ANNALS OF GASTROENTEROLOGY 2001, 14(3):187-195

Prevention of recurrent variceal bleeding. Endoscopic and pharmacologic treatment

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SUMMARY

Bleeding from esophageal and gastric varices is the most severe complication of portal hypertension. The long-term probability of rebleeding of patients surviving a variceal bleed is about 60%, with a mean risk of death of about 45%. Thus, all patients who survive an episode of variceal bleeding must be treated to prevent rebleeding. Pharmacological therapy with beta-blockers has been shown to reduce the rebleeding rate by about 40%. Endoscopie methods such as sclerotherapy and rubber band ligation have also been shown to be effective in reducing the incidence of variceal rebleeding. Banding was markedly superior to sclerotherapy in preventing rebleeding, while mortality was similar with either treatment. The advantage of combining sclerotherapy with beta-blockers appears to be small. The value of combining banding and sclerotherapy with the aim of reducing variceal recurrence is still unproven. In conclusion, the first line treatment for prevention of recurrent variceal haemorrhage is either β-blockade or band ligation. In patients who have a contraindication to β -blockers therapy or who have bled while on β-blockers, band ligation is the preferred treatment to prevent recurrent variceal hemorrhage.

Key Words: Portal hypertension, Variceal haemorrhage, beta-blockers, sclerotherapy; endoscopie banding ligation, meta-analysis

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INTRODUCTION

Gastrointestinal bleeding is the most severe complication of portal hypertension. Although cirrhotic patients may bleed from a variety of portal-hypertension related causes (i.e. portal hypertensive gastropathy, colopathy, hemorrhoids and rectal varices), esophageal and gastric varices are by far the most common sources of bleeding in these patients.

If a patient survives an episode of variceal bleeding, he has a high probability of rebleeding.

Rebleeding can be conventionally divided into two phases: early (within 6 weeks of the bleeding episode), and late (after 6 weeks). The reported incidence of early rebleeding ranges between 30 and 40% within the first six weeks.[1] The risk is maximal in the first 5 days, then declines slowly over the first 6 weeks, and becomes virtually equal to that before bleeding after the sixth week.[2] In a recent Italian survey[3], rebleeding within 6 weeks occurred in 37 of 199 patients (18.6%), with 40.5% of rebleeds occurring in the first 5 days. Early rebleeding is significantly associated with the risk of death within 6 weeks. This suggests that its prevention should be a primary objective of therapy of the acute bleeding episode.

Data on long-term rebleeding can be obtained by analyzing the control groups of 21 randomized controlled trials carried out between 1982 and 1991, in which pharmacologic treatment with beta–blockers or endoscopic sclerotherapy were compared with placebo or non active treatment for prevention of rebleeding.[4-24] The incidence of rebleeding ranged between 32% and 84%, with a mean of 59%. (Figure 1). Long-term mortality in these patients ranged between 4% and 78%, with a mean of 46% (Figure 1). Because of these dismal figures, the general consensus[25] is that all patients who survive an episode of variceal bleeding must receive some effective

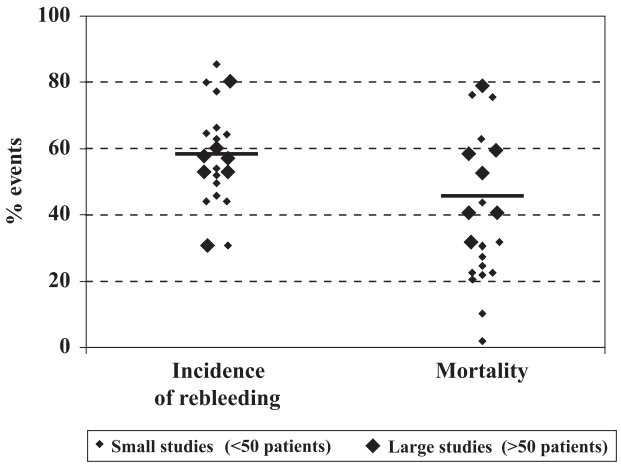

Figure 1: Incidence of rebleeding and long-term mortality in the placebo- (or non-actively-) treated control patients in randomized controlled trials for prevention of rebleeding. (Data from 21 trials including 977 patients; average incidence of rebleeding: 59%; average mortality: 46%).

