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Effect of the Activated factor VII on Prognostic and Reducing the Bleeding in Patients with Cerebral Hemorrhage

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Abstract: This study was accompanied due to high mortality and morbidity in these patients trying to find more useful treatment. A total 54 patient with ICH Next to stroke referred to Ahwaz Golestan hospital from Jul 2008 to 2009 were selected. Patients were randomly assigned to receive a single intravenous dose of 40 $\mu\text{g kg}^{-1}$ of rFVIIa or placebo. The performance by a clinical neurologist and based on the international ranking (Rankin's scale) on the first day of hospitalization and 90 days after discharge was evaluated. There was no significant difference in mean arterial blood pressure between placebo and patient groups. Percentage increase in both the second day of bleeding volume in the patient and placebo groups was 2.35 and 0.35%, respectively. The total difference between the first day and third day in the patient and placebo group was -7.76- and -2.99%, respectively. Patients with MAP value of more than 120 mmHg, showed a significant response to rFVIIa treatment. Recombinant activated factor VII has the potential to limit or even halt the progression of bleeding in brain hemorrhagic patients that would otherwise place growing pressure on the brain. As such, these data suggest that the use of rFVIIa holds promise in the setting of non-surgical intracranial bleeding. Whether this usage will have a positive impact on the neurological outcome lies in a future prospective clinical trial whose planning is underway.

Key words: Cerebral hemorrhage, activated factor VII, mean arterial blood pressure

INTRODUCTION

Stroke is one of the most common brains vascular accidents that of around 33% of the affected patients died within 1 month and only about 20% of patients meet the level of performance independent and without the need to help (Barber *et al.*, 2004). There is no specific medication that can ultimately act on clinical features of the disease progression or prevent bleeding (Barber *et al.*, 2004; Broderick *et al.*, 1999; Diringer *et al.*, 2008, 2009). Recombinant activated factor VII (rFVIIa) was originally developed to treat patients with hemophilia who had developed inhibitors to either factor VIII or factor IX. Several studies were done on the role of this factor in other patients prone to placebo the bleeding due to trauma surgery (Broderick *et al.*, 1993; Von Heymann *et al.*, 2008; Dunkley *et al.*, 2008; McCall *et al.*, 2006; Ingimarsson *et al.*, 2008; Phillips *et al.*, 2009). It remains to be seen whether these newer medications will become first-line therapies for thrombosis in the coming decade. This study aims to elucidate the main events

within the coagulation cascade as it is currently understood to operate *in vivo*, with a brief discussion focusing on hypercoagulable states and also a short review of the history of anticoagulants as they relate to this model (Adams and Bird, 2009). Its mechanism of action suggests that its haemostatic enhancing effects are limited to the site of injury and that systemic thrombosis due to activation of the coagulation cascade does not occur (Roberts, 1998; Kubisz and Stasko, 2004).

In this study, the effects of the prescribed activated factors VII on clinical eventually brain hemorrhage patients through changes in bleeding volume in CT scans has been investigated. The patients evaluated based on this measure in comparison to a group under a maintenance and supportive therapy (placebo group).

MATERIALS AND METHODS

Study design: This is a prospective, double-blind study of 54 subjects (27 patients, 27 placebo). This study was performed during Jan 2008 to 2009 in our hospital. The

study was approved by the University Hospital and Ahwaz Jondishapour University of Medical Sciences Ethics Committees and all subjects and their guardians in case of children, granted informed consent to participate.

Inclusion and exclusion criteria: The patients selected among patients that referred to the emergency center and secondary causes of bleeding in their brain has been rejected within 5 h of initial onset of symptoms (causes such as DIC, pregnancy, use of anticoagulation drugs, infection, accident, trauma, low platelets count, likely to have the AVM, aneurysm, history of Myocardial infarction, history pulmonary embolism, history of DVT). Patients that records these symptoms, within the placebo or in patient groups, were excluded.

Patient evaluation: The CT scans of patients and bleeding volume in comparison with the placebo group has been studied to assess the treatment effect in reducing bleeding volume. The bleeding volume measured and compared during of the first, second and third days for evaluation of treatment effect. The patients also were examined while admitted in the hospital during the first days and 90 days after discharge (referring to the clinic outpatient) by neurologist based on the standard international unit (Rankin scale) of clinical and functional status compared with placebo patients. The main selection criteria for placebos or patient is considered that performance level before the stroke was desirable, able to do personal things and had Rankin scale score of the above 2 (Uyttenboogaart *et al.*, 2007). Any possible complications were evaluated daily by EKG, cardiac enzyme levels and lower extremity Doppler ultrasound (if DVT symptoms present).

