Original Article

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EFFICACY OF FACTOR VIIa IN CIRRHOTIC PATIENTS WITH ACTIVE ESOPHAGEAL VARICEAL BLEEDING

*Bassim A. Asker **Akram A. Najeeb *** Talib A. Majid

Abstract:

Introduction: Upper gastrointestinal bleeding (UGIB) is a severe complication of cirrhosis and portal hypertension, with bleeding from varices accounting for approximately70% of all UGIB episodes..Early control of bleeding episode is associated with better survival, possibly because secondary coagulopathy is prevented.Correction of single specific key deficiency is an attractive alternative. Factor seven may be such an alternative since lack of this factor is most pronounced .This study aimed to investigate the efficacy of recombinant factor VIIa (rFVIIa) in normalization of prothrombin time, control of variceal bleeding within the first 24 hours, prevention of rebleeding and improvement of overall mortality rate within five days in patients with chronic liver disease in comparisom to non factor VII treated subgroup.

Setting: Gastroenterogy and Hepatology Teaching Hospital- Medical City - Baghdad.
Methods: A total of 100 cirrhotic patients (Child- Pugh A=3, B=34 and C=63) with active esophageal variceal bleeding , irrespective to the aetiology , were randomized equally into two main subgroups. Placebo - treated subgroup and rfVIIa (8 doses of 80 µg/kg/dose)-treated subgroup.Clinical data , vital sign monitoring and endoscopic sclertherapy , were carried out for every patient. Blood sample for coagulation status assay were done at 0, 24 , 48 , and 72 hours after admission.
Results: The study engaged 100 patients during one year period, 79 were males and 21 famales with mean age of 47.84 years. All patients had prothrombin time above the normal value (10-13.5 seconds) at admission. Normalization of PT within 72 hours of study period was observed in all patients (100 %) after rfVIIa dosing versus 2% in non rfVIIa - treated subgroup. Over all eleven cases of variceal rebleeding between first 24 hours and fifth day related to non rfVIIa-treated subgroup in which the prothrombin time (mean 18.3) failed to normalize. No variceal rebleeding was observed in rfVIIa - treated subgroups; ($p< 0.01$). 10 out of eleven patients with variceal rebleeding were Child-Pugh class C and one of B class, The overall mortality rate of studied patients within 0-5 days was 10 % , moreover mortality rate as consequence of variceal rebleeding was 7 % . However , no death was reported as consequence of variceal rebleeding in patient receiving rfVIIa,whereas 7 cases of death was reported in non - rfVIIa- treated patients ; ($P<0.01$).
Conclusion: rFVIIa had a good efficacy in normalization of prothrombin time , prevention of rebleeding and improvement of overall mortality rates within five days in patients with chronic liver disease of different aetiology with esophageal variceal bleeding.
Keywords: VIIa factor, cirrhosis, esophageal varices.

Introduction:

Upper gastrointestinal bleeding (UGIB) is a severe complication of cirrhosis and portal hypertension, with bleeding from varices accounting for approximately70% of all UGIB episodes.(1)(2)
Up to 30% of initial bleeding episodes are fatal, and recurrent bleeding episodes further contributing to mortality are common.(3) Early control of bleeding episode is associated with better survival, possibly because secondary coagulopathy is prevented.(4
However, it is not documented that fresh frozen plasma improves survival and the volume necessary to correct the coagulation status may be prohibitive large correction of single specific key deficiency, therefore, is an attractive alternative. Factor seven may be such an alternative since lack of this factor is most pronounced. (5)
This study was designed to investigate the efficacy of rFVIIa in normalizationof prothrombintime, control acute variceal bleeding within first 24 hours, prevention of rebleeding and improvement of over all mortality rate within 5 days, in patients with chronic liver disease of different etiology.

