

Primary prophylaxis of variceal bleeding in cirrhotics unable to take β -blockers: a randomized trial of ligation

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Accepted for publication 14 March 2005

SUMMARY

Aim: To compare endoscopic banding ligation vs. no treatment in cirrhotics with intolerance or contraindications to β -blockers for prevention of first bleeding in portal hypertension.

Methods: A sample size of 214 was planned with all sizes of varices. However, the trial was stopped due to increased bleeding in 52 patients in the ligation group. The baseline severity liver disease and endoscopic features were similar. Ligation group: 25 (M/F = 21/4, mean age: 60 ± 9.37 years); 27 not-treated group: 27 (M/F = 17/10, mean age: 63 ± 10.27).

Results: The mean follow-up period was 19.5 ± 13.3 months: five bled in the ligation group (20%), three from varices (two after banding at 11 and 17 days; one during the procedure), and two from gastropathy; two bled in the not-treated group (7% – two both varices) ($P = 0.24$). There were seven deaths in the ligation group and 11 in the not-treated group ($P = 0.39$).

Conclusion: Sixty per cent of the bleeding in the banding group was probably iatrogenic, requiring the study to be stopped. Endoscopic banding ligation was no better than no treatment. This study suggests that ligation may be harmful when used as primary prophylaxis, similar to prophylactic sclerotherapy in the past.

INTRODUCTION

The risk of first variceal bleeding in cirrhotics is related to liver dysfunction, large varices and endoscopic red signs.¹ The estimated probability of bleeding within 1 year for Child-Pugh grade A patients with large varices and moderate red signs is 24% compared with 20% for Child C patients with small varices and no red signs.² Thus some patients with small varices have an important risk of first bleeding. Indeed only 30% of patients who bleed have the worst risk

factors.² The effectiveness of primary prophylaxis depends on treating all patients at risk (providing therapy is safe), thus some trials have included those with small varices^{3, 4} or included only patients with small varices.⁵

Propranolol is the first choice prophylactic therapy. Sclerotherapy has been abandoned because the largest trial^{6, 7} and three others⁷ had increased mortality, as well as morbidity due to deep ulcers, with bleeding, stricture and perforation.^{6, 8} However, as endoscopic band ligation has replaced sclerotherapy for the prevention of rebleeding,⁹ with faster variceal eradication and reduced complications, it is used in primary prophylaxis and as alternative therapy to non-selective β -blockers.¹⁰

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In the 16 randomized trials, comparing ligation with no treatment (NT; $n = 7$),^{11–17} or β -blockers ($n = 9$),^{10, 18–25} only cirrhotics with large varices were treated with two exceptions.^{11, 18} Meta-analysis shows that ligation reduced both the risk of first portal hypertensive bleeding (OR, 0.25; 95% CI, 0.17–0.37) and mortality (OR, 0.42; 95% CI, 0.29–0.60) compared with NT, whereas ligation reduced the risk of first bleeding (OR, 0.59; 95% CI, 0.39–0.91), but not mortality (OR 1.03; 95% CI, 0.69–1.54) compared with β -blockers.

In these studies^{10–25} ligation appears safer than sclerotherapy. However, iatrogenic bleeding caused by ligation, as is the case with sclerotherapy, occurs: either due to oesophageal ulcers or during the procedure,^{10, 14, 16, 23, 25} and is sometimes life-threatening or fatal.¹⁰ When complications are reported, post banding ulcer is observed in the range of 0–80%,^{22, 25} retrosternal pain 6–33.3%,^{15, 22} throat pain 0–34.3%,^{16, 22} dysphagia 4–17%,^{16, 22} fever 0–11.4%,^{15, 22} aspiration pneumonia up to 1.5%¹⁴ and oesophageal perforation up to 2.9%.¹⁶

Our aim was to evaluate the effectiveness and safety of endoscopic banding ligation (EBL) in preventing first portal hypertensive bleeding in cirrhotic patients with intolerance or contraindications to β -blockers with varices of any size in a randomized trial vs. no therapy.

PATIENTS AND METHODS

The study was planned in 1998, approved by the Hospital Ethics Committee in early 1999 when four randomized studies^{11–13, 16} were published, two as abstracts, and started in late 1999.

Three centres contributed to this study: (a) Evangelismos Hospital, Athens, a tertiary referral centre for liver diseases, (planning of the study, patients' enrolment, follow-up and analysis of the data), (b) 'Polikliniki Hospital' a General City Hospital (patients' enrolment and follow-up), and (c) Royal Free Hospital, London a tertiary referral centre for liver diseases (planning of the study, randomization of the patients and analysis of the data).

All patients met the following inclusion criteria: (a) age >18 and <76 years, (b) varices of any size (assessed endoscopically by two independent observers; large varices: diameter of largest varix >5 mm – measured with open forceps and not disappearing on oesophageal insufflation; small varices: <5 mm diameter), (c) contraindication or intolerance to β -blocker therapy, (d) no prior bleeding from portal hypertensive sources, (e) no

previous prophylactic sclerotherapy or banding, (f) absence of terminal disease (likelihood of dying within 6 months), (g) ability to give written informed consent and (h) no contraindication to banding.

After a baseline endoscopy when varices were confirmed, written consent was obtained for enrolment and randomization to either banding or NT using sealed opaque envelopes, opened in numbered sequence, containing the allocated treatment (1:1 proportion) derived from a random number table using a blocked code.