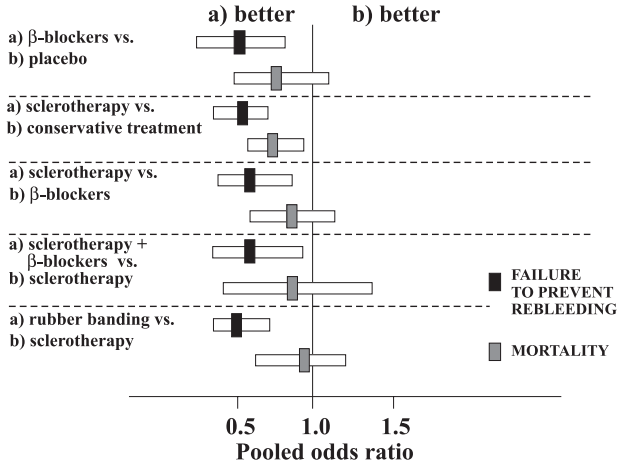

Figure 2. Meta-analyses of randomized controlled trials for prevention of variceal rebleeding.

form of treatment to prevent rebleeding.

In this paper we will review the available pharmacologic and endoscopic treatments to prevent rebleeding.

Beta blockade versus placebo

Eleven randomized controlled trials compared beta-blockers with placebo.[5,7-11,15,17-19,23] Meta-analysis (Figure 2) showed a highly significant reduction of rebleeding in patients receiving beta-blockers,[26] while the reduction in mortality rates with beta-blockers just missed statistical significance.[26]

Long-term sclerotherapy vs. conservative measures

Sclerotherapy has been compared with conservative measures[4,6,12-14,18,20-22,24] in 10 trials including a total of 1259 patients (Table 1). Meta-analysis showed a significant reduction of rebleeding in sclerotherapy-treated patients (P.O.R. 0.57; 95% C.I. 0.45-0.71) (Table 1, Figure 2). Mortality was also significantly reduced (P.O.R. 0.72 ; 95% C.I. 0.57-0.90) (Figure 2). It is noteworthy that the complication rate was higher in patients treated by sclerotherapy in all trials.

Sclerotherapy vs long-term beta-blockers

Nine trials[18,27-34] with a total of 752 patients compared

Table 1. Randomized controlled trials of treatments for the prevention of variceal rebleeding-I

Author	Yr.	Ref N°	Treatment	N° Pts.	% Rebleeding	% Mortality
Sclerotherapy (Sc) vs. conservative treatment (C)						
Barsoum	1982	54	Sc/C	50/50	26/58	26/42
Terblanche	1983	58	Sc/C	37/38	38/53	62/63
EVASP	1984	55	Sc/C	93/94	48/54	65/78
Westaby	1985	59	Sc/C	56/60	55/81	32/53
Korula	1985	60	Sc/C	63/57	21/54	33/33
Paquet	1985	56	Sc/C	20/22	20/32	33/77
Sφderlund	1985	57	Sc/C	57/50	28/32	47/58
Burroughs	1989	61	Sc/C	102/104	55/59	47/59
Gregory	1990	62	Sc/C	122/131	52/60	52/42
Rossi	1991	63	Sc/C	26/27	50/63	23/33
pooled data				626/633	43/57	46/54
P.O.R. (95% C.I.)					0.57 (0.45-.71)	0.72 (0.57-0.90)

sclerotherapy with long-term beta-blockers (Table 2). In this group of trials meta-analysis showed a significant reduction of rebleeding in favor of sclerotherapy (P.O.R. 0.64; 95% C.I.: 0.48-0.85, Table 2, Figure 2). However, an important qualitative heterogeneity between trials results has been shown[26] which approaches significance (P =0.07), and weakens the results of meta-analysis, suggesting that the advantage of sclerotherapy may be small. None of the trials showed a significant difference in mortality in either direction, and this is reflected in the meta-analysis (P.O.R. 0.82; 95% C.I. 0.60 -1.11).

Sclerotherapy vs sclerotherapy + b-blockers

In 10 trials,[35-44] involving 600 patients (Table 3) sclerotherapy was compared with a combined treatment of sclerotherapy plus beta-blockers. In these trials, the combined treatment was significantly better than sclerotherapy alone in preventing rebleeding (P.O.R. 0.65; 95% C.I. 0.46-0.92), but qualitative heterogeneity in trials results was found,[26] and thus meta-analysis should be interpreted with caution. Mortality was similar with the two treatment regimes (P.O.R. 0.81, 95% C.I. 0.50-1.29, Table 3, Figure 2).