Patients and methods:

This study was conducted at gastroenterogy and hepatology teaching hospital in the medical city (Baghdad) between 1st of December 2005 and 1st of December 2006.
The study engaged 100 consecutive patients admitted to the hospital if they had known or

*C. A. B. M , F. I. C. M. GE & H, The gastroenterogy and hepatology teaching hospital / medical city (Baghdad) ,
**D.M, F.I.C.M.S , F. I. C. M. GE & H, The gastroenterogy and hepatology teaching hospital / medical city (Baghdad) ,
***F. R. C. S, F. R. C. S Ed, consultant surgeon ,The gastroenterogy and hepatology teaching hospital / medical city (Baghdad).

presumed liver cirrhosis with active esophageal variceal bleeding, either known from previous encounters or endoscopically proven at the present episode.

No patients fulfilled the exclusion criteria, that is, none : (a) had known hypersensitivity to rFVIIa ; (b) had received treatment with prothrombin - complex concentrates within the last 7 days ; (c) had received treatment with vasopressin or antifibrinolytics within the last 3 days ; (d) pregnant women .

An upper endoscopy was carried out for every patient after initial resuscitation and haemodynamic stabilization for precise diagnosis of the source of bleeding as well as initiation of endoscopic therapy (95 patients had been treated by alcohol injection sclerotherapy and 5 patients had been treated by variceal band ligation).

At baseline after hospital admission, full clinical data for all cases were obtained including; history and physical examination including concomitant medications and illnesses; other safety data included vital signs and monitoring of adverse and rebleeding events; laboratory tests (complete blood picture, serum bilirubin, serum albumin, blood urea, serum creatinine, potassium and sodium);coagulation status(prothrombin time, activated partial thromboplastin time, and international normalized ratio(INR)).

Blood samples for coagulation status assay were drawn 0(before drug treatment), 24, 48, and 72 hours after admission.

Each patient, who was treated by rFVIIa, received intravenous injection of 8 doses of rFVIIa 80 µg/Kg/dose. These doses were given at time 0 (immediately after endoscopy) ,2 ,4 ,6 ,12 , 18, 24 and 30 hours after admission .

Materials:-Recombinant FVIIa is identical in structure and activity to human FVII. rFVIIa (Novoseven) was supplied as a freeze - dried powder in 2 ml vials. Each vial was reconstituted immediately before use in 2 ml sterile water. Reconstituted rFVIIa contains 0.6 mg/ml rFVIIa.Recombinant FVIIa was administered as a slow i.v. bolus injection (80 µg/Kg) over two minutes.

Study Design:-The study was a single - centre, open label pilot trial - duration 5 days per patient.

The studied group; 100 patients; was subdivided equally in 2 subgroups(50 patients for each subgroup).

First subgroup-(Non-factorVII treated subgroup) was treated with supportive therapy ; including plasma transfusion , blood transfusion , intravenous vitamin K , oral propranolol , antibiotics , fluid therapy , hypertonic glucose ,vitamin B1 , diuretics , latulose, omeprazol and rectal enema plus octreotide i.v. 0.05 mg every 2 hours for 48 hours (1 ml ampoule = 0.05 mg octreotide)..

Second subgroup-
(FactorVII treated subgroup)
was treated with supportive therapy and 8 doses of rFVIIa iv. 80µg/ Kg/dose given at time 0, 2 , 4, 6 ,12 ,18 , 24 and 30 hours of the admission .

Results: During one year period (from first of decomber 2005 to first of December 2006), the study engaged 100 patients who were eligible for inclusion if they had a known or presumed liver cirrhosis and actively bleeding from esophageal varices .

Of 100 patients, 79 were males and 21 females (M/F was 3.7/1). The mean age was 47.84 years (range 7- 90 years) with peak age of 40-60 years. .

The aetiology of cirrhosis of studied groups was hepatitis B virus in 20 patients , alcoholic in 9 , hepatitis C in 7 , primary biliary cirrhosis in 4 , immune hepatitis in 2 and one patient equally reported in methotrexate - induced, hepatic fibrosis,α1 antitrypsin deficiency and Wilson s disease. The vast majority of etiology of cirrhosis in our studied group was unknown (55 patients).

