Egyptian Journal of Anaesthesia

ISSN: (Print) 1110-1849 (Online) Journal homepage: https://www.tandfonline.com/loi/teja20

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Hossam A. ELShamaa & Sherif A. ELokda

To cite this article: Hossam A. ELShamaa & Sherif A. ELokda (2015) Effect of activated recombinant factor VII versus tranexamic acid infusion on bleeding during spine surgery, randomized, controlled, double blinded trial, Egyptian Journal of Anaesthesia, 31:2, 149-153, DOI: 10.1016/j.egja.2014.12.009

To link to this article: https://doi.org/10.1016/j.egja.2014.12.009

Egyptian Journal of Anaesthesia (2015) **31**, 149–153

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Egyptian Journal of Anaesthesia

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Research Article

Effect of activated recombinant factor VII versus tranexamic acid infusion on bleeding during spine surgery, randomized, controlled, double blinded trial

Hossam A. ELShamaa [a,*], **Sherif A. ELokda** [b]

[a] *Anesthesia Department, Faculty of Medicine, Cairo University, Egypt*
[b] *Anesthesia Department, Faculty of Medicine, Ain Shams University, Egypt*

Received 7 November 2014; revised 15 December 2014; accepted 23 December 2014
Available online 7 February 2015

KEYWORDS

Tranexamic acid;
Recombinant factor VII;
Spine;
Bleeding

Abstract *Background:* Antifibrinolytic drugs, such as tranexamic acid are medications that facilitate hemostasis and decrease blood loss and the need for blood transfusion during major surgery. Activated recombinant coagulation factor VII is a novel hemostatic agent, studies revealed that it is helpful hemostatic in disorders with impaired hemostasis, as well as in patients with normal hemostatic function to minimize perioperative blood loss. This study aimed to compare the efficacy of activated recombinant factor VII with tranexamic acid in reducing the perioperative blood loss.
Methods: 50 patients undergoing spine surgery were enrolled in this study. Group A patients were given activated recombinant factor VII and group T patients given tranexamic acid. In both groups, anesthesia was induced using fentanyl 3 μg/kg and propofol 2 mg/kg; muscle relaxation was initiated using cisatracurium 0.2 mg/kg. Transfusion of blood and its products was done according to a value guide. The primary outcome variable of the study was the total volume of blood loss in the perioperative period. Secondary outcome variables include perioperative transfusion requirement, and the number of patients who needed transfusion, as well as time of operation. A *P*-value less than 0.05 is considered statistically significant.
Results: The current study showed that the total perioperative blood loss in group A was significantly lower than group T. None of the patients required ICU admission, as well as reentry to operating theater. Furthermore, no significant difference was detected in the number of patients needed blood transfusion. Intraoperative bleeding was associated with a slight decrease of hemoglobin in group A.
Conclusion: The present study concluded that administration of activated recombinant factor VII in spine surgery reduces the total perioperative blood loss and the total volume of intraoperative blood transfusion compared with tranexamic acid, with no evidence of adverse effects.

* Corresponding author at: Erfan & Bagedo General Hospital, King Fahad St. Alfaisaleya, P.O Box 6519 Jeddah 2452, Saudi Arabia. Tel.: +966500984921.

Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2014.12.009

1. Introduction

Antifibrinolytic drugs, such as tranexamic acid and aprotinin, are easily accessible medications that facilitate hemostasis and decrease blood loss and the need for allogenic blood transfusion during major surgery. Their efficacy has been evaluated in different types of surgical operations as orthopedic, cardiovascular and hepatic operations [1,2]. Tranexamic acid is a well known pharmacological agent; it is a simple and inexpensive agent that interferes with the process of fibrinolysis thus decrease blood loss and the risk of blood transfusion during surgery [3,4]. It produces its action by blocking the lysine binding site of plasminogen preventing its conversion to plasmin on the surface of fibrin inhibiting fibrinolysis and thus reducing the intra and postoperative blood loss, so becoming commonly used in orthopedic surgery [5].