Sclerotherapy vs. sclerotherapy + subcutaneous octreotide

In three trials,[45-47] sclerotherapy was compared with sclerotherapy plus subcutaneous octreotide. These trials differed greatly in study design, dosage and time of octreotide administration, and gave contrasting results. In the first one, 58 patients were randomized after bleeding control to receive sclerotherapy alone (32 patients.) or plus subcutaneous octreotide, 100μg t.i.d. for one month (26 patients.). The rebleeding rate throughout three months of follow-up was not significantly different in the two treatment groups (34% vs. 31%, p = 0.73). Ninety-day mortality was also similar in the two groups (22% vs. 38%; p =0.16). In the second trial[46] 32 patients were enrolled three weeks after a variceal bleeding episode which had been controlled with two sessions of sclerotherapy. The patients (16 in each group) were randomized to sclerotherapy every three weeks, alone or plus octreotide (50 μg b. i. d. for 6 months). Rebleeding (6% and 44% respectively, p = 0.037) and mortality (0% and 25% respectively, p <0.02) were both significantly better in patients receiving the combined treatment. The study was not double-blind and there was no check for compliance in the administration of octreotide. The 44% rebleeding rate in patients treated with sclerotherapy alone is exceedingly high, since patients were enrolled three weeks after the index bleed and after two sessions of sclerotherapy, when the rebleeding risk is markedly decreased. This raises the question of a severe selection bias. The third study[47] had a complex design. After bleeding control, patients were randomized to octreotide (100 μg t.i.d. for 15 days) or placebo (131 patients for each group). Patients were stratified according to whether they were eligible or not for long-term treatment according to clinical criteria. Those eligible could receive beta-blockers, sclerotherapy or both. As a result, only 23 patients were randomized to sclerotherapy (± nadolol) plus octreotide, and 28 to sclerotherapy (± nadolol) plus placebo. The six-week rebleeding rate was 25% in the former group, and 70% in the latter (p= 0.02). Again, the extremely high rebleeding rate in patients treated with sclerotherapy alone raises the doubt of selection bias. From the results of these 3 studies, the clinical efficacy of subcutaneous octreotide in reducing early rebleeding in pa-

Table 2. Randomized controlled trials of treatments for the prevention of variceal rebleeding-II

Author	Yr.	Ref. N°	Treatment	N° Pts.	% Rebleeding	% Mortality
Sclerotherapy (Sc) vs. b-blockers (β)?						
Fleig	1988	64	Sc/β	36/34	28/29	8/15
Terıs	1993	65	Sc/β	59/57	34/51	30/21
Alexandrino	1988	66	Sc/β	31/34	55/74	29/32
Dollet	1988	67	Sc/β	28/27	64/44	54/44
Westaby	1990	68	Sc/β	56/52	45/54	38/42
Liu ¶	1990	69	Sc/β	60/58	33/57	28/38
Rossi	1991	63	Sc/β	26/27	50/48	23/26
Martin	1991	70	Sc/β	34/42	53/55	24/31
Dasarathy	1992	71	Sc/β	45/46	42/67	22/41
pooled data				375/377	43/54	29/35
P.O.R. (95% C.I.)					0.64 (0.48-0.85)	0.82 (0.60-1.11)

Table 3. Randomized controlled trials of treatments for the prevention of variceal rebleeding-III

Author	Yr.	Ref. N°	Treatment	N° Pts.	%Rebleeding	%Mortality
Sclerotherapy (Sc) vs b-Blockers + sclerotherapy (SP or SN)						
Westaby	1986	72	SP/Sc	26/27	27/30	35/26
Jensen	1989	73	SP/Sc	15/16	20/75	6/ 7
Gerunda ¶	1990	74	SN/Sc	30/30	20/23	3/10
Lundell	1990	75	SP/Sc	19/22	63/50	—/—
Bertoni	1990	76	SN/Sc	14/14	7/28	7/21
Vinel	1992	77	SP/Sc	39/35	18/40	13/14
Acharya	1993	78	SP/Sc	58/56	17/21	9/12
Avgerinos	1993	79	SP/Sc	45/40	31/52	18/18
Vickers	1994	80	SP/Sc	39/34	51/53	23/26
Villanueva ¶	1992	81	SN/Sc	22/18	55/39	9/ 0
pooled data				307/293	30/39	13/15
P.O.R. (95% C.I.)					0.65 (0.46-.92)	0.81 (050-1.29)

SP = Sclerotherapy + propranolol

SN = Sclerotherapy + nadolol

tients undergoing sclerotherapy remains uncertain.

