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Schistosomal portal hypertension: Randomized trial comparing endoscopic therapy alone or preceded by esophagogastric devascularization and splenectomy

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ABSTRACT

Background. Upper gastrointestinal bleeding is a major cause of morbidity and mortality in patients with portal hypertension secondary to schistosomiasis mansoni. **Aim.** To evaluate the efficacy of combined surgery and sclerotherapy versus endoscopic treatment alone in the prophylaxis of esophageal variceal rebleeding due to portal hypertension in schistosomiasis. **Material and methods.** During a two-years period consecutive patients with schistosomiasis and a recent bleeding history were evaluated for prospective randomization. Absolute exclusion criteria were alcoholism or other liver diseases, whereas platelet count < 50,000/mm^3, INR > 1.5 or presence of gastric varices were relative exclusion criteria. By random allocation 25 (group A) have received endoscopic sclerotherapy for esophageal varices alone and 22 (group B) combined treatment: esophagogastric devascularization with splenectomy followed by sclerotherapy. Interim analysis at 24 months has shown significant statistical differences between the groups and the randomization was halted. **Results.** Mean age was 38.9 ± 15.4 years and 58.46% were male. Mean follow-up was 38.6 ± 20.1 months. Endoscopic comparison of the size of esophageal varices before and after treatment did not show significant differences among the two groups. Treatment efficacy was assessed by the rate of recurrent esophageal variceal bleeding, that was more common in group A- 9/25 patients (36.0%) *vs.* 2/22 (9.0%) in group B (p = 0.029). Other complications were odynophagia, dysphagia and esophageal ulcer in group A and ascites and portal vein thrombosis in the surgical group. **Conclusion.** In portal hypertension due to schistosomiasis, combined surgical and endoscopic treatment was more effective for the prevention of recurrent esophageal variceal bleeding.

Key words. Treatment of portal hypertension. Sclerotherapy. Surgery for portal hypertension. Hepatosplenic schistosomiasis. Variceal bleeding prophylaxis.

INTRODUCTION

Schistosomiasis is a parasitic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*.[1,2] By conservative estimates, at least 230 million people worldwide are infected with *Schistosoma* spp. *Schistosomiasis mansoni* causes periportal fibrosis and portal hypertension in approximately 6% of all infected subjects.[3,4] Upper gastrointestinal bleeding (UGIB) secondary to variceal rupture is one of the main complications of the portal hypertension due to schistosomiais occurring in approximately 30% to 40% of patients.[3-5] Despite advances in therapy, the case-fatality rate has remained high and the mortality rate from a single episode of variceal bleeding is around 20%.[5-7] For secondary prevention of variceal hemorrhage in patients with schistosomal portal hypertension (SPH) the reported efficacy of endoscopic sclerotherapy alone ranges from 54% to 82.3%.[8,9] However, the reported recurrence rate of esophageal varices after variceal eradication can be as high as 62% with rebleeding rates of 46%.[9,10] Although beta-blockers have been found to be very effective in both primary and secondary prophylaxis of variceal bleeding in cirrhotic patients, published data evaluating beta-blockers in SPH are scarce and its efficacy in this setting is yet to be confirmed.[11-13] Of the several surgical procedures proposed as treatment for the control of upper

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digestive tract hemorrhages from SPH, the most commonly used in Brazil is the esophagogastric devascularization with splenectomy (EGDS).[14,15] Recently several case-series indicate that combining surgical and endoscopic therapy may be more efficacious than using one technique alone.[6,12] In fact, a retrospective study showed that endoscopic sclerotherapy was more effective in patients who had previously undergone surgical treatment for portal hypertension.[16] In the absence of a prospective controlled data, the present randomized, phase III trial was designed to compare sclerotherapy alone versus sclerotherapy combined with surgery for preventing recurrent bleeding from variceal rupture.

MATERIAL AND METHODS

Study design

Consecutive patients with SPH presenting to our Liver clinic with recent history of upper gastrointestinal bleeding secondary to esophageal varices, were evaluated for the study from March 2005 till May 2007. After applying selection and exclusion criteria they were randomly allocated (1:1) to receive endoscopic sclerotherapy or EGDS followed by sclerotherapy (Figure 1). Esophageal variceal bleed was diagnosed if active bleeding was seen from the varix, a white nipple or a clot was seen on the varix, or if there was blood in the stomach in a patient with an esophageal varix and no other potential bleeding source All patients had hematemesis and melena and for most of them it was the first episode of bleeding. None of the few patients with previous episodes of bleeding have being submitted to any endoscopic treatment. Clinical measures, usually associated with vaso-constrictors, namely octreotide, was the proposed treatment during the bleeding episodes, before randomization.

