

# EFFICACY OF ABSOLUTE ALCOHOL INJECTION COMPARED WITH BAND LIGATION IN THE ERADICATION OF ESOPHAGEAL VARICES

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**ABSTRACT - Background** - Endoscopic sclerotherapy is an absolute indication for treating esophageal varices. Re-bleeding is common during the treatment period, before all varices become eradicated. **Aim** - To compare two techniques of endoscopic esophageal varices eradication: sclerotherapy with absolute alcohol and banding ligation. **Patients and Method** - Forty-six patients with liver cirrhosis and esophageal varices were prospectively randomized into two treatment groups: endoscopic sclerotherapy with absolute alcohol and banding ligation. Patients were included if they had large varices with signs of high bleeding risk. Informed writing consent was obtained from every patient and the Ethics Committee of Federal University of São Paulo, SP, Brazil, approved the study. After eradication, all patients were followed up to 1 year to look for re-bleeding episodes and variceal recurrence. **Results** - Both groups were similar except that male gender was more common in the sclerotherapy group. There was no statistical difference regarding variceal eradication (78.3% in sclerotherapy group vs 73.9% in the ligation group), recurrence (26.7% vs 42.9%, respectively) and death related to any cause (21.7% vs 13.9%). In the sclerotherapy group more sessions were need to obtain complete variceal eradication. In this group we did observe a high re-bleeding rate (34.8%) and more ulcers associated with retrosternal pain right after the procedure. There was no difference regarding overall morbidity and mortality. **Conclusions** - Banding ligation requires fewer sessions than sclerotherapy with absolute alcohol to eradicate esophageal varices. Both methods are equally efficient regarding variceal eradication and recurrence during a short follow-up period.

**HEADINGS** – Esophageal and gastric varices, therapy, Sclerotherapy. Ligation. Hypertension, portal. Gastrointestinal hemorrhage.

## INTRODUCTION

Cirrhosis is a common cause of portal hypertension and esophageal varices (EV) are present in 30% to 40% of patients with compensated disease (no ascites, encephalopathy or severe jaundice) and up to 60% with decompensated disease<sup>(4, 18, 23)</sup>. It is estimated that the annual incidence of varices in cirrhotic patients varies between 5% and 20%<sup>(18)</sup>.

Gastrointestinal bleeding caused by EV rupture is a major clinical complication and occurs in up to 30% of patients with chronic liver disease<sup>(38)</sup>. Mortality associated to the first bleeding episode ranges between 30% and 50%<sup>(18)</sup>. If untreated, 60% of patients who survive the first bleeding episode will rebleed<sup>(7)</sup>.

Endoscopic sclerotherapy (ES) has been widely used in the treatment of EV<sup>(21)</sup>. Absolute alcohol injection requires shorter time to eradicate varices when compared

to 5% ethanolamine oleate<sup>(30)</sup>, with similar rebleeding and complication rates.

Band ligation (BL) of varices was first reported by Van STIEGMANN et al.<sup>(39)</sup>. Currently it is considered the treatment of choice in the prevention of rebleeding<sup>(5, 9, 18, 34, 36)</sup>.

Although BL is considered the gold standard in the eradication of varices, ES is still widely used because it is an easy and cheap technique, with proven efficacy. Among available sclerosants, absolute alcohol is the cheapest. The aim of this prospective study was to compare the results of ES with absolute alcohol and BL in the treatment of EV in cirrhotic patients.

## PATIENTS AND METHOD

This randomized prospective study was conducted at the Division of Gastroenterology of Federal University of São Paulo (“Escola Paulista de Medicina – UNIFESP-

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EPM”, São Paulo, SP, Brazil) and was approved by the Ethics Committee of this University.

Between November 1998 and August 2001, cirrhotic patients with EV requiring treatment were randomized (using closed envelopes) into two groups: ES with absolute alcohol and BL.

Inclusion criteria were: patients older than 18 years with portal hypertension due to cirrhosis, with medium or large size EV, history of variceal bleeding or high-risk of bleeding (medium or large size varices with red-spots), who had undergone less than two previous sessions of ES or BL performed during an acute bleeding episode.