Activated recombinant coagulation factor VII is a recently used novel hemostatic agent. Many bleeding disorders are managed nowadays using it, including congenital hemophilia with inhibitors, congenital factor VII deficiency, acquired hemophilia as well as thrombocytopenia, furthermore, studies revealed that activated recombinant factor VII is also helpful as a hemostatic in some other disorders associated with impaired hemostasis. However, other studies evaluated the efficacy of activated recombinant factor VII in patients with normal hemostatic function to minimize perioperative blood loss during orthopedic surgery [6,7].

Spine surgeries may vary from simple to complex e.g. spinal fixation and scoliosis surgery and may vary also in the anticipated blood loss. Multiple factors make this surgery potentially associated with moderate to major bleeding that usually necessitates blood transfusion, that is why multiple measures are used to decrease the possibility of transfusion as hypotensive anesthesia [8]. Increased concerns about the risks of transfusion including acquired infections, anaphylaxis, transfusion related acute lung injury (TRALI) and hemolytic reaction, in addition to immune modulation effects of allogenic blood that may increase infection rates aroused the importance of investigating using the various hemostatic agents such as recombinant activated factor VII of the coagulation factors and antifibrinolytic drugs e.g. tranexamic acid to minimize the blood loss during this surgery [9].

The aim of this randomized, controlled, double-blinded study was to compare the efficacy of activated recombinant factor VII with tranexamic acid in reducing the perioperative blood loss as well as the possibility of blood transfusion in patients undergoing spine surgery, and to assess their safety as regard causing postoperative thrombo-embolic complications.

2. Patients and methods

After obtaining approval from the Clinical Research Ethics Committee of Erfan and Bagedo General hospital and obtaining informed consent. 50 patients aged (18–65 years), ASA physical status I, II & III, undergoing spine surgery (three level spinal fusion or scoliosis) were enrolled in this study. The patients were randomly divided, using concealed envelope method, into 2 equal groups: Group A patients ($n = 25$) were given Activated recombinant factor VII and group T patients ($n = 25$) given tranexamic acid. Exclusion criteria include: patients outside the age range, history of thrombo-embolic event e.g. pulmonary embolism, deep venous thrombosis, traumatic spine injury, morbid obesity (weight > 125 kg), known congenital bleeding disorder, known allergy to the used drugs and known pregnant or lactating patients. Inclusion criteria were the ability to consent, and absence of renal and hepatic diseases.

All patients were premedicated with 5 mg midazolam I.M. 30 min before shifting to OR. After OR admission, the standard monitors including noninvasive arterial blood pressure, electrocardiography and pulse oximetry were applied. A 20 gauge intravenous catheter was inserted and 4 mg ondansetron IV was given. 22 gauge arterial catheter was inserted before induction of anesthesia and invasive blood pressure was monitored. In both groups, anesthesia was induced using fentanyl 3 μg/kg and propofol (Deprivan) 2 mg/kg; muscle relaxation was initiated using cisatracurium (Nimbex) 0.2 mg/kg. Then patients were intubated after 3 min of face mask ventilation using endotracheal tube of appropriate size via direct laryngoscopy, with lidocaine 1 mg/kg IV given before intubation to minimize stress response. Anesthesia was maintained by 2% sevoflurane with 50% nitrous oxide in oxygen.

In group A, activated recombinant factor VII (NovoSeven®, Novo Nordisk A/S, 2880 Bagsvaerd, Denmark) 100 μg/kg in 50 ml normal saline was administered IV before skin incision, followed by intravenous infusion of normal saline as a placebo as simulation of tranexamic acid infusion in group T. while in group T, tranexamic acid (cyklokapron, Pfizer Canada Inc, Kirkland, Quebec, H9J 2M5) 100 mg/kg in 50 ml normal saline was infused IV before skin incision, followed by intravenous infusion of tranexamic acid at rate of 1 mg/kg/h. Infusions in both groups were discontinued after closure of skin incision. Intravenous solutions were prepared in the pharmacy outside the operating theatre and sent to the anesthesiologist as apparently identical drip with a predetermined rate depending on the patient body weight. Transfusion of blood and its products was done according to a value guide; where packed RBC is transfused if hemoglobin level is less than 10 g/dl, fresh frozen plasma (FFP) is given if prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) become 1.5 the normal preoperative value, platelet was transfused if its count is less than 100,000/cmm. During surgery coagulation parameters were tested every hour.

