

THE ROLE OF RECOMBINANT FACTOR VII IN CONTROLLING THE INTRAOPERATIVE BLOOD LOSS IN PATIENTS WITH SEVERE COAGULOPATHY AND PORTAL HYPERTENSION DURING LIVING DONOR LIVER TRANSPLANT SURGERY

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Abstract:

Objective:

Liver transplantation is the standard form of treatment for patients with end stage liver disease, with the use of blood product as a standard method for transfusion. Recombinant factor VIIa (rVIIa) may help those patients to acquire less amount of transfusion. This will have an impact not only the morbidity and mortality of the recipient and the donor, but also on the economical aspect of this tremendously expensive procedure. We conducted this study to verify the possible beneficial effects of using rVIIa at a lower dose than the standard dosage, which could have an impact on the future use of rVIIa.

Methods:

Twenty-four patients scheduled for orthotopic liver transplantation, divided into 2 groups; a control group and an rVIIa group. Both groups received the same anesthetics enlisted in our protocol for liver transplantation. The rVIIa group received a loading dose of 30 ug/kg of rVIIa following the induction of anesthesia, followed by a maintenance dose of 5 ug / kg until the end of the dissection phase. Demographic data, coagulation profile [prothrombin time (PT), prothrombin concentration (PC), partial thromboplastin time (PTT), International normalized ratio (INR)], blood loss, transfusion requirements, the duration of the dissection phase, the duration of surgery, hemoglobin concentration (Hb), and platelet count were done immediately after induction and 1, 2, 3 and 6 hours post induction (dissection phase). Finally, a Doppler assessment of the graft vessels was performed subsequent to anastomosis

Results:

The rVIIa group had a lower PT in the first two hours of the dissection phase in relation to the baseline and significantly lower than the control group ($P = 0.0002$). The INR showed a significant improvement in the rVIIa group during the dissection phase compared to the control group, and during the first two hours compared with the baseline in the rVIIa group ($P = 0.0002$). When compared to the control group, the rVIIa group had a significant increase in the platelet count, in all samples taken during the dissection phase. There was a significant decrease in the intraoperative requirements of packed red blood cells ($P = 0.014$), platelets ($P = 0.0005$) and fresh frozen plasma ($P = 0.01$) in the rVIIa group compared to the control group

Conclusion:

We conclude that administering low dose of rVIIa would be helpful during liver transplantation surgery. Improvement in the coagulation profile, transfusion requirements, and consequently postoperative morbidity and mortality could be achieved.

Introduction:

Liver transplantation is the standard of care for patients with end stage liver disease with discrepancy between the number of patients awaiting transplantation and the number of available donor organs. The associated coagulopathy, anemia, malnutrition, and severe portal hypertension have made this procedure more demanding and the use of blood products almost universal.

Recombinant factor VIIa (Novoseven) was introduced to clinical medicine in the 1980s as a prohemostatic agent (1). Based on the current insight into the function of blood coagulation *in vivo*, recombinant factor VIIa is thought to act locally at the site of tissue injury and vascular wall disruption, by binding to exposed tissue factor and generating small amounts of thrombin that are sufficient to activate platelets. The activated platelet surface can then form a template on which recombinant factor VIIa can directly or indirectly mediate further activation of coagulation, resulting in the generation of much more thrombin and, ultimately, fibrinogen to fibrin conversion (2, 3). Clot formation is stabilized by inhibition of fibrinolysis, due to factor VIIa-mediated activation of thrombin-activatable fibrinolysis inhibitor. Initially, recombinant factor VIIa was used in patients with congenital or acquired hemophilia and inhibiting antibodies toward factor VIII or IX, for which it has been licensed in the United States, Europe, and many other parts of the world (4). In recent years, the potential of recombinant factor VIIa to act as a prohemostatic agent in other categories of patients with coagulation defects or in patients with a preexistent normal coagulation system but who experience excessive bleeding, for example, as a result of trauma or surgery, has been explored (5).

Material and Methods:

After institutional committee approval and after informed written consent, 24 patients were included in the study in the duration between January 2004 and march 2006. All patients had undergone live related liver transplantation surgery.

