ORIGINAL ARTICLE

# Comparative evaluation of the effects of hydroxyethyl starch on coagulation state of patients during brain tumor surgeries in comparison to crystalloids by thromboelastography

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**Background:** Hypercoagulability has been reported in primary brain tumors which can lead to thrombotic complications. Hydroxyethyl starch (hetastarch) is a synthetic colloid solution with adverse effects on blood coagulation. The aim of this study was to evaluate the protective effect of hetastarch in reducing thromboembolic events in these patients. **Materials and Methods:** In a double-blinded clinical trial, 60 brain tumor surgery patients were randomly divided into two groups and given 10 mL/kg hetastarch or normal saline during surgery. Blood coagulation was compared before and after infusion of these fluids within and between groups by thromboelastography (TEG). **Results:** There were no significant differences in bleeding ($P = 0.126$), duration of surgery ($P = 0.504$), and fluid intake (0.09L) between the two groups. Percentage of changes in R (R: Time to initiate fibrin formation), K (K: Measure of the speed taken to reach a specific level of clot strength), and Ly30 (Ly30: Percent of fibrin distraction after 30 minutes of clot formation) in the crystalloid group were −20.61 ± 26.46, −30.02 ± 49.10, and 1.27 ± 22.63, and that in the colloid group were 22.10 ± 26.11, 41.79 ± 37.15, and 59.09 ± 37.12, respectively. Deterioration in hemostasis during and after surgery was not observed. **Conclusion:** There was a reduction in the speed of clot formation and increase in clot lysis in the hetastarch group. Coagulability was decreased in the colloid group. Infusion of 10 mL/kg hetastarch in brain tumor resection surgeries can probably decrease susceptibility of these patients to deep vein thrombosis (DVT) and thromboembolic events.

**Key words:** Brain tumor, hetastarch, hypercoagulability, thromboelastography

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## INTRODUCTION

Hypercoagulability is a well-known state in primary brain tumors.[1,2] Inadvertent clot formation or disseminated intravascular coagulation (DIC) has been reported during brain tumor surgeries.[2] Thrombotic complications [deep vein thrombosis and/or pulmonary embolization (DVT/PE)] occur in 18 to 50% of the patients harboring brain tumors who undergo neurosurgical procedures.[3] Clinical risk factors associated with venous thromboembolic (VTE) events are paresis, prior thrombotic disease, chemotherapy, location, and histology of tumor.[4] Studies involving brain tumor tissue cell cultures have implicated factors released by the tumor or surrounding neural tissues that activate the coagulation system or inhibit fibrinolysis.[4]

During surgeries, crystalloid and colloid solutions are used as volume expanders or for the replacement of blood loss. One of the most frequently used colloid volume expanders is hydroxyethyl starch (hetastarch).[5]

Hetastarch is a synthetic colloid solution. It produces dilutional effects similar to other volume expanders and reduces the levels of factor VIIIc and von Willebrand factor (vWF) by 50 to 80% in a dose of 1 to 1.5 L, with prolongation of the partial thromboplastin time. Hetastarch also can interfere with platelet adhesion and clot formation by reduction in glycoprotein IIb/IIIa availability and direct movement of the hetastarch molecules into the fibrin clot.[6] Adverse effects of hetastarch on blood coagulation have been confirmed by multiple studies.[7-12]

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Goh and colleagues evaluated the coagulation profile of patients with brain tumors undergoing surgery by using thromboelastography (TEG) and concluded that TEG is useful in the perioperative assessment of hemostatic profile of patients with large brain tumors.[1]

TEG evaluates the elastic properties of whole blood and provides a global assessment of hemostatic function.[13]

The aim of this study was evaluation of the effects of the use of hetastarch during brain tumor surgeries on coagulation and reduction of the hypercoagulable state in these patients with the intention of decreasing complications such as VTE and DIC.

## MATERIALS AND METHODS

After approval of the ethical committee, approximately 90 patients who suffered from brain tumors and were candidates for craniotomy at Al-Zahra Medical Center presented for eligibility and 74 of them agreed to participate in this double-blinded clinical trial study; they also provided written informed consent.

