group, 701 (96) ml in the HES group and 674 (108) ml in the albumin group (ns).

Standard haemostasis tests and TEG were within normal limits before surgery (T0) (Tables 3, 4). After operation, there was a significant but similar decrease in packed cell volume in each group. Platelet counts were significantly lower after HES but values remained within normal limits. In patients receiving gelatin, there was a significant decrease in r and r+k times and an increase in α angle (Table 4).

Discussion

TEG is a global test of haemostasis which investigates blood clot formation by continuous measurement of its
viscoelastic properties.\textsuperscript{8} It is a unique test which allows diagnosis of hypercoagulability after surgery by a shorter delay of onset of coagulation (diminished $r$ and $r+k$ times), a shorter delay in completion of the clotting process (increased $\alpha$ angle) and strengthened clot (increased MA).\textsuperscript{9} \textsuperscript{10} The postoperative TEG of patients who received gelatin as a blood substitute showed significant hypercoagulability compared with control tracings and with the albumin and HES groups. How gelatin enhances coagulation is unknown but could be a consequence of its rheological properties, affecting onset of clotting processes (shortened $r$ and $\alpha$ angle), but not clot strength (normal MA).\textsuperscript{11} \textsuperscript{12} Ruttmann, James and Viljoen showed a similar coagulation profile in an \textit{in vitro} study,\textsuperscript{13} although others found an \textit{in vitro} hypocoagulable tendency.\textsuperscript{14} An hypothesis for this normal MA could involve interaction of fibronectin and gelatin, with clot-incorporated gelatin–fibronectin complexes impeding polymerization of fibrin.\textsuperscript{15} The duration of this hypercoagulability after administration of gelatin and whether or not it is dose-dependent and clinically significant deserve further investigation. Deep vein thrombosis was detected after operation in two patients (one in the gelatin group and one in the albumin group). These thromboembolic events were detected clinically. No specific investigations for venous thrombosis were carried out systematically. Unfortunately, we did not measure thrombin–antithrombin complexes or prothrombin fragments, as we did not expect this gelatin-related hypercoagulable state before the study. These assays would indicate \textit{in vivo} thrombin formation.

There was no difference between the three groups which could explain these TEG results. The volume infused was deliberately higher for gelatin to prevent occurrence of postoperative hypovolaemia as a result of rapid urinary elimination. Nevertheless, postoperative packed cell volume was similar in the three groups and the amount of plasma expander administered to patients was always less than the maximum recommended dose. Although the TEG showed a state of hypercoagulability, no clinically significant change in standard tests of haemostasis was observed. Bleeding time was increased after operation. Although these changes were statistically significant, values remained within the normal range. Prothrombin and fibrinogen were lower as a result of haemodilution but although statistically significant, values remained within normal limits. The same was true for platelets, which decreased after operation, first in group HES and after 24 h in all groups, but again values remained within the normal range. Intraoperative blood salvage with a cell saver was not considered as a source of bias because it was used similarly in each group and did not affect coagulation tests. Moreover, two studies found no effect of the cell saver’s heparin on coagulation tests during surgery.\textsuperscript{16} \textsuperscript{17}

In summary, moderate haemodilution by partial substitution of intraoperative blood loss by plasma expanders did not provoke hypercoagulability. Indeed, gelatin was responsible for changes in TEG that indicated a state of hypercoagulability.

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