Study intervention: Patients were randomly assigned to receive a single intravenous dose of 40 µg kg⁻¹ of rFVIIa (NovoSeven, Novo Nordisk) or placebo. Randomization was performed in blocks of four patients by means of sequentially numbered, identical-appearing containers. Treatment was given within 1 h after the baseline CT and no later than 4 h the onset of symptoms. The study drug was supplied as a freeze-dried powder in vials containing either rFVIIa or placebo and was reconstituted in sterile water before being administered intravenously over a period of 1 to 2 min. The dose was calculated on the basis of estimated body weight.

Statistical analysis: All data are reported as Mean±SE. The independent samples t-test procedures, one-way ANOVA using the general linear model were calculated by

the SPSS 15.0 (SPSS for Windows, v. 13; SPSS, Inc., Chicago, IL). A value of p<0.05 was considered to be significant.

RESULTS

Among 54 study subjects (patients and placebo) 32 males and 22 females were participating (59 or 41% of men and women). Average ages of the patient and placebo groups were 60.9 and 65.5%, respectively. Age distribution among the patients and placebo groups was discussed in detail in Table 1. There was no significant difference in mean arterial blood pressure (MAP) between placebo and patient groups (Fig. 1). We study the average percentage change in the bleeding volume between the first and the second day also the third with second day. Percentage increase in both the second day of bleeding volume in the patient and placebo groups was 2.35 and 0.35%, respectively. Comparison between the second and third day both groups showed reduced bleeding volume in the patient group has value of -10-% and in the placebo group was -2.76-%. The total difference between the first and third day in the patient

Table 1: Age distribution in both patients and placebos, as well as according to gender

Variables	Numbers	Mean±SD	Range	
			Minimum	Maximum
Groups (Age, years)				
Patients	27	60.9±10.1	30	80
Placebo	27	65.5±10.6	44	81
Groups (Age, years)				
Male	32	65.2±10.4	30	80
Placebo	22	60.3±9.9	42	81
Total	54	63.2±11.2	30	81
Average percent reduction in bleeding volume than the first day of the third day				
Patients	27	-7.7±16.2	----	----
Placebo	27	-2.9±28	----	----

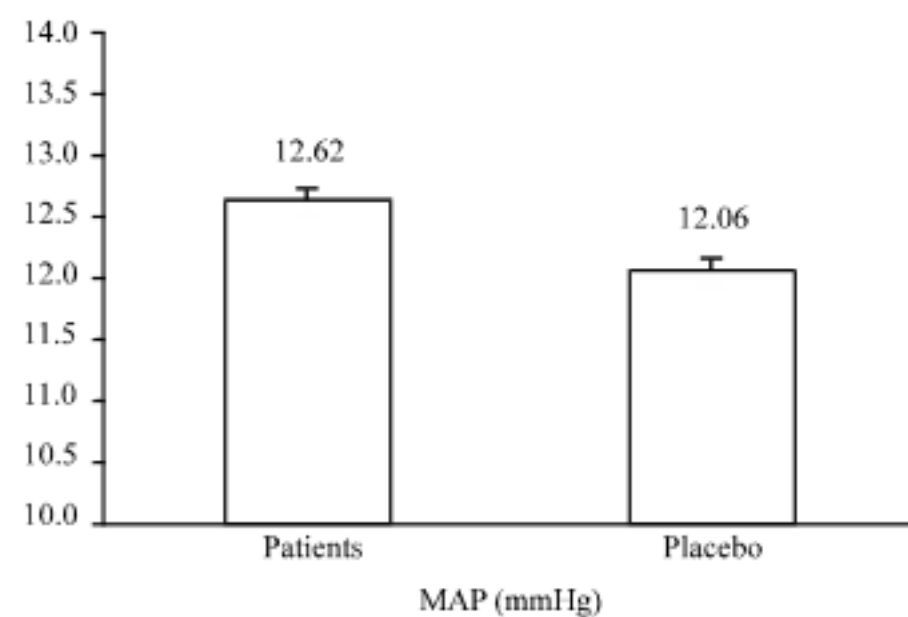


Fig. 1: Mean Arterial blood Pressure (MAP) in the case and placebo groups (p>0.05)