According to Child - Pugh classification (6), it was found that 3 patients class A, 34 (22 of non rFvlla-treated subgroup) patients class B and class C in 63 (25 of non rFvlla-trated subgroup) patients. Emergency upper endoscopy was performed for every patient at presentation and showed esophageal varices of grade III to IV (6) as bleeding source in all patients of studied group and bleeding was controlled immediately either by injection sclertherapy or band ligation. The immediately preceding prothrombin time was used as entry value. All patients had prothrombin time above the normal value (10-13.5 seconds).

Failure to control bleeding within first 24 hours was defined by presence of a new haematemesis together with (a) decrease in systolic blood pressure > 20 mmHg and / or (b) a transfusion of > 6 units of blood to increase haemoglobin level to >9 gm/dl according to Baveno II criteria.(7) Failure to prevent rebleeding between 24 hours and 5 days was defined by the occurrence of new haematemesis and /or new melena together with transfusion of> 2 units of blood in any 24 hours period in which one or more of following haemodynamic criteria were fulfilled :(a) systolic blood pressure < 100 mmHg, (b) postural change > 20 mmHg , or (c) pulse rate > 100 beats/min , according to Baveno II criteria.(7)

Normalization of prothrombin time , within 72 hours of study period after first trial drug administration , was observed in all patients (100%) after rFVIIa dosing.One out of 50 patients (2 %) receiving both octreotide and supportive measurements showed normalization of prothrombin time. (Table 1).

No failure to control bleeding within first 24 hours was observed in all 100 studied patients.

Attacks of variceal rebleeding between 24 hours and 5 days were high in non factorVII treated subgroup (22%). No varecial rebleeding was observed in rFVIIa treated patients ($p < 0.01$) ** (Table 2).

An exploratory analysis of the subgroups of variceal rebleeding with Child - Pugh scores A,B and C indicated 10 out of 11 patents with variceal rebleeding were Child - Pugh C and one of Child - Pugh B score .

All eleven cases of variceal rebleeding were related to non rFVIIa - treated subgroup in which prothrombin time (mean 18.3) failed to normalize.

The over all mortality rate of studied group patients within 0 - 5 days was 10 % (10 of 100). Of these, 7 % (7 of 100) with non rFVIIa - treated patients. Moreover severe variceal rebleeding was the leading cause of death in those patients.
No death was reported as consequence of variceal rebleeding in the remained 3 patients with rFVIIa subgroup. However renal failure (2 patients) and hepatic coma (1 patient) were the main causes of death in this subgroup.

An exploratory analysis of the subgroups of mortality with Child - Pugh scores A,B and C indicated 9 out of 10 patients were Child - Pugh C and one of Child - Pugh B score.
Moreover , no death was reported as consequence of variceal rebleeding in patients receiving rFVIIa , whereas 7 cases of death was reported in non rFVIIa treated patients ($p < 0.01$)** (Table 3 , 4) .

Table1: Distribution of studied patient with PT controlled to normal within 72hr of admission

Groups of studied patients	Total number of patients in each group	Patients with PT controlled to normal	
		Number	%
Non rFVIIa - treated subgroup	50	1	2%
rFVIIa - treated subgroup	50	50	100%
Total number	100	51	51 %
Value of LSD		13.34**	

LSD = low standard deviation
** = very significant statistically

(P<0.01)**

Table 2: Distribution of patients with variceal rebleeding within 5 days of admission

Groups of studied patients	Total number of patients in each group	Variceal rebleeding in each group											
		No. and %		Child s class						PT control to normal			
		No.	%	A		B		C		controlled		uncontrolled	
Non rFVIIa treatedsubgroup	50	11	22	0	0	1	4.54%	10	40%	0	0%	11	22%
rFVIIa treated subgroup	50	0	0	0	0	0	0	0	0	-	-	0	0%
Total number	100	11	11	-	-	1	-	10	-	-	-	11	11%