Inclusion criteria were Adult patients more than 18 years, Child C classification, and Portal hypertension.

Exclusion criteria were Paediatric patients, renal insufficiency (creatinine more than 1.7 mg/dl, history of thromboembolic events, known hereditary bleeding disorders, known history of arterial or venous thrombotic events and receiving plasma products, platelets or hemostatic drugs within 1 week before surgery.

Patients were divided into control group(n=12) and Novoseven group (n=12).

Both groups received the same medications enlisted in our protocol for liver transplantation which included propofol, atracurium and fentanyl for induction of anesthesia.

Maintenance of anesthesia was maintained using inhalational sevoflurane with atracurium and fentanyl infusions. Calcium chloride infusion was used guided by serum ionized calcium level.

Patients in both groups received a protonin 150.000 unit per hour till the end of the dissection phase.

Novoseven group received a loading dose of 30 ug/kg after induction of anesthesia and maintenance of 5 ug/kg for maintenance till the end of the dissection phase.

The following data were collected in both groups;

Preoperative data:

Including demographic data (age, weight, height and sex) and preoperative coagulation profile

Intraoperative data:

blood loss, transfusion requirements , duration of dissection phase ,duration of surgery, coagulation profile (done after induction,1,2,3 and 6 hours after induction) including prothrombin time , prothrombin concentration ,partial thromboplastin time , INR , hemoglobin concentration and platelet count and finally, doppler assessment of graft vessels after anastomosis.

Postoperative data;

Blood loss, postoperative thromboembolic events and Doppler assessment of graft vessels

Statistical analysis;

Data were presented as mean (SD) or median (range), as appropriate. Coagulation parameters were compared between the groups using repeated measures analysis of variance (ANOVA) with post hoc Tukey's Honest Significant Difference (HSD) if the results of ANOVA proved significant. Other parameters were compared between the groups using unpaired Student's t-test. Requirements of blood transfusion and cost analysis were performed using Mann-Whitney U test. Categorical data were analyzed using Chi-squared test or Fisher's exact test, as appropriate. P values < 0.05 were considered statistically significant.

Results:

Demographic data are shown in table 1. Preoperative data are shown in table 2, all patients had preoperative platelet count less than 40,000 and INR >2 and one group received novoseven (30 ug/kg loading followed by continuous infusion of 5 ug/kg/hour till the end of dissection phase. Control group received only drugs enlisted in our anesthesia protocol discussed above.

Laboratory studies carried during dissection time showed a significant decrease in prothrombin time in Novoseven group in relation to base line in the same group at 1 and 2 hours (p value=0.0002) and in relation to values taken in the same time in the other group in all samples.

INR and prothrombin concentration showed similar significant improvement in Novoseven group compared to control group and compared to baseline in the same group at 1 and 2 hours (p value=0.0002 for both) after drug administration.

Platelet count in Novoseven group showed no significant change in relation to baseline but showed a significant increase in relation to control group in all samples taken during dissection phase. Control group showed a significant decrease in platelet count in relation to base line values in all samples taken during dissection phase. Laboratory investigations during period of the study are shown in table 3.

Table 4 shows Intraoperative and postoperative transfusion requirements in both groups showing a

significant decrease in Intraoperative requirements of packed red blood cells (p=0.0141), platelets (p=0.0005) and fresh frozen plasma (p=0.0111) in Novoseven group compared to control group. Postoperative requirements showed no difference between both groups in blood product requirements (p value for PRBCs=0.3408, for FFP=0.7728 and for platelets=0.8174).

Table 5 shows costs of treatment. Novoseven group show a significant decrease (p=0.0179) in the cost of blood products compared to the control group but the total cost of Novoseven and blood products is significantly higher (p=0.0003) in Novoseven group than the control group.

Regarding safety of novoseven, no Intraoperative or early postoperative thromboembolic events were diagnosed in both groups.

Table 1: Demographic and operative data [mean (SD) or ratio].

	Novo-Seven (n = 12)	Control (n = 12)
Age (year)	50 (6.0)	50 (7.0)
Sex (M/F)	6/6	8/4
Weight (kg)	80 (8.3)	78 (6.3)
Diagnosis (HCV/HBV)	10/2	9/3
Dissection time (h)	3.9 (0.57)	4.1 (0.49)

HCV = Hepatitis C virus; HBV = Hepatitis B virus.