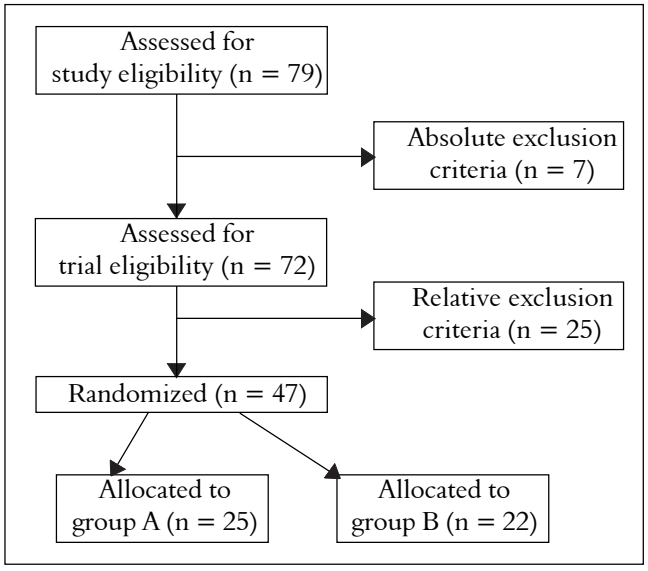

Figure 1. *Distribution of patients with schistosomal portal hypertension, according to randomization procedure (groups A and B). Group A: endoscopic sclerotherapy of esophageal varices alone. Group B: esophagogastric devascularization with splenectomy followed by sclerotherapy.*

Randomization was performed 20 to 60 days after bleeding, according to protocol and the time elapsed between randomization and starting therapy has varied, being a little bit shorter for the group on sclerotherapy. No bleeding episodes occurred in the meantime for both groups.

Local ethics committee approval was obtained before enrollment of any patient into the study, which was performed in accordance with the Declaration of Helsinki and its subsequent amendments as well as the Good Clinical Practice Guidelines. Signed informed consent was obtained from all patients before study entry.

Randomization and masking

This was a randomized open phase III trial conducted in one center in Brazil. Using a numbered sequence of opaque, sealed envelopes patients were randomized to receive either of the therapies: sclerotherapy alone or EGDS followed by sclerotherapy. For obvious reasons, patients and investigators could not be masked to treatment allocation.

Procedures

Patients were eligible if they had an established diagnosis of hepatosplenic schistosomiasis as the cause of portal hypertension, recent history (20 to 60 days) of hematemesis and melena and proven to have esophageal varices as the bleeding source on upper gastrointestinal endoscopy. For all patients included in the study, the diagnosis of schistosomiasis was based on clinical, epidemiological or histological data, as required. Other key eligibility criteria included age between 15 and 65 years and ability to understand and perform the required study procedures. Exclusion criteria were:

- Chronic alcoholism.
- Evidence of decompensated liver disease.
- Evidence of potential mixed etiology of portal hypertension.
- Any major contraindication for surgery.
- Platelet count < 50,000/L; 6- INR > 1.5.
- Presence of gastric varices at upper endoscopy.

Chronic alcoholism was defined as an alcohol intake ≥ 60 g/EtOH/day in men and ≥ 40 g/EtOH/day in women.

The standard laboratory workup included a complete blood count, platelet count, International Normalized Ratio (INR), liver enzyme panel [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT)], total bilirubin, and serum total protein and protein fractions. The possibility of comorbid hepatitis B and C was ruled out by means of serologic markers (HBsAg, anti-HBs, anti-HBc, anti-HCV), using a third-generation ELISA assay.

Pre- and post-treatment liver fibrosis was assessed by means of real-time two-dimensional ultrasound with pulsed-wave Doppler. Fibrosis was classified according to Cairo Working Group standards as grade I (mild), grade II (moderate), and grade III (advanced).[17] A similar ultrasound technique was used to test for portal vein thrombosis (PVT) in the immediate postoperative period (within 15 days of surgery) and at 1-year follow-up.

The mean time between the sclerotherapy sessions was of three weeks and it varied from two to six weeks. Number of sessions were a minimum of two and a maximum of five, according to number and size of varices. The sclerosing agent used was 2.5% monoethanolamine oleate. The size of esophageal varices was assessed according to Paquet's classification.[18] At the time the protocol was prepared, local conditions prompted the group to choose sclerotherapy instead of band ligation of varices.