(p<0.01)**

Table 3:Total mortality in each subgroup within 5 days of admission

Groups of studied patients	Total number of each group	Total mortality in ea ch group															
		No. and %		Child s class						PT control to normal				Mortality cause			
		No.	%	A		B		C		controlled		uncontrolled		Directly due to variceal rebleeding		Due to causes other than variceal rebleeding	
Non rFVIIa treated ubgroup	50	7	14%	0	0%	1	4.45%	6	24%	0	0%	7	14%	7	14%	0	0%
rFVIIa treated subgroup	50	3	6%	0	0%	0	0%	3	7.89%	3	6%	0	0%	0	0%	3	6%
Total number	100	10	10%	0	0%	1	1%	9	9%	3	3%	7	7%	7	7%	3	3%
Value of LSD	3.64 **																

(p<0.01)**

Table 4: Distribution of studied patients with mortality directly due to vericeal rebleeding within 5 days of admission

Groups of studied patients	Total number of patients in each group	Mortality Directly due to variceal rebleeding	
		Number	%
Non rFVIIa treated subgroup	50	7	14%
rFVIIa treated subgroup	50	0	0%
Total number	100	7	7 %

(p<0.01)**

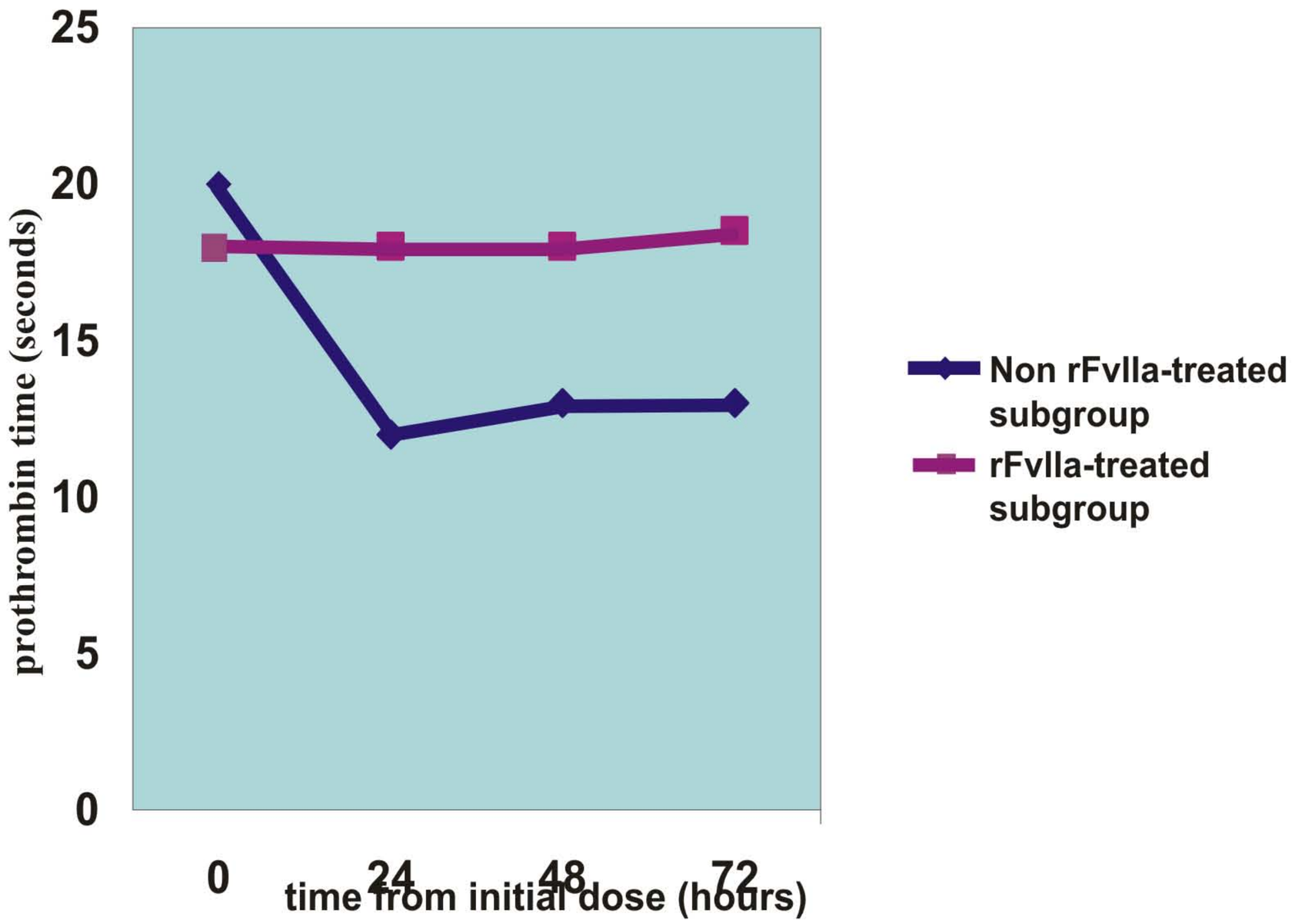

Figure 1: prothrombin time (mean value) by treatment subgroups.

Discussion:

Factor VIIa has been used for bleeding in patients who have experienced variceal bleeding from the esophagus and stomach.(8) (9) A number of pilot studies suggested that rFVIIa could normalize PT and might improve haemostasis with cirrhosis and esophageal variceal bleeding associated with abnormal clotting. (10) (11)

The finding that the effect of rFVIIa treatment in normalization of PT within 72 hours in our study was most pronounced (100 % in rFVIIa - treated subgroup versus 2% in non rFVIIa - treated subgroup ; $p < 0.01$) . Normalization of prothrombin time (10 - 13.5 seconds) was observed in all patients of rFVIIa subgroups during first 24 hours post - bleeding episode. However, the promise of these initial findings was supported by a number of pilot studies suggested that rFVIIa could normalize PT and might improve haemostasis with cirrhosis and esophageal variceal bleeding associated with abnormal clotting(9) (10),and early control of bleeding episode is associated with better survival , possibly because secondary coagulopathy is prevented (4) . Our finding is similar to these findings indicated that early treatment with factor VIIa has greater success rate with fewer doses being required.