Patients who did not agree with this study, with portal hypertension due to schistosomiasis, currently under pharmacological treatment or with previous surgical treatment for portal hypertension, with severe clinical diseases associated to the chronic liver disease preventing follow-up (1 year), pregnant or breast-feeding women, were excluded.

Diagnosis of chronic liver disease was established through medical history, physical examination, abdominal ultra-sound and liver function blood tests. Liver biopsy was eventually performed. Patients were graded according to the Child-Pugh classification<sup>(3)</sup>.

During endoscopy, the number and size of varices and the presence or absence of red-spots were recorded. Variceal sizes were graded as small (straight varices that disappear with insufflation), medium (tortuous varices slightly deformed by insufflation) or large (tortuous varices not deformed by insufflation).

The presence of esophageal ulcers (with or without bleeding), variceal hemorrhage during the study period (re-bleeding), stenosis and esophageal perforation were considered major complications. Minor complications included retrosternal pain and dysphagia. X-rays or any other exams were performed whenever necessary.

Patients were followed-up for 1 year after complete eradication, with endoscopic examinations at 3, 6 and 12 months.

Endoscopies were performed under conscious sedation every 7-10 days until variceal eradication. Proceedings were eventually postponed in the presence of ulcers secondary to treatment. Varices were considered eradicated after complete disappearance.

In the ES group 0.5 to 1.0 mL of absolute alcohol was injected into each varix (maximum 4 mL per session). Injections were performed close to the cardia and all varices were treated in the same session whenever possible.

In the BL group multiple band kits were used following usual technique. Up to six bands were placed in each session. Ligation started close to the cardia and all varices were ligated in the same session whenever feasible.

Three end-points were compared between the two groups: variceal eradication, complications and recurrence. Some factors associated to these end-points were taken into account: age, gender, etiology of liver disease, hepatic function according to Child-Pugh classification, primary or secondary prophylaxis, presence or absence of red-spots, number of sessions and technique used. Significance of qualitative data was established using the Chi-square ( $\chi^2$ ) test or Fisher exact test. Quantitative variables were compared by using Student *t* test. Significance level adopted was 5% ( $\alpha = 0.05$ ).

## RESULTS

Forty-six patients were included and randomized, 23 in each group. Table 1 shows the characteristics of both groups.

TABLE 1 – Patients' characteristics in both groups. Numbers in brackets indicate percentages

	ES Group	BL Group
Gender		
male	21	15
female	2	8
Age (years)		
mean $\pm$ standard deviation	49.3 $\pm$ 10.7	49.1 $\pm$ 13.2
range	32 – 65	21 – 78
median	50	50
Etiology		
alcohol	12 (52.2)	10 (43.5)
hepatitis B	3 (13.0)	1 (4.3)
hepatitis C	6 (26.1)	8 (34.9)
others	2 (8.7)	4 (17.4)
Child		
A	8 (34.8)	9 (39.1)
B	12 (52.2)	10 (43.5)
C	3 (13.0)	4 (17.4)
Previous variceal bleeding		
yes	9 (39.1)	12 (52.2)
no	14 (60.9)	11 (47.8)

There was a male predominance in both groups although there were more women in the BL group than in the ES group ( $P = 0.03$ ). Although some patients had more than one etiology, alcohol and virus were the most frequent. Patients were graded as Child B (47.8%), Child A (37%) and Child C (15.2%). Twenty-five patients (54.3%) had no history of variceal bleeding (primary prophylaxis). None of these factors reached statistically significant difference.

In the ES group 18/23 (78.3%) had their varices eradicated. Two patients abandoned treatment before eradication and three died before finishing the treatment. Mean number of sessions was  $4.7 \pm 3.0$ . In the BL group eradication was achieved in 17/23 patients (73.9%). Four patients did not complete treatment and other two died before the end of the study. Mean number of effective sessions was  $2.9 \pm 2.0$ .