The surgical procedure performed was esophagogastric devascularization with splenectomy. Surgery was performed at least 20 days after the most recent episode of variceal bleeding. Abdominal ultrasound with doppler was used to evaluate the presence or not of portal vein thrombosis (PVT). A preoperative control was followed by another exam at the immediate postoperative period (within 15 days of surgery) and at the 1-year follow-up visit. Endoscopic sclerotherapy of esophageal varices was systematically started 2 months after surgical intervention. After completing sclerotherapy, that was similar for both groups, patients were endoscopically controlled every six months during the whole follow-up period

All patients included in the trial were clinically evaluated every 3 months during the first year of follow up and every 6 months thereafter.

Statistical analysis

We calculated that a sample size of 62 patients would provide 95% power to detect a relative reduction in incidence of recurrent bleeding by at least 5% in favor of any of the treatment groups. The lost to follow-up rate was assumed to be 20%. All analyses were based on the intention-to treat principle and drop-outs (5 cases) were included in analysis When the assumptions of normality and homoscedasticity were met for data obtained from both groups (A and B), analysis of variance (ANOVA) and Tukey's multiple comparisons test were used for analysis. When these assumptions were rejected, the Kruskal-Wallis test and Dunn's multiple comparisons tests were used instead. Fisher's exact test was used for comparing the rates of recurrent bleeding between groups. The Wilcoxon test was used for comparing the size of esophageal varices before and after sclerotherapy, as the collected data did not meet parametric assumptions. A significance level of 0,05 with 2-sided testing was used.

The investigators conducted pre-specified interim analysis at 24 months after first patient in.

RESULTS

Pre-specified interim analysis at 24 months after inclusion of the first patient disclosed a rate of recurrent bleeding of 28.6% (7 of 25 patients) in group A (endoscopic treatment alone), *vs.* 9.0% (2 of 22 patients) in group B. Due to the unacceptably high rebleeding rate in group A, randomization was halted and the remainder of the study consisted of longitudinal follow-up of the patients included hitherto.

During the follow-up period, five patients (5/47) did not complete the proposed therapy regimen. Three patients in group A did not complete endoscopic sclerotherapy and in group B one refused and another one had incomplete sclerotherapy after the initial surgical intervention. They were considered non-compliant with the study treatment assigned. All patients maintained follow-up and analysis was performed as intention-to-treat.

The mean patient age was 38.9 ± 15.4 years, with a predominance of males in both groups. Patients in group A (n = 25) received endoscopic treatment alone, i.e. endoscopic sclerotherapy of esophageal varices, until eradication of varices. Patients in group B (n = 22) received surgical treatment, i.e. esophagogastric devascularization with splenectomy followed by endoscopic sclerotherapy of esophageal varices 2 months postoperatively, with follow-up every 6 months thereafter. Treatment efficacy outcome was assessed by the rate of recurrent esophageal variceal bleeding and comparison of the size of esophageal varices pre- and post-sclerotherapy. Medical records were reviewed for early and late complications related to study procedures. The mean length of follow-up was 38.61 ± 20.07 months (range, 24–72 months).

Table 1 shows the pre-treatment laboratory values of patients included in the study. Table 2 shows a comparison of recurrent bleeding rates in the trial groups (A and B). The frequency of UGIB recurrence was higher in group A (sclerotherapy alone) than in group B, where sclerotherapy was preceded by EGDS (9 of 25 [36.2%] *vs.* 2 of 22 [9.1%], p = 0.029).

Table 1. Statistical comparison of the baseline laboratory values in the studied groups.

Parameter	Group A (25) Mean ± SD	Group B (22) Mean ± SD	P
Hematocrit*	32.3 ± 7.0	30.8 ± 6.8	0.5235
Hemoglobin*	10.0 ± 2.4	9.6 ± 2.1	0.5705
White blood count*	3280 ± 1346	2587 ± 1285	0.1214
Platelets*	112989 ± 49324	102387 ± 51430	0.4765
INR**	1.29 ± 0.15 a	1.27 ± 0.11 a	0.6922
Albumin (g/dL)*	3.8 ± 0.5	3.7 ± 0.5	0.8863
AST*	38.8 ± 20.9	40.7 ± 23.8	0.7531
ALT**	31.1 ± 15.5	36.7 ± 21.9	0.4172
ALP**	155.1 ± 197.6	109.0 ± 50.5	0.8946
GGT**	51.5 ± 52.3	65.4 ± 60.1	0.7157
Bilirubin, direct**	0.39 ± 0.35	0.51 ± 0.67	0.4562
Bilirubin, indirect*+	0.65 ± 0.60	0.64 ± 0.44	0.5623

**Mean values followed by the same superscript letter were statistically similar (Tukey's test) (p < 0.05). **Mean values followed by the same superscript letter were statistically similar (Dunn's test) (p < 0.05). Group A: endoscopic sclerotherapy of esophageal varices alone. Group B: esophagogastric devascularization with splenectomy followed by sclerotherapy.*

Table 2. Clinical assessment of recurrent bleeding in the randomized trial groups.