(12) Dr. Ayse Leyla Mindikolgu presented his finding at 103rd annual meeting of American Gastroenterological association and Digestive Disease week (DDW) that rFVIIa administration to coagulopathic patients with advanced liver disease result in a rapid improvement in PT lasting 4 to 6 hours. Another interesting observation in our study is that no statistically significant reduction in failure rate of PT normalization was observed with non rFVIIa - treated subgroup patients with Child - Pugh score A ,B and C (100% , 95.5 % and 100 % respectively). In patients whom the source of rebleeding was established of variceal origin , the failure rate of rebleeding seemed to be higher with non rFVIIa - treated subgroup (11 of 50 [22%]) patients than with rFVIIa - treated subgroup (0 of 50 [0 %] ; $p < 0.01$).

In non rFVIIa - treated subgroup of Child - Pugh B and C were most likely to rebleed (1 of 22 [4.5%] , 10 of 25 [40 %] respectively) than those receiving rFVIIa subgroup patients (0 of 12 [0%] , 0 of 38 [0 %] respectively). However , variceal rebleeding was not reported in Child - Pugh A of non rFVIIa - treated subgroup (0 of 3 [0 %]) . It is not documented that plasma improves survival, and the volume necessary to correct the coagulation status may be prohibititively large. Correction of single specific Key deficiencies, therefore, is an attractive alternative. FVII may be such an alternative since lack of this factor is the most pronounced deficiency.(5)

Jaime Bosch. et.al, were observed in their study that the prevention of rebleeding end point (8 failures in 61 placebo - treated patients versus 3 failure in 60 rFVIIa - treated patients; $p = 0.13$). The observed failure rate were higher with rFVIIa than placebo in patients in whom the source of bleeding was either unconfirmed or not of variceal origin (8 of 42 rFVIIa - treated patients and 3 of 39 placebo - treated patients). (13) This study confirmed similar results from a study done in Denmark. (9) Mortality as consequence of initial bleeding is reported on average about 30 %. (3) (11) (14) (15)

In this study , normalization of PT in initial control of bleeding was achieved in 100% of patients treated with rFVIIa compared to 2% in non rFVIIa - treated subgroup, whereas, variceal rebleeding was prevented in all rFVIIa - treated patients in comparism to 22% in non rFVIIa treated subgroup. These success rates of PT normalization and preventing early rebleeding highly contribute to significant reduction in mortality rate within 5 days in rFVIIa - treated subgroup (6%) versus (14%) in non rFVIIa - treated patients, however , high mortality rate was reported in Child - Pugh C with non rFVIIa - treated subgroup (6 of 25 [24%]) ; a subgroup which showed the highest variceal rebleeding rate (10 of 25 [40%]) .