Table 2: Baseline laboratory investigations [mean (SD)].

	Novo-Seven (n = 12)	Control (n = 12)
PC (%)	41 (3.2)	38 (2.8)
PT (sec)	32 (2.4)	34 (2.2)
PTT (sec)	63 (5.3)	66 (5.5)
INR	2.4 (0.20)	2.6 (0.19)
Hb (g/dl)	9.7 (0.76)	9.2 (0.82)
Platelets (1000/mm ³)	32 (7.0)	32 (6.0)

PC = Prothrombin time; PT = Prothrombin concentration; PTT = partial thromboplastin time; INR = International normalized ratio; Hb = Hemoglobin concentration

Table 3: Laboratory investigations over the duration of the study [mean (SD)].

		Novo-Seven (n = 12)	Control (n = 12)
Prothrombin time (sec)	Baseline	32 (2.4)	34 (2.2)
	1 h	25 (2.5)*†	33 (3.1)
	2 h	27 (1.9)*†	34 (4.1)
	3 h	30 (2.5)†	33 (3.3)
	4 h	30 (2.5)†	33 (3.3)
	Prothrombin concentration (%)	Baseline	41 (3.2)
1 h		48 (5.0)*†	37 (3.6)
2 h		44 (3.0)*†	36 (4.9)
3 h		40 (3.4)†	36 (4.2)
4 h		40 (3.3)†	37 (3.8)
International normalized ratio		Baseline	2.4 (0.20)
	1 h	1.9 (0.21)*†	2.6 (0.25)
	2 h	2.1 (0.16)*†	2.7 (0.33)
	3 h	2.4 (0.21)†	2.6 (0.27)
	4 h	2.3 (0.21)†	2.6 (0.26)
	Partial thromboplastin time (sec)	Baseline	63 (5.3)
1 h		14 (1.7)*†	20 (3.2)*
2 h		16 (1.9)*†	22 (1.9)*
3 h		17 (2.3)*†	24 (1.9)*
4 h		22 (3.0)*†	29 (3.3)*
Platelet count (1000/mm ³)		Baseline	32 (7.0)
	1 h	33 (6.0)†	25 (6.0)*
	2 h	33 (5.9)†	24 (5.9)*
	3 h	33 (6.2)†	25 (6.1)*
	4 h	33 (5.6)†	25 (6.1)*

*P < 0.05 relative to baseline values in the same group.

†P < 0.05 relative to the control group at the same time of measurement.

Table 4: Transfusion requirements (units) in the two groups of the study [median (range)]

		Novo-Seven (n = 12)	Control (n = 12)
Intraoperative	PRBCs	4 (0–44)*	9 (4–32)
	FFP	0 (0–14)*	11 (6–30)
	Platelets	0 (0–24)*	12 (0–42)
Postoperative	PRBCs	0 (0–12)	0 (0–16)
	FFP	0 (0–12)	0 (0–16)
	Platelets	0 (0–36)	0 (0–24)

PRBCs = Packed red blood cells; FFP = Fresh frozen plasma.

*P < 0.05 compared with the other group.

Table 5: Cost of treatment (Egyptian pound) [median (range)].