In general,  $1.8 \pm 0.8$  more sessions were necessary in the ES group compared with BL group ( $P = 0.02$ ; IC 95%: 0.28 – 3.37). No difference was found regarding overall success rate in eradicating varices in both groups (Table 2).

In the ES group, 18 patients that achieved eradication were followed up to verify recurrence. One patient abandoned the study and two other died. Among the 15 patients studied at 1 year after eradication, 4 (26.7%) had variceal recurrence. In the BL group, 17 patients that had their varices eradicated

TABLE 2 – Eradication (intention to treat) and variceal recurrence in both groups

	Group 1 n (%)	Group 2 n (%)	Total n (%)
Eradication			
yes	18 (78.3)	17 (73.9)	35 (76.1)
no	5 (21.7)	6 (26.1)	11 (23.9)
Recurrence			
yes	4 (26.7)	6 (42.9)	10 (34.5)
no	11 (73.3)	8 (57.1)	19 (65.5)

were followed-up. One patient died and other two abandoned the study. Variceal recurrence was observed in 6/14 (42.9%) patients. No significant difference was found ( $P = 0.45$ ).

All patients developed ulcers after ES and 19/23 (82.6%) of patients in the BL group had such complication. No significant difference was observed. Although ulcer depth evaluation is very subjective, deep ulcers were more frequent in the ES group ( $P = 0.001$ ).

Bleeding was observed in 8/23 patients (34.8%) treated with ES and in 2/23 (8.7%) treated with BL ( $P = 0.03$ ). The difference between both groups was estimated in  $26.1\% \pm 11.5\%$  (CI 95%: 3.5%-48.7%). When variceal bleeding and ulcer bleeding were analyzed separately there was no difference between groups ( $P = 0.40$ ).

Mortality in both groups was similar ( $P = 0.7$ ) with five (21.7%) and three (13%) deaths respectively in the ES and BL group. Table 3 shows that there was no difference in mortality associated or not to endoscopic treatment ( $P = 0.9$ ).

TABLE 3 – Major complications in both groups

Complications	Group 1 n (%)	Group 2 n (%)	Total n (%)	P
Ulcers	23(100)	19(82.6)	42(91.3)	NS
shallow	4(17.4)	17(74.0)	21(45.6)	0.001
deep	19(82.6)	2(8.7)	21(45.6)	0.001
Hemorrhage	8(34.8)	2(8.7)	10(21.7)	0.032
variceal	5(21.7)	--	5(10.8)	NS
ulcer	3(13.0)	2(8.7)	5(10.8)	NS
Death	5(21.7)	3(13.0)	8(17.3)	NS
related	3(13.0)	2(8.7)	5(10.8)	NS
non-related	2(8.7)	1(4.3)	3(6.5)	NS

NS – non signific

The three deaths in the ES group were secondary to bleeding in esophageal ulcers within 7 days after injection. The other deaths were due to appendicitis (one) and hepatic failure (one) after variceal eradication. In the BL group, two deaths were secondary to bleeding esophageal ulcers after endoscopic procedures. The other death was due to liver failure, with no relation to the endoscopic treatment and occurred after eradication.

Dysphagia and retrosternal pain resolved spontaneously. Even in patients with severe and prolonged dysphagia no stenosis was seen. Retrosternal pain was more frequent in patients undergoing ES when compared with BL ( $P = 0.03$ ). No difference was observed regarding dysphagia.

## DISCUSSION

Numerous sclerosants have been used to perform endoscopic sclerotherapy: polidocanol (1% to 3%), ethanolamine oleate (2,5% to 5%), sodium tetradecyl sulfate (1% to 2%), sodium morrhuate (5%), ethanol, hypertonic glucose, phenol (3%), and associations of them<sup>(9,17)</sup>. None of these agents has proved to be better than the others<sup>(31)</sup>. SARIN et al.<sup>(28)</sup> have compared absolute alcohol with 50% alcohol and showed that varices could be eradicated in fewer sessions using absolute alcohol. With this

in mind we decided to compare a very cheap treatment (ES with absolute alcohol) with the current gold standard (endoscopic BL). In this randomized prospective study 46 cirrhotic patients were divided into two groups (23 patients in each group). Seven patients (15.2%) had advanced liver disease (Child C).