Long-term endoscopic therapy vs. long-term beta-blockers + nitrates

Two recent trials by the same group of investigators have compared sclerotherapy with a oral medical treatment consisting of nadolol plus isosorbide-5-mononitrate[48,49] (Figure 3). In the first study,[48] eleven of 43 (25.6%) patients on the medical regimen rebled, as compared with 23 of 43 (53.5%) treated by sclerotherapy (P < 0.001). The rebleeding rate of medically treated patients in this study is the lowest ever reported in trials of medical prevention of variceal rebleeding, while that of patients in the sclerotherapy arm is among the highest reported for this kind of treatment. The corresponding figures for mortality were 9.3% and 20.9% (P = 0.07). In the second trial,[49] 139 patients were randomized to receive either band ligation (70 patients) or nadolol plus isosorbide-5-mononitrate (69 patients.). During a mean follow-up of 20 months, 35 patients (50%) in the band ligation group and 24 patients (38%) in the medical treatment group rebled (p= NS). Mortality was 39% and 32% respectively (p = NS). If the results of these studies are confirmed, the combination of beta-blockers + nitrates is likely to become the first-choice medical therapy to prevent variceal rebleeding, and the standard with which alternative therapies should be compared.

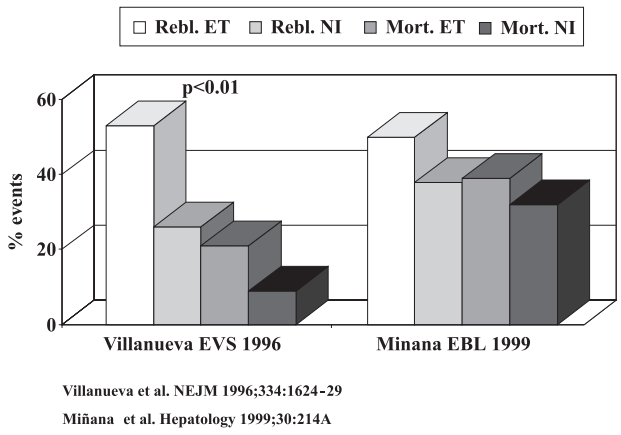

Figure 3. Randomized controlled trials comparing endoscopic treatments with medical treatment (Nadolol + Isosorbide-5-Mononitrate) for prevention of variceal rebleeding.

Long-term sclerotherapy vs. long-term rubber band ligation

Fourteen trials[50-63] with a total of 1181 patients have compared long-term sclerotherapy with long-term rubber band ligation (Table 4). Ligation was better than sclerotherapy in preventing rebleeding in all studies, and was significantly so in 5.[52,54,55,57,62,63] Meta-analysis shows a strong benefit for rubber banding (P.O.R. 0.45, 95% C.I. 0.35 - 0.59, Table 4, Figure 2). Only 11 trials give figures for mortality: in 2 rubber banding was significantly better than sclerotherapy[51,54] while the other studies showed small, not significant changes in either direction. Meta-analysis confirms that the two treatments are equivalent (P.O.R. 0.84; 95% C.I. 0.62-1.15).

Table 4. Randomized controlled trials of treatments for the prevention of variceal rebleeding-IV

Author	Yr.	Ref. N°	Treatment	N° Pts.	%Rebleeding	%Mortality
Rubber banding (L) vs. sclerotherapy (Sc)						
Stiegmann	1992	87	L/Sc	64/65	36/48	25/45
Laine	1993	88	L/Sc	38/39	24/31	10/15
Gimson	1993	89	L/Sc	54/49	30/53	39/35
Young	1993	95	L/Sc	13/10	20/38	20/31
Jensen ¶	1993	90	L/Sc	37/39	31/35	26/24
Mundo ¶	1993	96	L/Sc	11/ 8	25/27	25/36
Avgerinos	1997	97	L/Sc	37/40	27/40	21/20
Lo	1995	91	L/Sc	61/59	15/44	16/32
Hou	1995	92	L/Sc	67/67	18/32	21/16
Sarin	1995	94	L/Sc	48/47	6/21	6/ 6
Baroncini	1995	98	L/Sc	43/46	2/ 9	—/—
Fakhry * ¶	1995	93	L/Sc	24/25	4/ 8	—/—
Masci ¶	1996	99	L/Sc	50/50	24/48	22/14
De La Pña	1999	100	L/Sc	45/45	31/54	—/—
pooled data				591/590	21/35	22/25
P.O.R. (95% C.I.)					0.45 (0.35-0.59)	0.84 (062-1.15)

Symbols and abbreviations used in tables and figures:

¶ = published in abstract form, * = study containing patients with schistosomiasis, P.R.D. = pooled rate difference