A note of caution is that all of patients receiving rFVIIa did not have variceal rebleeding episode per 5 days post drug dosing , a finding might indicate that 6% mortality rate reported in this group related to hepatic coma (one patient) and renal failure(two patients).

Conclusion:

rFVIIa had a good efficacy in normalization of prothrombin time , prevention of rebleeding and improvement of overall mortality rates within five days in patients with chronic liver disease of different aetiology with esophageal variceal bleeding.

References:

1- Stanley A.J. , Robison I. , Forrest, Jones A.I. , Hayes P.C. , Haemodynamic parameters predicting variceal haemorrhage and survival in alcoholic cirrhosis . QJM 1998; 91:19-25.

2- D'Amico G, de Franchis R, Cooperative-study Group. Upper digestive bleeding in cirrhosis. post therapeutic outcome and prognostic indicators . Hepatology 2003; 38:599-612.

3- Graham DY, Smith J.L., The course of patients after variceal hemorrhage. Gastroenterology 1981; 80:800-809.

4- Levacher S , Letoumelin P , Pateron D , Blaise M ,Lapandry Pourriat J. L. Early administration of terlipressin plus glycotrinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet 1995; 346:865-8.

5- Rapaport Sl, Rao L.V.M.Initiation and regulation of tissue factor-dependent blood coagulation .Arterioscler. thromb .1995; 12:1111-2.

6- Vijay H. Shah, Patrick S. Kamath. Portal hypertension and gastrointestinal bleeding er

Sieisenger and Fordtran's gastrointestinal and liver diseases .2006; 8th edition: chapter 87:1901 - 1913.
7- de Franchis R. Developing consensus in portal hypertension. J Hepatol 1996; 25: 390 - 394.
8- Thabut DFR, Bendtsen F. Efficacy of Recombinant FVIIa in cirrhotic patients with upper gastrointestinal bleeding: a randomized placebo controlled multicentral trial . Proc Dig Dis week.2003.Abstract 102422.
9- Ejlersen E, Melsen T,Ingerslev J,Andreasen RB , Vilstrup H. Recombinant activated factor VII (rFVIIa) acutely normalize prothrombin time in patients with cirrhosis during bleeding from esophageal varices . Scand J Gastroenterol. 2001; 36; 1081 - 1085.
10- Bernstien D E,Jeffers ,Erhordlen E, Reddy K R, Glazer S, Squiban P,etal. Recombinant factor VIIa corrects prothrombin time in csirrhotic patients : Gastroenterology 1997 ; 113 : 1930 - 1937 .
11- D, Amico G, de Franchis R, Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post - therapeutic outcome and prognostic indicator. Hepatology 2003 ;38: 599 - 612 .
12- Lusher JM. Early treatment with recombinant factor VIIa results in greater efficacy with less product. Eur. Hamatol1998; 61(suppl 63):7-10.

13- Jaime Bosh, Dominque Thabut, Flemming Bendsen, etal. Rocombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: A Randomized, Duoble-blind Trail. Gastroenterology .2004; 127:1123-1130. 14- Chalasani N, Kahi C, Francois F , Pinto A,Marathe A,Bini E j,Pnadya P,etal. Improved patient survival after acut variceal bleading : a multicenter , cohort study . Am J Gastroenterol 2003; 98:653 - 659.
15- Mc Cormik P A,O, Keefe C. Improving procnosis following a first variceal haemorrhage over four decades . Gut 2001; 49; 682 - 685.