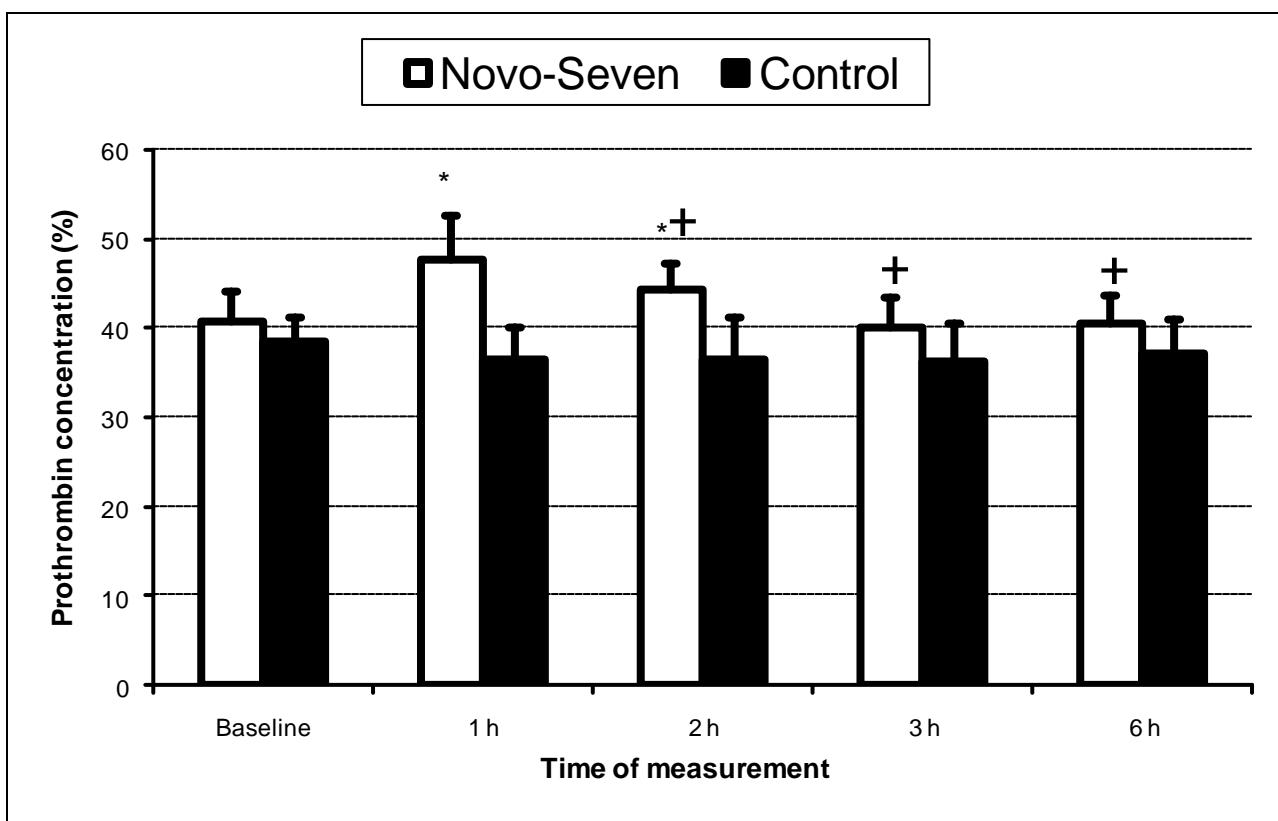
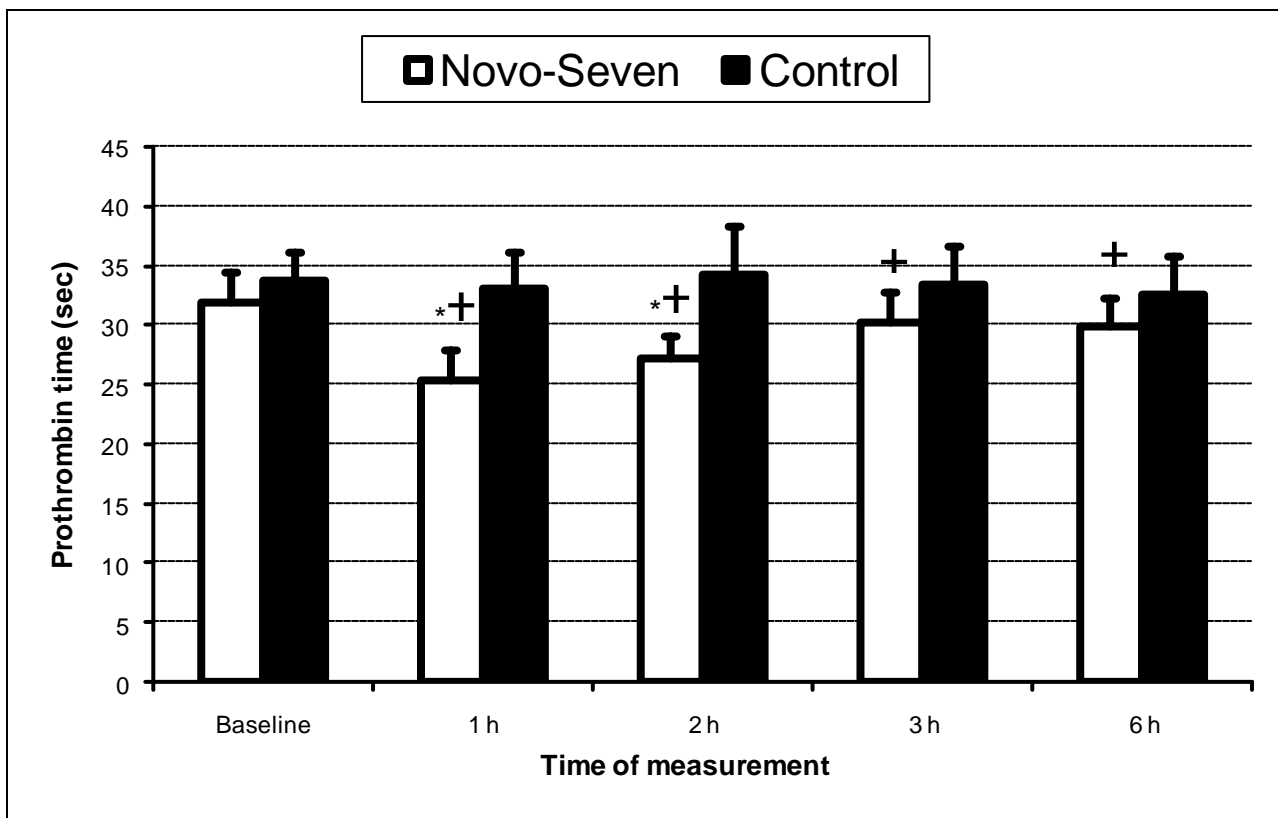
	Novo-Seven (n = 12)	Control (n = 12)
Blood products	1,720 (0–39,580)*	11,075 (7,440–41,140)
Total cost	29,620 (22,800–68,080)*	11,075 (7,440–41,140)

