



The influence of intravascular volume maintenance with a hydroxyethyl starch solution on coagulation in patients undergoing transurethral resection of the prostate

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Abstract

Background and Aims: Disorders of haemostasis by hydroxyethyl starch (HES) are mostly affected with large and highly substituted HES molecules or with longer duration and larger amount of HES infused. The development of HES solution with lower molecular weight and lower degree of substitution (HES 130/0.4) provides important advantage which affects less coagulation *in vivo* (8, 11, 13, and 16). We conducted a pilot study to evaluate influence of the HES 130/0.4 solution on coagulation parameters in patients with benign prostatic hyperplasia (BPH) undergoing transurethral resection (TURP) in spinal anaesthesia.

Patients and Methods: Seventeen patients scheduled for TURP were enrolled in this pilot study. For intravascular volume replacement, only HES 130/0.4 was used during and 1 hour after surgery. The venous blood samples have been taken 1 hour before surgery (as control) and 1 hour post-operative. Standard coagulation parameters prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, platelet count, fibrinogen were measured and whole blood coagulation was assessed using thromboelastography (TEG).

Results: Coagulation time (CT) and clot formation time (CFT) increased significantly postoperative both in Intrinsic Thromboelastography (INTEM) and Extrinsic Thromboelastography (EXTEM). Maximum clot firmness (MCF) decreased significantly in postoperative period in all TEG test INTEM, EXTEM and Fibrinogen Thromboelastography (FIBTEM) and alpha angle (α) decreased significantly both in INTEM and EXTEM. Despite significant postoperative changes of TEG parameters, they were still within normal clinical range.

Discussion: We concluded that intravascular replacement exclusively with HES 130/0.4 may be a safe choice for patients during TURP estimated by TEG.

INTRODUCTION

Adequate maintenance of intravascular volume is an important factor in managing surgical patients. The choice of an ideal solution for volume replacement is still a matter of debate, as the type and amount of replacement fluid can affect the coagulation process signifi-

cantly. Except crystalloid solution, synthetic colloids such as HES are commonly used to prevent and treat volume deficit. The advantage of HES compared to crystalloid solutions is a faster restoration of intravascular volume deficit using less fluid, however HES can significantly affect blood coagulation (3). This was more often present within first generation of HES solutions, which had higher molecular weight (Mw) and higher degree of substitution (DS). When these solutions are administered in larger volume, they may cause platelet dysfunction by reducing availability of the functional receptor for fibrinogen on the platelet surface (GP IIb-IIa) in greater proportion than that expected only by simple plasma dilution, as shown *in vitro* (7) and *in vivo* studies (3, 8).

The development of a new HES solutions with lower Mw (130,000 Daltons) and lower DS (0.4) as HAES 130/0.4 have improved physicochemical profile of synthetic colloids, compared to standard medium-molecular weight HES (HES 200/0.5), or high-molecular weight HES (HES 450/0.7) solutions (19). This leads to less disruption in coagulation process, an important clinical advantage of HAES 130/0.4. Also, other advantages of HES 130/0.4 are enhanced metabolism and renal elimination and lower tissue storage after repeated administration compared to the old one (6, 19). During transurethral resection of the prostate (TURP) there can be significant changes in intravascular volume, mostly caused by bleeding which demands adequate treatment, with solutions that have little impact on the coagulation. This study assesses the influence of the HES 130/0.4 for intravascular volume maintained on coagulation impairment in patients with benign prostatic hyperplasia undergoing TURP.

PATIENTS AND METHODS

Seventeen men (median age 68.4, range 64.7–72.1) with obstructive symptoms clinical and laboratory evidence suggesting of BPH were included in the study, after having given informed consent. The study was approved by the Regional Ethical Committees. The patients were ASA classification I or II, scheduled for TURP.

Exclusion criteria were pre-existing bleeding disorders, renal insufficiency (serum creatinin > 120 µm/L), liver disease and altered liver function, preoperative anaemia (Hgb < 100 × 10⁶g/L), preoperative coagulation abnormalities (prothrombin time [PT] < 70, platelet count < 100 × 10⁹g/L, partial thromboplastin time [aPTT] > 33s, fibrinogen < 1.8g/L), use of non-steroid anti-inflammatory drugs (NSAID) 5 days before surgery.

All patients fasted 10 hours before surgery and received routine premedication 30 minutes before surgery (oral midazolam 7.5 mg).

Prophylactic anticoagulation was performed through subcutaneous administration of low molecular weight heparin nadroparin 0.4 mL (Fraxiparine, Sanofi-Synthelabo-LEK, Ljubljana, Slovenia) 10–12 h before surgery.