	Group A (n = 25)	Group B (n = 22)	
Length of follow-up	47.2 ± 22.4	35.4 ± 19.6	
Recurrent bleeding			p-value
Present	9 (36.0%)	2 (9.0%)	0.029
Absent	16 (52.63%)	20 (90.9%)	

Group A: endoscopic sclerotherapy of esophageal varices alone. Group B: esophagogastric devascularization with splenectomy followed by sclerotherapy.

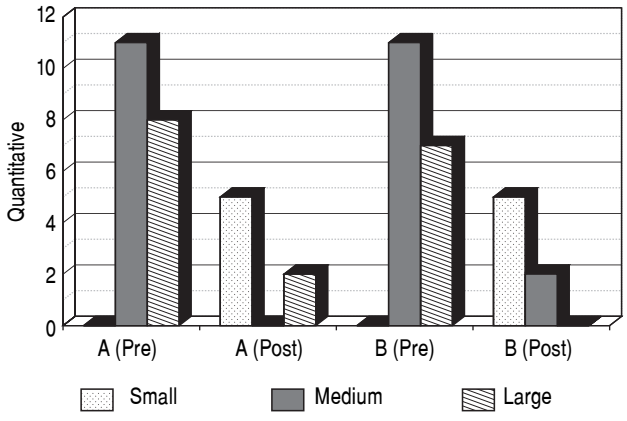

Figure 2. *Results of endoscopic examination of variceal size, pre- and post-treatment, in groups A, and B. Group A: endoscopic sclerotherapy of esophageal varices alone. Group B: esophagogastric devascularization with splenectomy followed by sclerotherapy. Before treatment, all patients had only medium- or large-sized varices. After treatment, small varices were seen in both groups, but large varices only after endoscopic treatment alone.*

The change in esophageal varix size over time (from baseline to the end of sclerotherapy) in both study groups is shown in figure 2.

On ultrasound examination, a greater frequency of grade II periportal fibrosis was found, with no between-group differences. The portal vein diameter ranged from 1.0 to 2.2 cm (mean, 1.42 ± 0.22 cm).

Analysis of complications in group A showed a high frequency of odynophagia and dysphagia, affecting 8 patients (36.0%), whereas esophageal ulcers were detected in two patients with UGIB, in addition to a single case of dissecting esophageal hematoma. The most common complication in the surgery group was ascites, which occurred in 8 patients (36%) and was easily addressed by diuretic therapy. Assymptomatic postoperative partial PVT occurred in 10 patients (45%) from group B; and 6 of them with early ultrasound diagnosis have received anti-coagulation. Complete recanalization of the portal vein was observed in eight patients, whereas two with a more extensive thrombosis did not recanalyze completely.

During the follow-up period only one patient in group B with incomplete sclerosis of esophageal varices experienced severe UGIB secondary to variceal rupture at 13 months and died. Therefore, the overall letality rate during the study was 2.1% (1/47).

DISCUSSION

This study used strict methodological criteria to ensure homogeneity across groups, as required in randomized trials. Therefore, patients with gastric varices were excluded, as they are not amenable to standard endoscopic treatment. Patients with platelet counts < 50 x 10^9/L or INR > 1.5., with higher bleeding risk during surgical treatment were also excluded from the trial.. Patients who met these "relative" criteria for exclusion were non-randomly allocated to a third group (a modified surgical treatment) as they were referred for standard treatment of UGIB at our Institution.

Nowadays band ligation is considered the best endoscopic therapy for the treatment of UGIB due to portal hypertension in cirrhosis.[19] In SPH a randomized trial comparing sclerotherpay with band ligation concluded that both treatments were equally effective in the eradication of esophageal varices.[20] The same Brazilian group studying the rate of bacteremia after both procedures neither found significant diferences.[21] As previous works associating surgical treatment were mainly with sclerotherapy,[9,14] this procedure was chosen to be performed during the trial. Besides that, ten years ago, when the protocol of this trial was written, the greater expertise of the local endoscopists was on sclerotherapy.