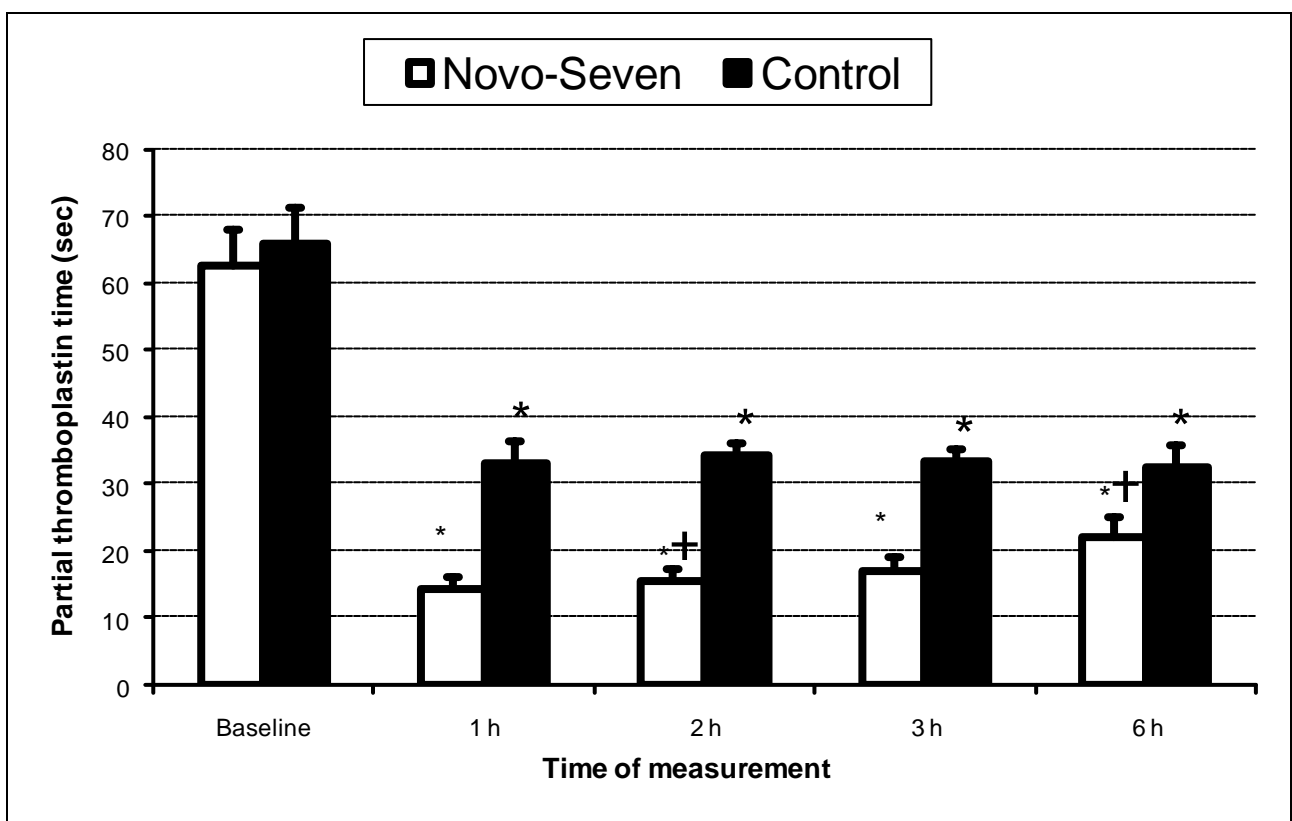
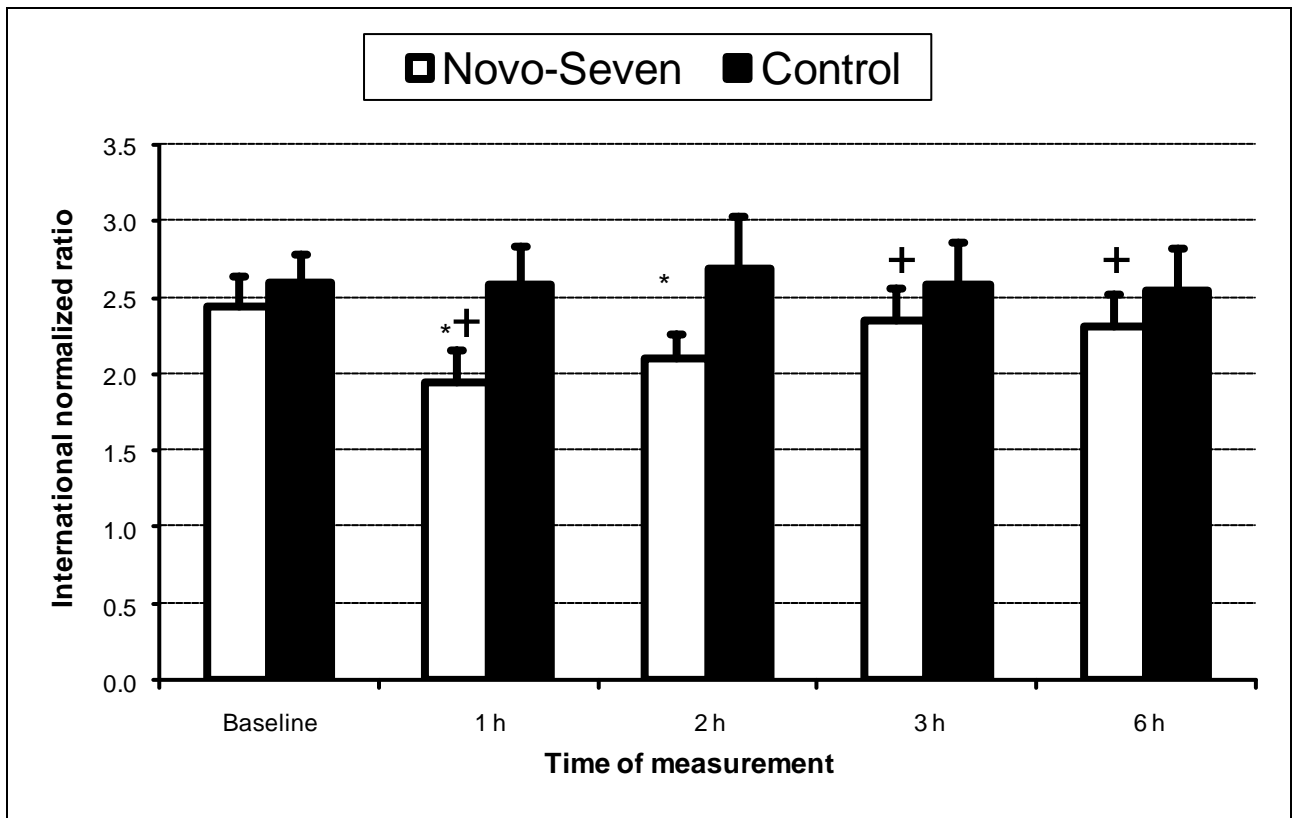
*P < 0.05 compared to the other group.