Inclusion criteria were age between 18 and 65 years, health status classification (ASA) I and II of the American Society of Anesthesiologists, no coagulation abnormality, hepatic, renal, or endocrine disease, and no use of nonsteroidal inflammatory dugs (NSAIDs), aspirin, or anticoagulant drugs in the previous week.

Nine participants could not participate in the study after screening on the basis of the exclusion criteria (uncontrolled hypertension, usage of NSAIDs or unknown drugs in the past week, abnormal creatinine level, and opium addiction). The participants were randomly allocated into crystalloid (normal saline) and colloid (hetastarch) study groups.

Two patients in the crystalloid group and three in the colloid group were excluded because of change in plan of surgery and technical problems in sampling and process of TEG. Finally, 30 patients remained in each group of the study [Figure 1] [for 80% power ($Z_2 = 0.84$), 0.05 significance level ($Z_1 = 1.96$), equal number of cases in both groups (r = 1) , and considering $S_1$ and $S_2$, respectively, 0.35 and 0.45 and d = 0.3 according to a previous partly similar study,[14] we calculated a minimum sample size of 29 patients in each group for our study].

All patients were given 2 mL/kg/hour of normal saline during the eight-hour fast before the surgery. In the operating room, routine monitoring [pulse oxymeter, noninvasive blood pressure (NIBP), electrocardiography (EKG), and temperature] was started and readings

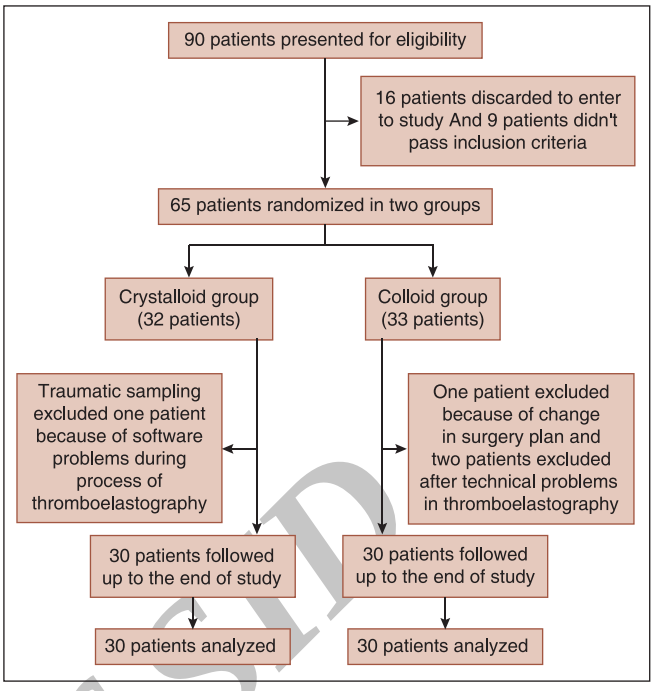


**Figure 1:** CONSORT flowchart of study

were recorded every five minutes during surgery. After induction of anesthesia (fentanyl: 3-4 µg/kg, sodium thiopental: 5-7 mg/kg, cisatracurium: 0.15 mg/kg, lidocaine: 1.5 mg/kg), central venous and arterial lines were inserted and blood sampling for TEG was done by atraumatic withdrawing of 2 mL of blood via antecubital vein from the hand that did not have the fluid infusion line.

After the first blood sample was taken, the patients were given 10 mL/kg of fluids in 30 minutes from covered coded boxters prepared by coworkers for the purpose of double blinding according to a randomized list created by Random Allocation Software.[15]

Sixty minutes (three time constants) after infusion of fluids, the second blood sampling was done. All blood samples were immediately sent to the operating room laboratory for TEG.

After the second blood sampling, the participants (in both groups) had similar fluid and blood component therapy during and after surgery.

The patients were given propofol (0.15-0.20 mg/kg/min), remifentanil (0.1 µg/kg/min), and cisatracurium (2 µg/kg/min) for maintenance of anesthesia.

At the end of surgery, cisatracurium was discontinued and the infusion of propofol–remifentanil reduced to 50%; 10 minutes later, the muscle relaxant was reversed by the administration of prostigmine (45 µg/kg) plus atropine (20 µg/kg).