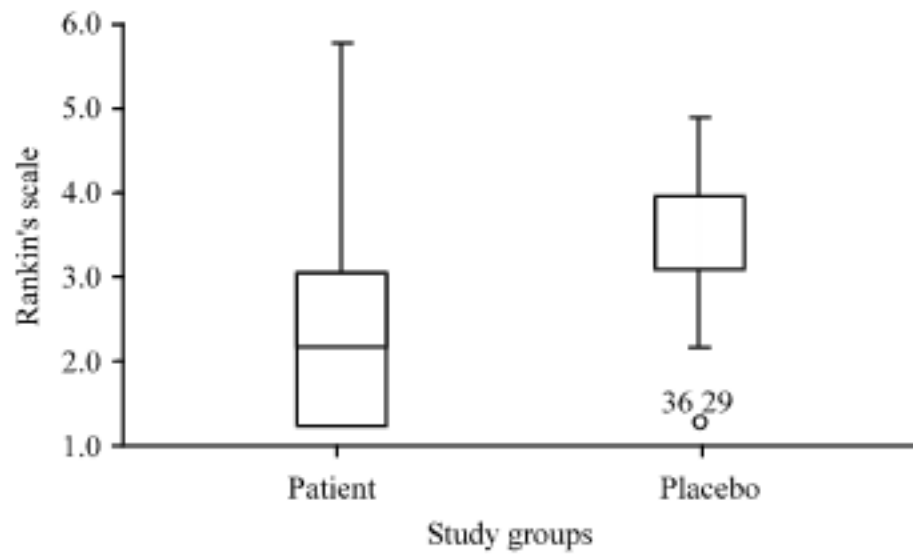


Fig. 2: The effect of rFVIIa treatment on the reduction of these Rankin's scale

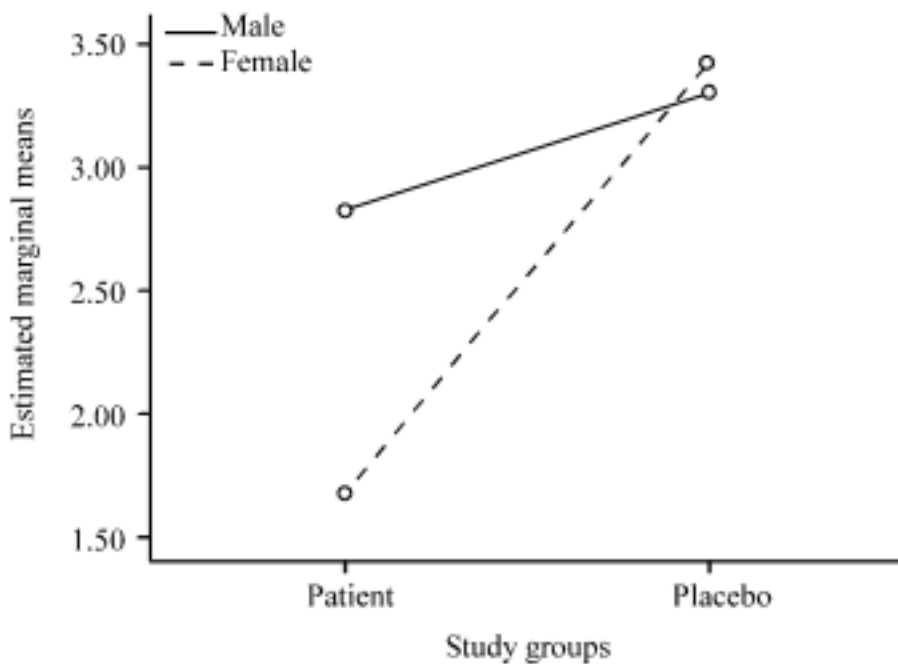


Fig. 3: The effect of rFVIIa treatment of various genders in reducing the Rankin's scale

and placebo group was -7.76- and -2.99%, respectively. Notable point was that mean percent changes in bleeding Rankin's scale among different ages, age influence on Rankin's Scale index was proving that represents the effect of drug in age range below 70 years (Fig. 4). The volume between study groups of the first, second and the third days have not been any significant meaning. Unlabeled indications did not accounted for 25 of the patient group, in small number of patients only complication present with active bleeding (n = 2).