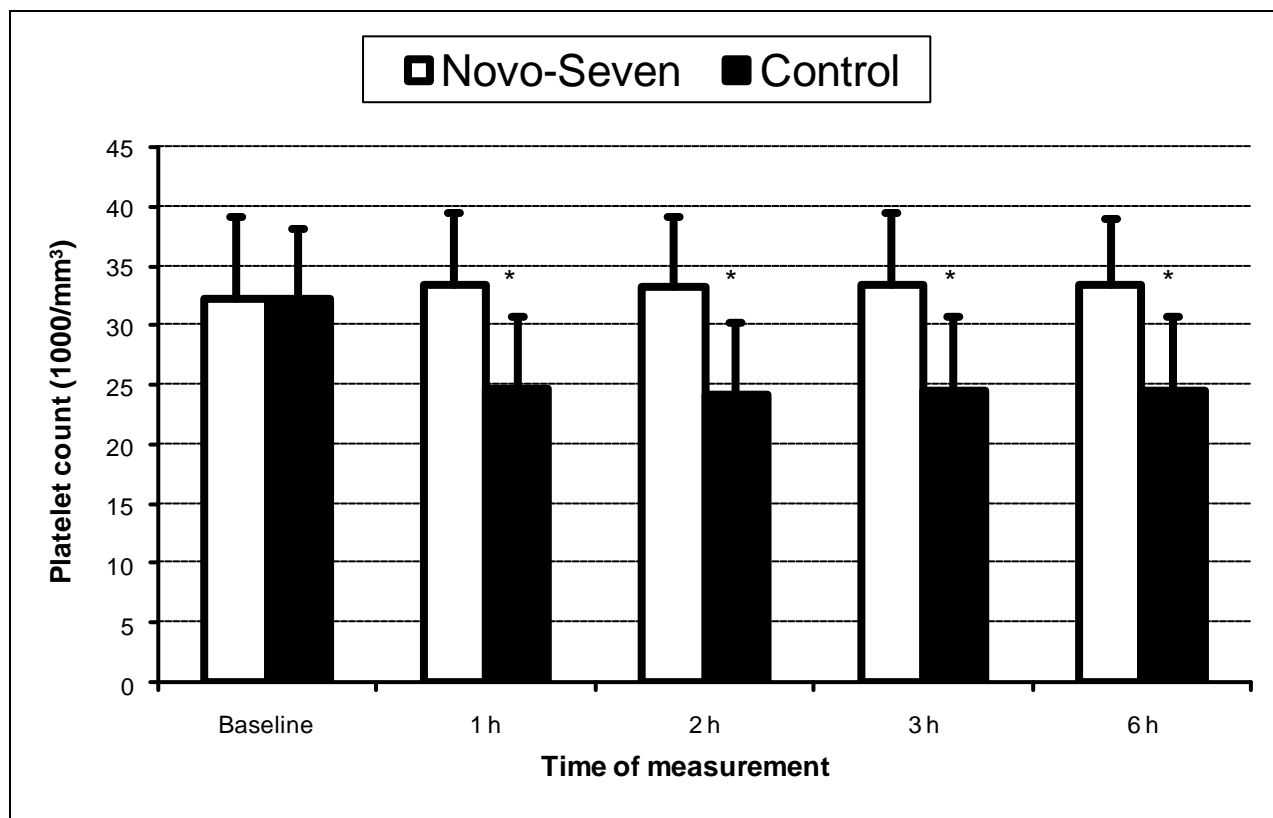
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Partial thromboplastin time (sec)	Baseline	63 (5.3)	66 (5.5)
	1 h	14 (1.7)*†	20 (3.2)*
	2 h	16 (1.9)*†	22 (1.9)*
	3 h	17 (2.3)*†	24 (1.9)*
	4 h	22 (3.0)*†	29 (3.3)*
Platelet count (1000/mm ³)	Baseline	32 (7.0)	32 (6.0)
	1 h	33 (6.0)†	25 (6.0)*
	2 h	33 (5.9)†	24 (5.9)*
	3 h	33 (6.2)†	25 (6.1)*
	4 h	33 (5.6)†	25 (6.1)*