All patients were anaesthetized in through spinal anaesthesia. Spinal anaesthesia was performed aseptically

using 24 gauges. Whitacre/Quincke spinal needle in L3-L4 subdural area with 15 mg 0.5% Levobupivacain (Chirocaine, Abbott Laboratories, UK).

Intraoperative and postoperative hemodynamic monitoring included, heart frequency, continuous measurement of electrocardiogram, systolic and diastolic blood pressure, medium arterial pressure, oxygen saturation.

Volume replacement was performed using exclusively HES 130/0.4 (6% Voluven, Fresenius Kabi, Bad Homburg, Germany).

The infusion was started before performing spinal anaesthesia and continued until first postoperative hour. The infusion volume did not have fixed value, fluid was initiated based on actual requirement of the patients taking hemodynamic parameters, actual and anticipated blood losses, to keep mean arterial pressure between 70–90 mmHg. After surgery all patients were sent to the intensive care unit.

From venous blood samples standard coagulation parameters: PT, aPTT, fibrinogen, platelet count were measured by using routine laboratory methods, while another venous blood was taken for performing Thrombelastography (TEG) by using a four-channel TEG analyzer (ROTEM, Pentapharm, Munich, Germany). During the study levels of haemoglobin (Hgb), haematocrite (Hct) and electrolytes were monitored.

TEG test was performed within 30 minutes after the blood sampling.

The following measurements were performed; INTEM Intrinsic activation (contact factor) of coagulation with 20 µL of partial thromboplastin via factors XII, XI, IX, VII, X, V, II (thrombin) and I (fibrinogen), including effects of fibrinolysis and platelets.

EXTEM: extrinsic activation of coagulation with 20 µL of tissue thromboplastin (tissue factor) via the factor VII, X, V, II (thrombin) and I (fibrinogen), includes effects of fibrinolysis and platelets.

FIBTEM: EXTEM activation (tissue factor) plus platelet blockade. FIBTEM is used to estimate the amount of functional fibrinogen in the sample.

The following TEG parameters are reported: coagulation time (CT), clot formation time (CFT), maximum clot firmness (MCF), alpha angle (α) and clot lysis 30 min after MCF (LI 30).

All measurements were performed 1 hour before surgery (before colloids were administered) and 1 hour postoperative (1h after the end of surgery). Each patient acted as their own control, using preoperative values as the baseline.

Data were tested for normal distribution using the Kolmogorov-Smirnov-test.

The effect of intravenous test infusion on TEG variables was analyzed by using a parametric test (dependent t-test). A *P* value < 0.05 was considered statistically significant.

RESULTS

There were no relevant differences in demographic variables between the patients. Hemodynamic parameters remained within normal ranges in all patients during the study period.

Mean haemoglobin concentration, Hct, electrolytes did not show deviation from normal through the study period. As expected, Hgb and Hct showed a decrease in postoperative period caused by haemodilution. During the surgery, no relevant differences in duration of surgery, volume of irrigation fluid were found between the patients.

The mean (95% CI) infused volume of HES from starts of infusion until 1 hour after the end of surgery was 1050 mL (926.0–1173.9).

PT and fibrinogen were significantly ($p=0,001$; $p=0,004$) decreased, but stay within normal clinical range. For other standard coagulation parameters (aPTT, platelet count) no significant differences were found.

Infusion of the HES 130/0.4 increased CFT (Figure 1) and CT (Figure 2) significantly in EXTEM ($p=0.002$; $p<0.001$) and INTEM ($p=0.002$; $p=0.049$), decreased MCF (Figure 3.) in all measured TEG assays (EXTEM, INTEM $p<0,001$; FIBTEM $p=0,002$) significantly and also α angle (Figure 4) (EXTEM $p=0,011$; INTEM $p=0,008$), when compared with baseline values, but all TEG data were within normal clinical range.

LI 30 was unchanged during study period.