The average score was achieved by Rankin's scale between the two groups together showed the significant differences, therefore, seems that exposure to rFVIIa is an effective way in reducing Rankin's scale (Fig. 2). The next step was, compare the effect of rFVIIa treatment of various genders in reducing the Rankin's scale using the one-way ANOVA and general linear model. Line graph shows a negative slope to reduce the Rankin's scale in exposed-patients of both genders, which is more obvious in females (Fig. 3). However, the statistical analysis suggests no significant differences between the sexes in

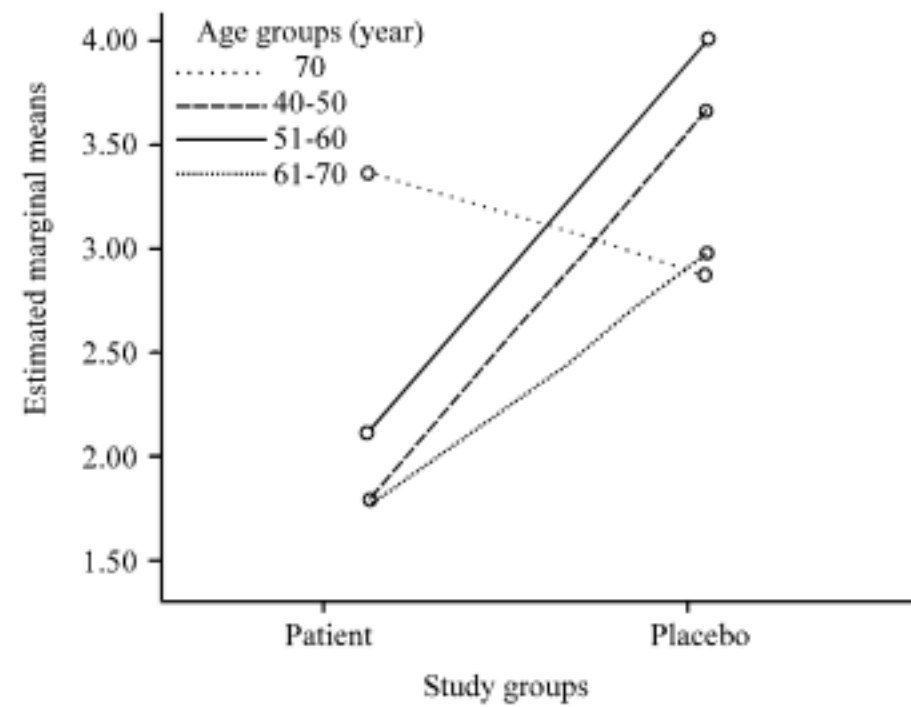


Fig. 4: Correlation with the effects of these treatments in reducing Rankin's scale among different ages

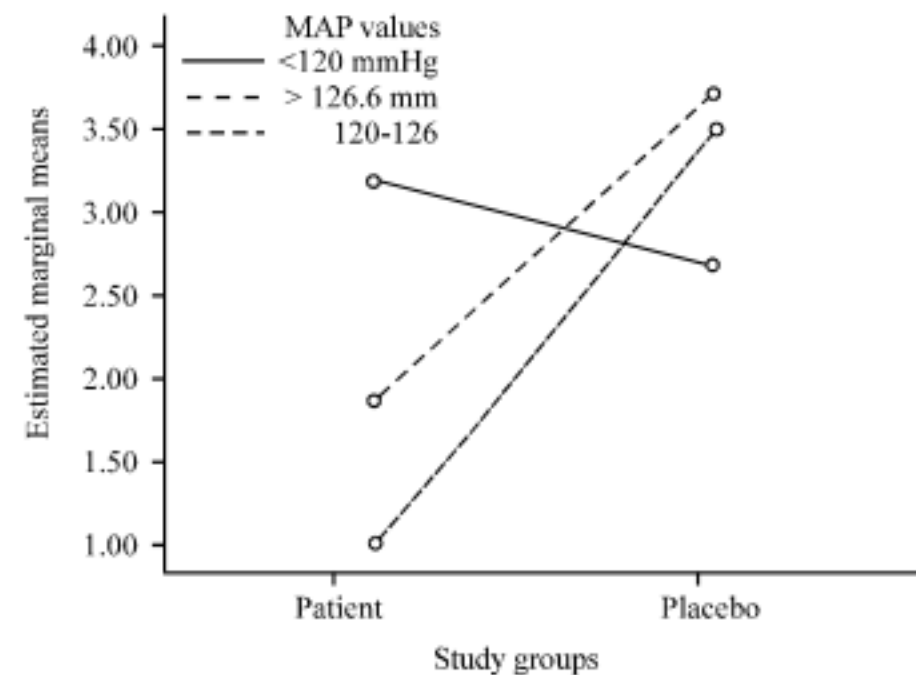


Fig. 5: MAP effect on the response to rFVIIa treatment with regard to the Rankin's scale factor