P.O.R. = pooled odds ratio, 95% C.I. = 95% confidence intervals

The strong difference in rebleeding rate in favor of rubber banding is probably the consequence of several factors: the number of treatment sessions required to achieve variceal eradication was significantly smaller with banding (2.5 to 4.1 sessions) than with sclerotherapy (2.9 to 6.5 sessions) in all but one of the 12 trials reporting this data.[53] In most studies, this corresponded to a shorter time to achieve eradication: decreasing such time reduces the 'vulnerable phase' of endoscopic treatment, (i.e. the time when the risk of rebleeding is decreased but still exists, owing to the incomplete eradication of varices). In addition, the number of clinically significant complications was generally lower in patients treated with banding:[64] esophageal stenosis after banding was reported in only one trial[62] (2%), while its incidence after sclerotherapy ranged between 0 and 33%; the incidence of bleeding from treatment-induced ulcers was lower with banding in all studies but two.[50,63] Finally, the incidence of septic complications (pulmonary infections, spontaneous bacterial peritonitis) and of fatal complications was also lower in patients undergoing rubber band ligation, although the difference with sclerotherapy was small.[64] In view of these results, rubber band ligation has become the endoscopic treatment of choice for the prevention of recurrent bleeding from esophageal varices.[65,66]

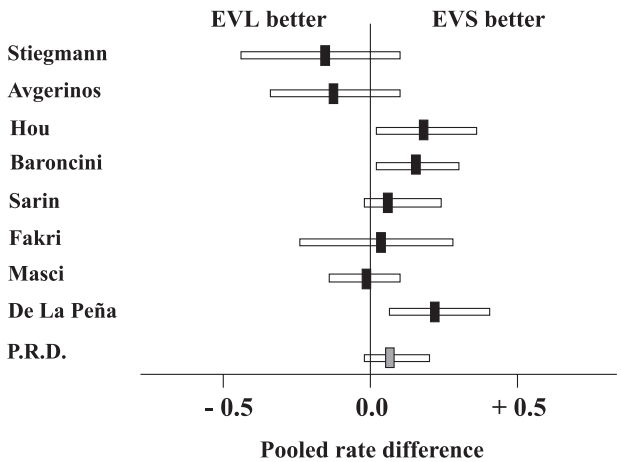

Figure 4. Meta-analysis of randomized controlled trials for prevention of variceal rebleeding: Sclerotherapy (EVS) vs. Rubber Band Ligation (EVL): Recurrence of varices (7 trials; 673 patients).

It is unclear whether banding ligation is followed by a higher rate of variceal recurrence in comparison with sclerotherapy. Of the 8 trials that give the information,[50,55-57,60-63] variceal recurrence was slightly more frequent after sclerotherapy than banding in three[50,60,62] and more frequent

after banding in 5,[55-57,61,63] with a difference reaching statistical significance in 3.[57,61,63] In the eight studies, recurrences ranged between 8% and 92% after banding, and between 2% and 55% after sclerotherapy. Interpretation of these results is made difficult by the different lengths of follow-up in the studies, and by differences in the definitions of variceal recurrence. Meta-analysis shows no significant difference between treatments (P.O.R. 1.31; 95% C.I. 0.89-1.94) (Figure 4). At any rate, in recent years several combinations of treatments have been proposed to reduce the recurrence rate of varices following band ligation. In two studies, banding was compared with a regimen consisting of band ligation plus simultaneous sclerotherapy.[67-68] The combined treatment was superior to banding alone in one[67] and showed no advantage in the other.[68] In another study, banding was compared with a sequential therapy with initial banding followed by low-dose sclerotherapy after varices were reduced to small residual cords.[69] The combined treatment significantly reduced both variceal recurrence and rebleeding. In a further study, a comparison was made between banding alone and banding followed by microwave coagulation of the lower esophagus, leading to mucosal fibrosis.[70] Variceal recurrence was observed in 15/25 (60%) of patients treated with banding alone, and in 4/25 (16%) of those treated with the combined regimen ($p=0.03$). In conclusion, it is still unclear whether variceal recurrence is more frequent after banding than after sclerotherapy. The clinical value of combined treatments to reduce variceal recurrence rates after banding is unknown.

CONCLUSIONS

The first line treatment for prevention of recurrent variceal haemorrhage is either β-blockade or band ligation.[65] In patients who have a contraindication to β -blocker therapy or who have bled while on β –blockers, band ligation is the preferred treatment to prevent recurrent variceal hemorrhage.[65]

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