Our group has studied the prevalence of bacteria in patients with schistosomiasis after ES and BL and found similar results in both groups. In patients with large varices, BL might be a better option as the need of injecting large amounts of sclerosants might raise complication rates<sup>(24)</sup>.

A very important point in EV treatment is the interval between endoscopic sessions. In this study, whenever we encountered esophageal ulcers the therapeutic sessions were postponed. SARIN et al.<sup>(27)</sup> have suggested not to postpone the treatment; they just avoided injecting alcohol in ulcerated areas. BARONCINI et al.<sup>(1)</sup> waited 7 days between BL sessions. After the first 10 patients they decided for a 14-day interval due to pseudopolyp formation caused by the rings. They suggested a greater risk of severe bleeding in these patients.

As in numerous studies<sup>(12,15,19,40)</sup> including ours<sup>(24)</sup> although ES and BL are equally efficient in eradicating varices, fewer sessions are necessary with BL. Variceal eradication was achieved in 78.3% of patients treated with ES and 73.9% in the BL group. Mean number of effective sessions (excluding sessions which were postponed) was  $4.73 \pm 3.04$  in ES group and  $2.91 \pm 2.04$  in the BL group ( $P = 0.02$ ).

After eradication with conventional ES, variceal recurrence is seen in 22% to 58% of patients after 2 years of follow-up<sup>(11)</sup>. Available literature suggests that variceal recurrence is greater in patients treated with BL<sup>(8,13,37)</sup>. In four studies<sup>(1,10,12,33)</sup> recurrence ranged between 30% and 70% of patients after 12 to 18 months of follow-up. Patients with para-esophageal varices greater than 5 mm in diameter have higher chances of recurrence<sup>(14,16)</sup>. In our study, recurrence was observed in 26.7% of patients in the ES group and in 42.9% in the BL group, without significant difference ( $P = 0.45$ ). Sample size and the length of follow-up are important factors in these results.

De la PEÑA et al.<sup>(8)</sup> have shown variceal recurrence in 23% of patients treated with ES and in 47% of patients treated with BL 1 year after eradication. After 3 years, recurrence was 55% in the first group and 92% in the second ( $P = 0.003$ ).

In 1997, SARIN et al.<sup>(33)</sup> compared ES with absolute alcohol and BL (single session) and observed a 10.4% stenosis rate in the ES group compared to none in the BL group. We have not seen any cases of stenosis nor perforation. The lack of stenosis might be explained by the criterious intravariceal injection (maximum 4 mL) as well as the postponing of sessions when ulcers were present.

Ethanol has not been extensively studied and most papers come from Italy, India and Brazil<sup>(20,22,26,29)</sup>. Among all sclerosants available, absolute alcohol is the least expensive although it has been associated with deep esophageal ulcers, stenosis and higher risk of re-bleeding<sup>(2,6,22)</sup>. It has been shown that intravariceal injection of small amounts of ethanol is effective in eradicating gastric and esophageal

varices with few complications<sup>(32, 29)</sup>. We might suggest that complications observed with ethanol might be related to sclerosant administration technique.

MEIRELLES-SANTOS et al.<sup>(20)</sup> have recently published a study conducted in Brazil including 157 patients comparing ES with either ethanolamine or absolute alcohol. This study differs from ours as 30% of their patients had schistosomiasis. Mean number of sessions necessary to eradicate EV was 5.4 and 5.9 in the alcohol and ethanolamine groups, respectively. Eradication was possible in 91% and 88.7% of patients, respectively with alcohol and ethanolamine. No differences were seen regarding complication and mortality. The authors concluded that ES with alcohol was as effective as with 5% ethanolamine. They questioned if the complications observed by others were not related to the incorrect use of alcohol.