response to receiving rFVIIa treatment (p>0.05). In correlation with the effects of these treatments in reducing MAP was calculated to assess its effect on the response to rFVIIa treatment with regard to the Rankin's scale factor. It should be mentioned that MAP value was divided into three groups: (1) less than 120 mmHg groups, (2) group in the range 120 to 126.6 mmHg and (3) 126.6 mmHg group. Between responses of the patient group in case of MAP significant different was seen. Patients with MAP value of more than 120 mmHg, showed a significant response to rFVIIa treatment (Fig. 5).

DISCUSSION

The use of hemostatic agents as treatment for acute ICH is a novel therapeutic approach with the potential to improve outcome and reduce mortality. It is noted that previous similar cases, while administration of rFVIIa in

different patients, serious complications in 0.8% (16/1975 cases) of patients has been that two symptoms of DIC were the other 3 patients deficiency factor VII, which had received about 40 times more recommended dose (Hemphill *et al.*, 2001; White *et al.*, 2009; Ji *et al.*, 2009). In total in other studies 3.6% of the patients receiving these drugs have been established non-serious symptoms (Fujitsu *et al.*, 1990; Nava and Carhuapoma, 2009; Mayer, 2005), while the multi-center study reported the presence of these symptoms have set in about 7% of all patients (Friederich *et al.*, 2003; Mayer *et al.*, 2005a,b; Anderson, 2009). The relationship between coagulopathy and traumatic brain injury using laboratory studies that are performed routinely in the emergency evaluation of trauma patients was focused in many recent researches. Any abnormality in the coagulation system is associated with increased odds of ICH progression, which in turn is associated with death (Zehtabchi *et al.*, 2008). Indeed, a direct relationship between severity and resulting coagulopathy is confirmed in various studies and possibly the severity of brain destruction (Saggar *et al.*, 2009). Mayer *et al.* (2005a, b) has conducted a study with use of different dosage (40, 80, and 160 $\mu\text{g kg}^{-1}$ of rFVIIa in 303 patients within 1 h after the baseline scan as well as were assessed the clinical outcomes at 90 days. They showed that Treatment with rFVIIa within four hours after the onset of intracerebral hemorrhage limits the growth of the hematoma, reduces mortality, and improves functional outcomes at 90 days, despite a small increase in the frequency of thromboembolic adverse events. The present study also showed that the low dose of rFVIIa is effective in controlling the hematoma, reduces mortality, and improves functional outcomes. O'Connell *et al.* (2006) reviewed the serious thrombo-embolic adverse events in 431 patients and reported unlabeled indications accounted for 151 of the reports, most with active bleeding (n = 115). Their reported adverse events were thromboembolic cerebrovascular accident (n = 39), acute myocardial infarction (n = 34), other arterial thromboses (n = 26), pulmonary embolism (n = 32), other venous thromboses (including deep vein thrombosis) (n = 42), and clotted devices (n = 10). In 36 (72%) of 50 reported deaths, the probable cause of death was the thromboembolic event. We only encountered 2 patients (n = 54) with adverse events which were active bleeding that may show the lower dose may not has remarkable adverse events.

CONCLUSION

The overall results obtained in this study seem to prescribe rFVIIa in patients with spontaneous cerebral

hemorrhage can improve the performance of sensor-motor defects and eliminate their neurological deficiency. However, to achieve optimal results the following notes should be considered: (1) doing further studies with higher dosage administration (80 and 160 μg); (2) add the number cases and placebo to increase the statistical safety factor; (3) faster access to patients and prescribe factors mentioned above (to eliminate the effects of the drug administration time factors), (4) investigate the effect of places of bleeding in response to treatment, (5) reviews. The onset of symptoms and the impact of the treatment on the patient's response were studied. This study suggests that the use of rFVIIa holds promise in the setting of non-surgical intracranial bleeding. Whether this usage will have a positive impact on the neurological outcome lies in a future prospective clinical trial whose planning is underway.

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