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The patients were extubated after resumption of spontaneous ventilation and transferred to the postanesthesia care unit (PACU) and then to the intensive care unit (ICU) for postoperative care.

The primary end point of this study was evaluating differences in bleeding during surgery and TEG criteria before and after infusion of colloids in comparison to crystalloids; so, the volume of bleeding during surgery and TEG data (R, K, α angle, MA, and Ly30)* were measured and compared within and between groups.

* R: Time to initiate fibrin formation; K: Measure of the speed taken to reach a specific level of clot strength; α angle: Measure of the speed of fibrin buildup and cross-linking, MA: Ultimate strength of clot and measure of platelet function, Ly30: Percent of fibrin distraction after 30 minutes of clot formation.

The major morbidity end points were defined as any signs and symptoms of bleeding tendency (ecchymosis, blood oozing, or abnormal bleeding in the surgical site), DVT (swelling, redness, and pain in legs), or thromboembolic events (dyspnea, chest pain, hemoptysis).

All data were expressed as the number of patients or mean ± standard deviation (SD). Data were examined for a normal distribution of variance with analysis of variance (ANOVA) and expressed as the mean ± SD. Discrete variables between the groups were compared using a chi-square test or Fisher's exact test and $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS 18.0 for Windows.

## RESULTS

There were no significant differences in the demographic data, duration of surgery, and duration of recovery care between the two groups. Volume of bleeding, urine output, and total volume of fluids infused during surgery were a little more in the crystalloid group but they were not statistically significant [Table 1].

The mean of heart rate, mean of arterial blood pressure, end-tidal carbon dioxide, peripheral oxygen saturation (SpO2), and temperature were similar between the groups during surgery [Table 1].

Based on the analysis of TEG variables, there were significant differences in R and K between measurements before and after crystalloid infusion, but α, MA, and Ly30 did not show any significant differences in this comparison [Table 2].

The TEG variable analysis in the colloid group showed significant differences in all variables (R, K, α, MA, and Ly30) [Table 3].

Statistical analysis of mean of changes in TEG variables by fluid infusion in the two groups clarified significant differences in R, K, and Ly30 between them [Table 4].

The length of stay in the ICU (1.56 ± 0.5 and 1.46 0.5 days, respectively, in the crystalloid and colloid groups; ($P = 0.447$) postoperatively was not different between the two groups.

There was only one patient who had transient (for less than 2 hours) tachypnea and dyspnea in the crystalloid group which was suspicious of a thromboembolic event ($P = 0.313$).

## DISCUSSION

This study was a prospective randomized double-blinded trial addressing the effects of 10 mL/kg hetastarch compared to crystalloid solution (normal saline) in patients undergoing brain tumor surgeries who are in a hypercoagulable state and the complications of this condition.

**Table 1: Demographic, duration of surgery, duration of care in postanesthesia care unit (PACU), fluids balance, and hemodynamic data**

| Group variables | Crystalloid | Hetastarch (HES) | *P* value |
|---|---|---|---|
| Age (years) | 56.56±10.55 | 58.46±4.41 | 0.177 |
| Sex (female/male) | 13/17 | 15/15 | 0.605 |
| Surgery time (min) | 254.5±73 | 260.5±56 | 0.504 |
| Recovery time (min) | 138±62 | 123±49 | 0.630 |
| Bleeding (cc) | 575±137 | 516±132 | 0.126 |
| Urine output (cc) | 1723±392 | 1584±260 | 0.076 |
| Infused fluids (cc) | 3850±680 | 3650±540 | 0.091 |
| Mean of HR during surgery (min) | 74.2±7.25 | 72.52±2.83 | 0.393 |
| Mean of MBP during surgery (mmHg) | 75.33±9.79 | 81.62±9.44 | 0.287 |
| Mean of SpO2 during surgery (%) | 97.38±1.27 | 97.28±1.49 | 0.531 |
| Mean of EtCO2 during surgery (mmHg) | 33.66±1.15 | 33.82±1.29 | 0.602 |
| Mean of T during surgery (degree celsius) | 36.49±0.50 | 36.43±0.26 | 0.174 |

HR=Heart rate; MAP=Mean arterial blood pressure; EtCO2=End-tidal concentration of carbon dioxide; T=Temperature; SpO2=Peripheral oxygen saturation