The primary outcome variable of the study was the total volume of blood loss in the perioperative period, which is considered as the time from the start of surgery (skin incision) till the end of the first 24 h postoperatively. This volume was calculated as the sum of the blood collected in the suction device, the drapes and swabs after being weighed postoperatively and the total volume of blood in the drains, after subtracting the fluid volume used for irrigation intraoperatively as the technique described by Jansen et al. [10]. Secondary outcome variables were perioperative transfusion requirement (total volume transfused of blood and its component), and the number of patients who needed transfusion, duration of operation (from skin incision till skin closure), total amount of IV fluids used both colloids (6% hydroxyethyl starch 130/0.4 "Voluven, Fresenius Kabi, Humborg, Germany") and crystalloids (lactated ringers solution), number of patients who needed ICU admission, in addition to the change in the value of the coagulation parameters (PT, aPTT, INR) or hemoglobin level (Hb)

which was measured preoperatively, every 2 h during surgery, immediately postoperatively and after 24 h, and finally the incidence of complications including severe postoperative bleeding or thrombo-embolic events as DVT, pulmonary embolism, and stroke.

Data were analyzed using computer statistical software system SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Sample size was estimated using the total blood loss as the primary variable with a hypothesis of its decrease by 50%, so a group size of 25 patients was found sufficient to achieve 90% power. Descriptive data are expressed as mean (±SD), and was compared using unpaired *t*-test, X^2 test, Wilcoxon rank sum test, and Fisher exact test as appropriate. A *P*-value less than 0.05 was considered statistically significant (see Fig. 1).

3. Results

The current study showed no significant differences in demographic data including age, sex, body weight or height between group A and group T as shown in Table 1, furthermore, the difference in the duration of surgical procedures between both groups was nonsignificant, group A 269 ± 25 min and group T 273 ± 29 min (Table 1).

The total perioperative blood loss (primary outcome) in group A was (1630 ± 495), which was significantly lower than group T (1970 ± 530) as indicated in Fig. 2, furthermore, the total volume of transfused blood intraoperatively (secondary outcome) showed a significantly higher result in group T (1349 ± 53) compared to group A (989 ± 49) as shown in Fig. 2 with $P < 0.05$.

Neither of the patients of the present study required ICU admission; all patients were shifted to the post-anesthesia care unit (PACU) then back to their units, furthermore, none of the patients needed reentry to operating theater. Besides, no patients in both groups developed postoperative adverse effects including bleeding or thrombo-embolic complications as shown in Table 2. No significant difference was detected in the number of patients needed blood transfusion between the groups of the present study as indicated in Table 2. As regards the total perioperative IV fluid infusion, intraoperatively colloid consumption for group A was slightly lower than group T with $P = 0.81$ with no significant difference, while crystalloid consumption was comparatively lower in group A with $P = 0.12$. On the other hand, postoperatively, group T showed insignificantly higher infusion of both colloids as well as crystalloids with $P = 0.55$ and $P = 0.61$ respectively as shown in Table 2.

Regarding the hemoglobin level, intraoperative bleeding was associated with a slight decrease of hemoglobin in group A that improved postoperatively following blood transfusion

Table 1 Demographic and operative data. Values are expressed as mean ± SD.

	Group A ($n = 25$)	Group T ($n = 25$)
Age (year)	41.6 ± 3.3	43.4 ± 3.9
Gender (M/F)	19/6	17/8
Body weight (kg)	80 ± 30	76 ± 28
Height (cm)	169 ± 5	174 ± 3
Duration of surgery (min)	269 ± 25	273 ± 29
Type of surgery		
Multiple level spinal fusion	16 (64%)	18 (72%)
Scoliosis correction	2 (8%)	1 (4%)
Spinal canal stenosis	7 (28%)	6 (24%)

No significant differences between the two groups. (*P* value > 0.05).