Randomization was halted due to significantly unfavorable outcomes in group A observed during pre-specified interim analysis. Nevertheless, a thorough follow-up of patients hitherto recruited for the study was performed. The occurrence of rebleeding increased from seven to nine cases in group A and remained the same in group B. Therefore, we had two groups of patients who had undergone treatment and long-term follow-up for observation of the initially proposed study outcomes, namely recurrence of upper gastrointestinal bleeding and change in size of esophageal varices as determined by endoscopic examination.

The endpoint chosen as the clinical criteria for treatment failure was recurrence of bleeding, whereas variceal eradication was the endoscopic parameter of effectiveness. There was a high prevalence of recurrent bleeding in group A (36.0%) as compared with groups B (9.0%) which demonstrates the poor efficacy of endoscopic sclerotherapy alone for management of SPH (p = 0.008). In a long-term follow-up study of nonsplenectomized patients undergoing sclerotherapy for eradication of esophageal varices, recurrence of EV was observed in 62% of patients , whereas another study of 204 patients subjected to endoscopic sclerotherapy, found a 46,6% rate of recurrent bleeding.[22]

Various studies have ascribed greater value to combined treatment –surgery plus endoscopic sclerotherapy– for prevention of recurrent bleeding in SPH, highlighting the importance of variceal eradication in the control of UGIB.[8,9,16] However, due to the absence of validated data, the consensus of the Brazilian Society of Hepatology (2010) recommends endoscopic band ligation alone or with beta-blockers for secondary prophylaxis of UGIB due to SPH, and advocate EGDS as the procedure of choice for surgical management of HSS.[23]

A review on management of SPH, has noted the lack of comparative studies[24] and the scarcity of appropriate methods for long-term assessment of late rebleeding.[25,26] This lack of data makes it difficulty to safely establish the optimal approach for SPH management. The identification of risk factors for portal hypertensive bleeding plays an essential role in the primary prevention of bleeding and in the prophylaxis of rebleeding, regardless of whether the etiology of PH is cirrhosis or schistosomiasis.[27-28]

In our study, analysis of the success of variceal eradication by examination of varices at baseline and immediately after the conclusion of sclerotherapy showed a significant reduction in the size of esophageal varices at the end of treatment in all groups (p = 0.0003). However, large varices were found only in two patients of group A (sclerotherapy alone). These cases were classified as treatment failures and referred for additional surgical therapy. This finding is similar to that of previous studies highlighting the importance of pre-sclerotherapy surgical intervention in the treatment of SPH.[22,26,30]

There were no between-group differences in serum enzyme measurements, despite isolated instances of altered GGT and ALP levels, which may be associated with changes in portal blood flow typical of HSS, as previously reported. Slight increases in bilirubin levels were also detected, as reported by other authors in cases of HSS.[31] Serum albumin levels were within normal limits and hypergammaglobulinemia was occasionally detected, indicating preservation of the liver's synthetic function and antigenic stimulation, as reported elsewhere in the literature.[7,32]

In our sample, baseline laboratory values showed major cytopenia as well as patients with platelet levels < 50 x 10^9/L and/or INR > 1.5, excluding 25 patients from the trial. These changes are probably attributable to congestive splenomegaly associated with secondary hypersplenism[33-35] or to increased consumption of coagulation factors due to shunting of flow to the collateral circulation, again secondary to hypersplenism.[33,36]

The high prevalence of portal vein thrombosis (45%) was common in patients who underwent EGDS, as expected, since it is recognized as the most common short-term complication of this procedure. On long-term follow-up, recanalization of the portal vein occurred in all patients. These data are consistent with the findings of

most authors, who have reported high rates of early thrombotic complications affecting the portal system after splenectomy, but despite this high incidence the clinical course is often benign.[37,38]

Several mechanisms may be involved in PVT pathogenesis, including reduced portal blood flow, worsening of venous stasis after ligation of portosystemic collaterals, and altered coagulability[39,40] although good evidence is still lacking.[34]

In conclusion this study showed that sclerotherapy alone is not an adequate treatment option for schistosomal portal hypertension, whereas sclerotherapy, preceded by esophagogastric devascularization with splenectomy constitutes a better therapeutic strategy for these patients. We could extrapolate that band ligation of varices, not evaluated in this trial, would be equally effective when preceded by surgical treatment.

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