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**Table 2: TEG data in crystalloid group**

| TEG variable | Before crystalloid infusion | After crystalloid infusion | *P* value |
|---|---|---|---|
| R | 6.50±1.78 | 5.16±1.66 | <0.001 |
| K | 3.93±2.62 | 2.75±1.24 | 0.004 |
| α | 50.89±15.05 | 52.09±11.21 | 0.516 |
| MA | 56.92±10.59 | 57.31±8 | 0.809 |
| Ly30 | 8.66±1.81 | 8.77±2.12 | 0.766 |

TEG=Thromboelastography; R=Reaction time; K=Kinetic time; α=α angle; MA=Maximum amplitude; Ly30=Lysis at 30 minutes

**Table 3: TEG data in colloid group**

| TEG variable | Before HES infusion | After HES infusion | *P* value |
|---|---|---|---|
| R | 6.74±1.51 | 8.23±2.02 | <0.001 |
| K | 3.23±0.80 | 4.58±1.60 | <0.001 |
| α | 55.46±8.77 | 52.13±8.12 | 0.001 |
| MA | 61.54±3.74 | 58.31±4.21 | <0.001 |
| Ly30 | 2.64±0.51 | 4.20±0.46 | <0.001 |

TEG=Thromboelastography; HES=Hydroxyethyl starch; R=Reaction time; K=Kinetic time; α=α angle; MA=Maximum amplitude; Ly30=Lysis at 30 minutes

**Table 4: Comparison of percentage of changes in thromboelastography variables between the two groups**

| TEG variable | Mean of changes in crystalloid group | Mean of changes in colloid group | *P* value |
|---|---|---|---|
| R | −20.61±26.46 | 22.10±26.11 | <0.0001 |
| K | −30.02±49.10 | 41.79±37.15 | <0.0001 |
| α | 2.35±25.80 | −6.00±15.21 | 0.1322 |
| MA | 0.68±16.32 | −5.24±6.23 | 0.0685 |
| Ly30 | 1.27±22.63 | 59.09±37.12 | <0.0001 |

TEG=Thromboelastography; R=Reaction time; K=Kinetic time; α=α angle; MA=Maximum amplitude; Ly30=Lysis at 30 minutes

No differences were observed in terms of volume of bleeding, duration of surgery, and duration of ICU care after surgery. TEG parameters showed delay in clot formation (increased R and K) and increase in fibrinolysis (increased Ly30) in the hetastarch group in comparison to the crystalloid group ($t > 1.699$).

Hetastarch has been reported to induce a type I von Willebrand-like syndrome with decreased factor VIII activity and decreased von Willebrand factor antigen and VIII-related cofactor level.[16]

These effects manifest as an increase in R and K and a decrease in MA and α angle on TEG that are associated with an actual decrease in coagulability of blood and in maximum (33 mL/kg) increase in bleeding during surgeries.[17-20] In a study, dose-dependent alterations in coagulation without an actual increase in blood loss were observed.[21]

There is a hypercoagulable state in patients suffering from brain tumors, and DVT and thromboembolic events are more common in them. This state can worsen by the patient lying on the operating table (or ICU bed) for a long time during craniotomy and ICU care.

The pharmacokinetic properties of hetastarch produce some degree of disturbances in hemostasis; hemodilution *per se* causes lower platelet availability which may pose to clot formation in response to venous stasis in the lower limbs during craniotomy and ICU care, and pharmacodynamic effects of these may increase this suitable side effect.

In this study, 10 mL/kg of hetastarch 200 which was infused early in the craniotomy surgeries did not increase the amount of perioperative blood loss compared to crystalloids.

Indeed, based on TEG parameters, hetastarch decreased the speed of clot formation and clot strength and increased lysis of the produced clot, but these changes did not deteriorate the levels of hemostasis which are needed during craniotomy.

This study had some ethical and budget limitations in confirming the clinical diagnosis of thromboembolic events by highly specific methods.

## CONCLUSION

Infusion of 10 mL/kg hetastarch in brain tumor resection surgeries decreases coagulability while preserving hemostasis, and it can probably decrease susceptibility of these patients to DVT and thromboembolic events.

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