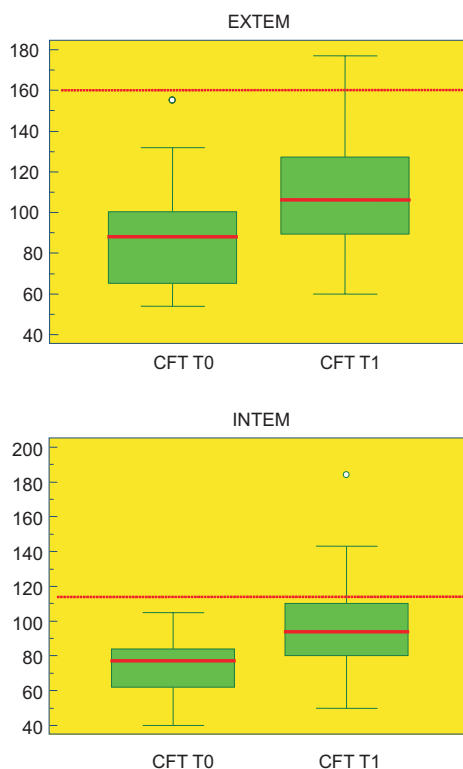


Figure 1. Changes in clot formation time (CFT) (normal EXTEM 34–159s; normal INTEM 30–110s) using EXTEM and INTEM.

DISCUSSION

HES are most commonly used artificial colloids with a good plasma volume expanding capacity. The extent and duration of plasma volume expansion, as well as their influence on the coagulation process differ between various HES specifications.

The impairment of haemostasis is the major concern with the infusion of HES, which is particularly seen in surgical patients. Some HES solutions have been associated with clinical coagulopathies and bleeding when administered in large volume. It appears that the effect on the coagulation system depends on the concentration, molecular weight as well as degree of substitution, but there is a difference between *in vitro* and *in vivo* study (8–12, 14).

The most pronounced effects on coagulation have been attributed to HES solution with higher molecular weight and greater degree of substitution (8–12, 16). *In vivo* and *in vitro* studies show that large molecules interfere with function of the vWF, FVIII, and also with fibrin formation and platelet function (8, 15, 16, 17, 18). Smaller molecular weight hydroxyethyl starches preserve coagulation better than larger molecular weight starches as judged by TEG (8, 12, 13), although some studies do not support this hypothesis (23, 24).

HES 130/0.4 with a low molecular weight of 130.000 dalton and low degree of substitution 0.4, achieves adequate medium-lasting colloidal volume efficacy, compared to HES 200/0.5. Clinically important advantage of

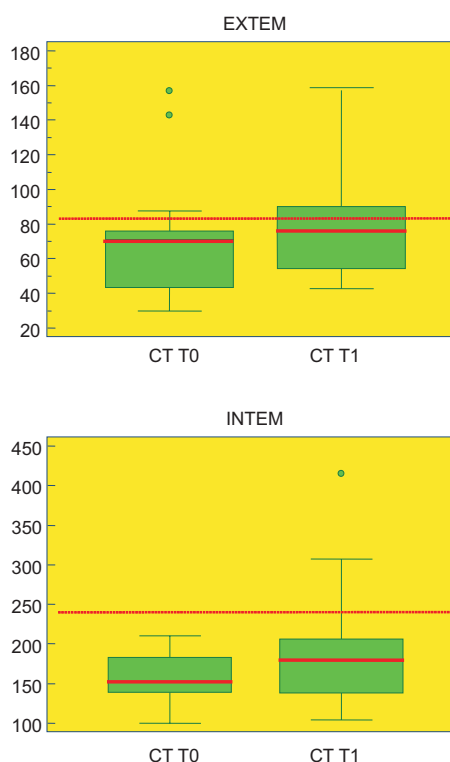


Figure 2. Changes in coagulation time (CT) (normal EXTEM 38–79s; normal INTEM 100–240 s) using EXTEM and INTEM.