Regarding esophageal ulcers, we have observed 19 cases (82.6%) of deep ulcers in the ES group and 17 cases (74%) of shallow ulcers in the BL group. During BL, deep ulcers are not common because suction is not deep enough<sup>(25)</sup>.

In our patients we observed eight cases of bleeding (34.8%) in the ES group and two (8.7%) in the BL group ( $P = 0.032$ ). The estimated difference is  $26.1\% \pm 11.5\%$  (95% CI: 3.5%-48.7%). Bleeding secondary to ulcers resulting in death was seen in three patients in the ES group and in two in the BL group.

Although we had deeper ulcers and more bleeding episodes in the ES group, mortality was not influenced by these two variables. Death was seen in five patients (21.7%) in the ES group and in three (13.0%) in the BL group, without significant difference. In 1997, SARIN et al.<sup>(33)</sup> compared ES with absolute alcohol and BL in 95 patients and observed three deaths in both ES and BL groups. SHAFQAT et al.<sup>(35)</sup> in a similar study using 75% alcohol observed death in 21% of patients in the ES group and 11% in the BL group.

Retrosternal pain and dysphagia were considered minor complications. Retrosternal pain was seen in 52.2% of patients in the ES group and 21.7% in the BL group ( $P = 0.03$ ). The low rate of abandon in the ES group supports the clinical irrelevance of this complication.

Our results allow us to conclude that ES with absolute alcohol and BL are equally effective in eradicating esophageal varices. ES is associated with higher rates of bleeding, deeper ulcers and retrosternal pain. Mortality and variceal recurrence are similar.

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Ferrari AP, Paulo GA, Macedo CMF, Araújo I, Della Libera, Jr E. Eficácia da injeção de álcool absoluto comparada com ligadura elástica na erradicação de varizes de esôfago. *Arq Gastroenterol* 2004;42(2):72-6.

**RESUMO – Racional** - Escleroterapia endoscópica tem indicação absoluta no tratamento das varizes de esôfago. Ressangramento é comum durante o período de tratamento, antes que as varizes sejam erradicadas. **Objetivo** - Comparar duas técnicas de erradicação endoscópica de varizes de esôfago: escleroterapia com álcool absoluto e ligadura elástica. **Pacientes e Método** - Quarenta e seis pacientes com cirrose hepática e varizes de esôfago foram prospectivamente randomizados em dois grupos de tratamento: escleroterapia endoscópica com álcool absoluto e ligadura elástica. Os pacientes foram incluídos no estudo se tivessem varizes de grosso calibre com sinais de alto risco de sangramento. Consentimento informado por escrito foi obtido de cada paciente e o estudo foi aprovado pelo Comitê de Ética da instituição onde o estudo foi realizado. Após a erradicação, todos os pacientes foram seguidos durante 1 ano para avaliar a taxa de ressangramento e a recidiva das varizes. **Resultados** - Ambos os grupos foram parecidos exceto no que se refere ao sexo masculino, mais comum no grupo da escleroterapia. Não houve diferença estatisticamente significativa em relação a erradicação das varizes (78,3% no grupo da escleroterapia vs. 73,9% no grupo da ligadura), recidiva (26,7% vs. 42,9%, respectivamente) e mortalidade relacionada a qualquer causa (21,7% vs. 13,9%). No grupo da escleroterapia houve necessidade de maior número de sessões para obtenção da erradicação completa das varizes. Neste mesmo grupo observou-se alta taxa de ressangramento (34,8%) e presença de mais úlceras associadas com dor retroesternal logo após o procedimento. Não houve diferença na morbimortalidade global. **Conclusões** - O tratamento com ligadura elástica requer menos sessões do que a escleroterapia com álcool absoluto para erradicar as varizes de esôfago. Ambos os métodos são igualmente eficazes, a curto prazo, no que diz respeito à taxa de erradicação e recidiva das varizes.

**DESCRITORES** – Varizes esofágica e gástricas, terapia, Escleroterapia, Ligadura. Hipertensão, portal. Hemorragia gastrointestinal.

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