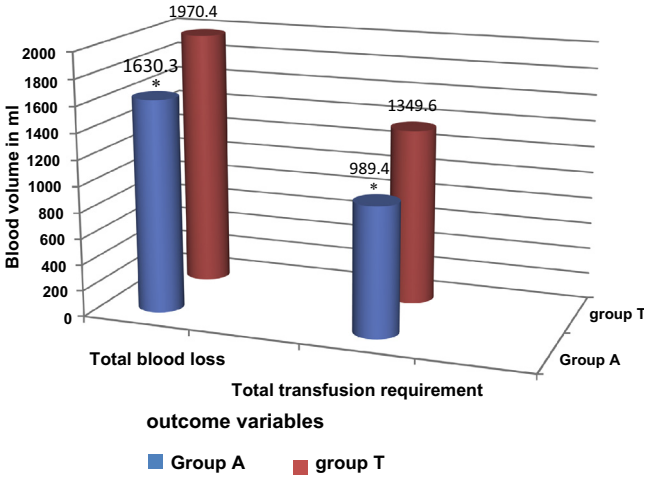

Figure 2 The primary (blood loss) and secondary (transfusion requirement) outcome variables. * indicates significant difference.

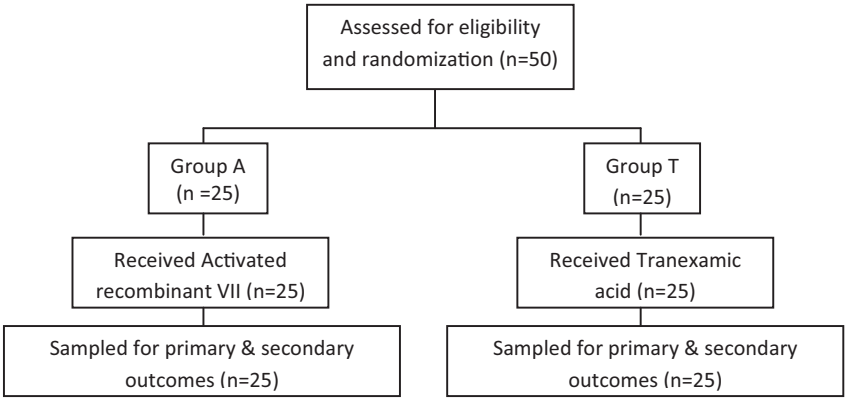

Figure 1 The patient selection, allocation, and analysis flow chart.

Table 2 Secondary outcome variables data. Values are expressed as mean ± SD.

	Group A (n = 25)	Group T (n = 25)
Patients who needed blood transfusion	15(60%)	18(72%)
Need for ICU admission	0	0
Need for reentry to OR	0	0
Total colloid infusion (ml)		
Intraoperative	980 ± 30	1076 ± 28
Postoperative	469 ± 50	474 ± 30
Total crystalloid infusion (ml)		
Intraoperative	2690 ± 25	2710 ± 29
Postoperative	1060 ± 110	1080 ± 130
Incidence of postoperative adverse effects	0	0

No significant differences between the two groups. (P value > 0.05).

which was not significantly different from group T as seen in Fig. 3, moreover, the coagulation parameters (PT, INR, and aPTT) in both groups were normal before the start of surgery. In group T it remained within normal preoperative ranges all through the study duration, both intraoperative and postoperative, nevertheless, group A showed shortening of PT (10.3 ± 0.4 s), aPTT (28 ± 1.7 s) and decrease of INR (0.8 ± 0.3) intraoperatively after recombinant factor VII injection which returned to initial value after 24 h postoperatively, however, both groups showed no significant difference among their patients.

4. Discussion

In the present study, it was found that the adminstration of 100 μg/kg activated recombinant factor VII during major surgical procedure as spine surgery, significantly decreased the blood loss both intraoperatively as well as postoperatively compared with tranexamic acid, furthermore, its use minimizes the total volume of intraoperative transfusion of blood and its products. In addition, the coagulation parameters evaluated in the present study including PT, INR, and aPTT were shortened after Recombinant factor VII administration compared to the tranexamic acid that showed no effect on these parameters, however, no postoperative complications especially thrombo-embolic events or major bleeding was reported, and none of the studied patient needed ICU admission.