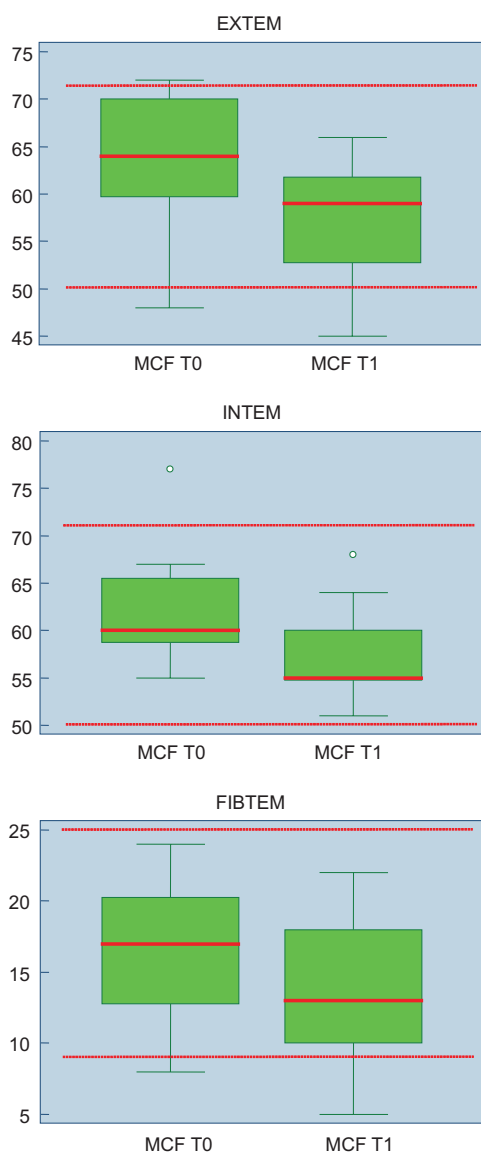


Figure 3. Changes in Maximum clot firmness (MCF) (normal EXTEM and INTEM 50–72mm; normal FIBTEM 9–25mm) using EXTEM, INTEM, FIBTEM. Results are mean (95% CI). T0=baseline values (before infusion of colloids); T1=1hour after surgery.

HES is enhancing metabolism and renal elimination, as well not accumulating in plasma following repetitive doses (19). *In vitro* and *in vivo* coagulation process is less affected by HES 130/0.4. than by other HES solutions (20, 21); HES 130/0,4 inhibits less the expression of activated glycoprotein IIb-IIIa on the platelet membrane (8, 22) Thromboelastographic analysis demonstrates that HES 130/0.4 compromises TEG parameters less than other HES solutions as shown in healthy male patients (2).

TEG measurement has become the gold standard for evaluation of coagulation status after intravascular volume replacement. TEG is a sensitive method for rapid assessment of possible coagulation disturbance in the operating room where large amounts of HES solution are

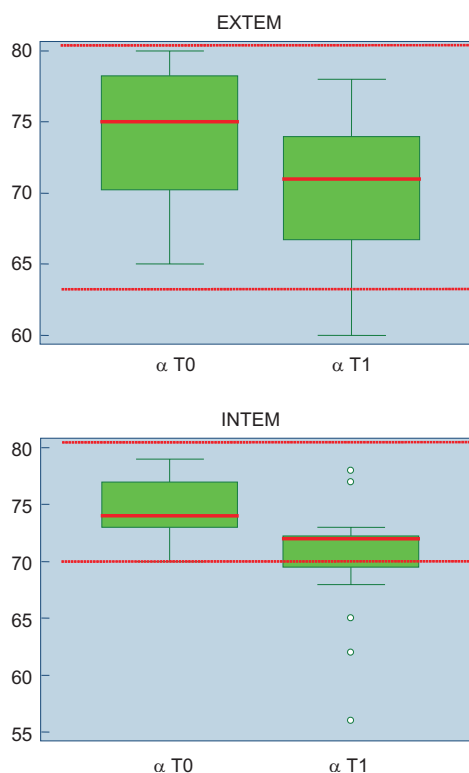


Figure 4. Changes in angle α (normal EXTEM 63–83°; normal INTEM 70–83°) using EXTEM and INTEM. Results are mean (95% CI). T0=baseline values (before infusion of colloids); T1=1 hour after surgery.

used. For now, value of the TEG is established only in the setting of orthotopic liver transplantation and cardiopulmonary bypass surgery. Correlation of TEG parameters with standard coagulation tests is deficient (25).

Therefore, administration of moderate doses of HES 130/0.4 preparations in previous clinical study was not associated with negative effects on haemostasis (1, 5, 12, 13). However, according to the available literature, there is not enough data on the application of these solutions in the TURP.

TURP remains one of the major routine surgical procedures which itself appears to be prothrombotic in variety of mechanisms (4). Haemostatic problems during and after TURP are common, although mostly seen as bleeding that require volume replacement with solutions which have little negative influence on the coagulation process.

We found that intravascular volume regime exclusively with HES 130/0.4 significantly increases CT and CFT and significantly decreases MCF and α without change in LI30, although all of them stay within normal clinical range. In our pilot study we demonstrate that moderate doses of HES solution in early postoperative period during TURP change coagulation parameters measured with TEG toward slightly hypocoagulability state, within normal range, which could be a desirable effect

for possible postoperative development hypercoagulable state in this type of surgical procedures.

Limitation of our study is a small number of patients and unattended influence absorption of irrigating fluid, release of prostatic tissue substances from the operating site with potential effects on the blood coagulation.

HES 130/0.4 seems to be a safe choice for intravascular replacement for patients during TURP, however for fully evaluating the influence of the HES 130/0.4 on coagulation in this clinical settings, which itself can be compromise with many surgery-related effects we need prospective, randomized, double-blind studies, with different time-points measurements.

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