*P < 0.05 relative to baseline values in the same group. †P < 0.05 relative to the control group at the same time of measurement.







Discussion:

In this study we tested the effect of a relatively low dose of rVII (Novoseven) which is a loading dose of 30 ug/kg followed by continuous infusion at a rate of 5 ug/kg/hour on hemostasis and blood product requirements in dissection phase during orthotopic liver transplant surgery. Our selection criteria were very challenging in an already challenging type of surgery. Our patients had a low platelet count (less than 40,000) and high (INR > 2) which increase the risk for bleeding and blood product requirements. Liver transplant surgery is associated with bleeding due to deficiency of coagulation factors as a result of liver dysfunction, portal hypertension and portosystemic shunts and thrombocytopenia and hence blood products are used. Bleeding and blood transfusion are both associated with long and short term effects on patient. Increased blood transfusion has a negative outcome on patient survival, graft survival, immunosuppression and transmission of infection. In our study we found a significant effect of Novoseven in preservation of platelets and significant reduction of requirements of blood products in the novoseven group compared to the control group. Coagulation profile was significantly

better in the novoseven group compared to control group. However, cost of Novoseven use despite following a relatively low dose regimen is significantly higher than using blood products without novoseven.

We conclude from this study that novoseven is a powerful procoagulant that can be used effectively in liver transplantation surgery as a prophylaxis to markedly decrease requirements of blood products but it is cost ineffective. So, is it important to use it in this type of surgery? In our opinion prophylactic use of Novoseven in high risk liver transplantation surgical patient should be always considered for the following reasons; we have evidence that increased blood loss is associated with increased post-operative morbidity and mortality in this population. For example, Mor et al. found that patient and graft survival were significantly lower in liver transplant patients who required more than 10 units of red blood cells (6). A research done at University Hospital Groningen found that patients who required less than five units of blood during their transplant had a 10-year survival rate of close to 90 percent, compared to a rate of about 75 percent in those patients who required more than 10 units(7). Finally, Sieders et al. found in a

multivariate analysis that blood loss index – expressed by blood loss in liters divided by the circulating blood volume – was an independent predictor of long-term survival in pediatric liver transplant recipients(8). A research group at Groningen has found that acute rejection rates in liver transplant patients are as high as 50 percent in patients who receive less than two units of blood during surgery, while rejection rates are as low as 25 percent in those who receive more than two units. So we should realize that by further reducing transfusion requirements in these patients, we might see more rejections. This means that we may have to increase immunosuppressive drug levels in this population, especially in the first postoperative course. The overall conclusion, then, is that blood transfusions in liver surgery have a negative impact – not only during surgery, but also postoperatively. So, Blood requirements more than 10 units and less than 2 units are both harmful to liver transplant recipients.

For cost effectiveness we used in this study a relatively lower dose of novoseven 30 ug/kg loading dose instead of 80ug/kg loading dose. However, this was cost ineffective. This is partly due to cost of the drug a partly to cheap price of blood products in Egypt relative to other countries. However, a larger study putting in mind the costs added due to transmission of infection, prolonged intensive care stay and increased rejection associated with increased blood product requirements should give us the whole picture of benefits of using prophylactic novoseven in liver transplant recipients with very high risk of bleeding.

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