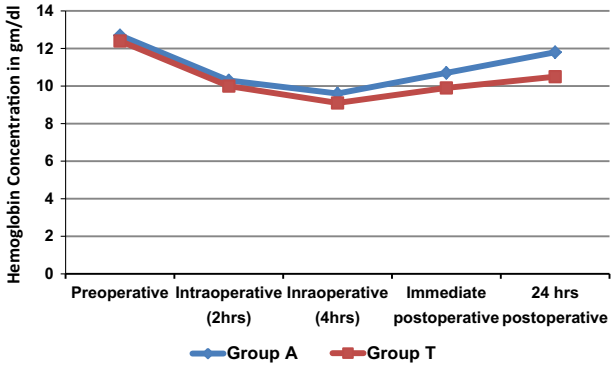

Figure 3 The hemoglobin concentration intra and postoperative. No significant difference (P > 0.05).

The utilization of activated recombinant factor VII for management of bleeding in non-hemophilic patients is increasing progressively [11]. Previous published studies in literature reported that the use of activated recombinant factor VII, showed hemostatic efficacy in patients with impaired haemostasis such as hemophilia A or B [12]. This was owing to the formation of a complex with tissue factor (TF), which is a membrane bound glycoprotein, available in the wound bed. This glycoprotein (TF) is present in the subendothelial cells which are separated from the blood stream, upon injury (traumatic or surgical) it becomes exposed to the blood stream due to disruption of the cell membrane [13]. Due to its affinity, TF binds to recombinant factor VII resulting in activation of factor X to Xa of coagulation factors resulting in generation of thrombin and subsequently the formation of fibrin, furthermore, fibrin activates other coagulation factors e.g. factors V, VIII, hence facilitating hemostasis [14].

Supporting the results of the present study were the results of the double blinded randomized study done by Friederich et al. [15], who studied the effect of activated recombinant factor VII on the perioperative blood loss in abdominal prostatectomy compared to placebo and concluded that its use in a dose of 40 μg/kg in the early phase of the surgical procedure improves hemostasis and minimizes blood loss, hence decreases the need for blood transfusion, suggesting that the use of higher doses may be more beneficial. In addition, in a study by Diprose et al. [16] assessing the effect of activated recombinant factor VII in non coronary cardiac surgery and the need of transfusion after the cardiopulmonary bypass, the authors concluded that administrating recombinant factor VII was beneficial and reduced the need for blood transfusion in such patients without causing any side effects. Moreover, Liu and colleagues [17] studied the value of recombinant factor VII in patients for intracerebral hematoma drainage having factor VII deficiency and found out that its use was effective in emergency neurosurgery. On the contrary, in a study by Bowels and colleagues [18] for predicting the response of non-hemophilic patients with bleeding to activated recombinant factor VII, they showed that only eight patients responded to an early single dose of factor VII who had good prognosis while patients with poor prognosis showed no response suggesting that its efficacy depending on the time of administration that may affect the prognosis. This may probably be explained in the present study by our use of activated recombinant factor VII as an early prophylaxis before the

incidence of bleeding. Furthermore, in a study by Raobaikady et al. [19], the authors studied the effect of activated recombinant factor VII on bleeding in patients undergoing surgery for traumatic pelvic fracture, and their results demonstrated that the prophylactic administration of recombinant factor VIIa in such patient does not reduce the intraoperative bleeding or minimize the perioperative blood loss. Compared to our study these results may be explained by the higher dose of factor VII used in the present study, besides the longer postoperative duration of their study may add to the total blood loss.

Going with the result of this study were the results of the study done by Good and colleagues [20] who showed that tranexamic acid may decrease the blood loss through reducing drained blood, yet it had minimal effect on concealed blood and hence the total blood loss. Whereas, many other studies concluded the beneficial effect of tranexamic acid on intraoperative bleeding.

In conclusion, the present study demonstrated that prophylactic administration of activated recombinant factor VII in spine surgery reduces the total perioperative blood loss and the total volume of intraoperative blood transfusion compared with tranexamic acid, with no evidence of side effects or ICU admission. However, further studies are required to assess the efficacy of various doses of activated recombinant factor VII, and to compare it with other antifibrinolytic agents, in addition to evaluation of its benefits against the risk of developing hypercoagulable state or thrombo-embolic complications.

Conflict of interest

No conflict of interest to declare.

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