Technique of EBL

Endoscopic banding ligation was performed as an outpatient procedure with midazolam 2.5–5 mg i.v. sedation, by four experienced endoscopists (100 ligation sessions each before the start of the study). The Multi-band Ligator 6 shooter (Wilson-Cook, Limerick, Ireland) was used with Olympus GIF 130 or GIF-Q160 EXERA endoscopes (Olympus Europa GmbH, Hamburg, Germany). Bands were placed starting at the gastro-oesophageal junction and then proximally in a helical fashion for approximately 5 cm, putting at least one band on each varix. The ligation sites were washed with water to check for bleeding. During subsequent sessions scheduled at 14-day intervals, the same procedure was used until the varices were too small to ligate (no effect of suction), i.e. varices were considered eradicated (interval to eradication calculated from first banding session).

Only varices without ulcers were banded – when healed banding was at next session. Vital signs were monitored for 2 h and liquid food was allowed from 6 h. Patients randomized to NT had yearly endoscopy and staging of liver disease.

Trial design and analysis

The end points were: (a) first episode of portal hypertensive bleeding (even if iatrogenic), (b) death, subdivided into bleeding related (within 6 weeks of bleeding) or not bleeding-related.

A sample size of 214 with an observation of 37 events was planned²⁶ based on an average variceal bleeding rate (at 2 years) of 24% in controls of β -blocker studies,²⁷ and average 10% bleeding rate with ligation from previous publications.^{16, 25}

Bleeding was considered to be portal hypertensive in origin when there was haematemesis or melaena, either

from a bleeding varix (active bleeding or a clot adherent to varix or variceal ulceration), portal hypertensive gastropathy, or presumed to be from these sources when there was no other visible lesion at endoscopy.

Non-portal hypertensive related bleeding was diagnosed when there was another lesion, e.g. peptic ulcer which had signs of bleeding in the absence of active bleeding from varices, a white nipple sign, or gastric mucosal bleeding. When in doubt endoscopy was repeated within 24 h.

Complications in the EBL group were as any symptoms reported by patients between endoscopy sessions, particularly dysphagia (liquids/solids), heartburn, chest pain or fever. Patients were asked to report these immediately.

Hepatic venous pressure gradient (HVPG) was measured at baseline. The technique has been described elsewhere.²⁸

The time intervals to first portal hypertensive related bleeding, and death were evaluated using Kaplan–Meier plots and differences tested using the log rank test. The number with bleeding and complications were compared using Fisher's exact test. According to the protocol, we evaluated the following variables at randomization in relation to the end points: age, sex, aetiology, endoscopic signs, laboratory indices, including Child-Pugh score. We evaluated the number of sessions to variceal obliteration and complications of EBL.

Data are shown as mean \pm SD, or median and range. A *P*-value < 0.05 was considered significant. Statistical analysis was made using Bio Medical Data Processing (BMDP, dynamic version 7; University of California, Los Angeles, CA, USA). The random effects model was the basis for meta-analysis.²⁹ Publication bias was assessed using the test for funnel plot for both bleeding and mortality.^{29, 30} Interim analysis was planned in 100 patients.

RESULTS

From December 1999 to November 2003, 239 patients with varices of any size and without previous of portal hypertensive bleeding were assessed for recruitment. From these 29 had contraindications and 34 intolerance to β -blockers, seven of which were critically ill and four gave no consent. Thus 52 were enrolled [Evangelismos Hospital ($n = 47$), Polikliniki Hospital ($n = 5$)]: 25 were randomized to EBL and 27 were controls (Figure 1). The trial was stopped in November 2003

due to twice as much bleeding than expected in EBL patients with some iatrogenic bleeding. As this trend was in the opposite direction from that expected, the clinicians, in the centres enrolling patients, asked the statistician (G.L.) to perform an unplanned interim analysis for those randomized to date. Following this, a new sample size calculation showed that between 300 and 2190 patients would be needed. If the bleeding rate of 20% with banding was to be maintained together with the expected rate of 24% with no therapy, then a sample size of 2190 (492 events) would be required²⁶ or if there were to be a bleeding rate of 15% with banding (i.e. slightly less than observed) and the expected 24% with no therapy this resulted in a new sample size of 300 (30 events). The clinicians felt the principle of 'primum non nocere' enshrined in Article 5 of the Helsinki Declaration would be breached by continuing the trial. Secondly, they considered the much larger sample size that would be required to test for differences. Thus a consensus decision was taken to stop randomization which was not challenged following consultation with the ethics committees of the major centre.

There were no significant differences in the severity and aetiology or endoscopic features at randomization (Tables 1 and 2). The mean HVPG was 16.7 ± 2.9 mmHg (7 NT) and 18.5 ± 3.5 mmHg (11 EBL) ($P = ns$).

Four patients were lost to follow-up: three before bleeding and death (two NT group at 12 and 13 months; one EBL group, at 10 months) and one, 6 months after variceal bleeding (EBL group). Two EBL patients refused continued participation, 1 month after randomization, neither bled, and both were lost to follow-up a month later, when follow-up was censored.

The mean follow-up in NT group was 20.6 ± 14.6 months, median: 17 (1–49) and in treatment group: mean 18.3 ± 11.8 months, median: 15 (1–43).

In the NT group, 17 had small varices (Child-Pugh A:4, B:7, C:6) and 10 large varices (Child-Pugh A:4, B:0, C:6). In the EBL group, 14 had small varices (Child-Pugh A:5, B:3, C:6) and 11 had large varices (Child-Pugh A:4, B:3, C:4).

First portal hypertensive bleeding

In the EBL group, five (20%) bled: three (12%) from varices and two (8%) from portal gastropathy who had varices eradicated (Table 3). In the NT group two (7.4%) bled from varices [one patient randomized in

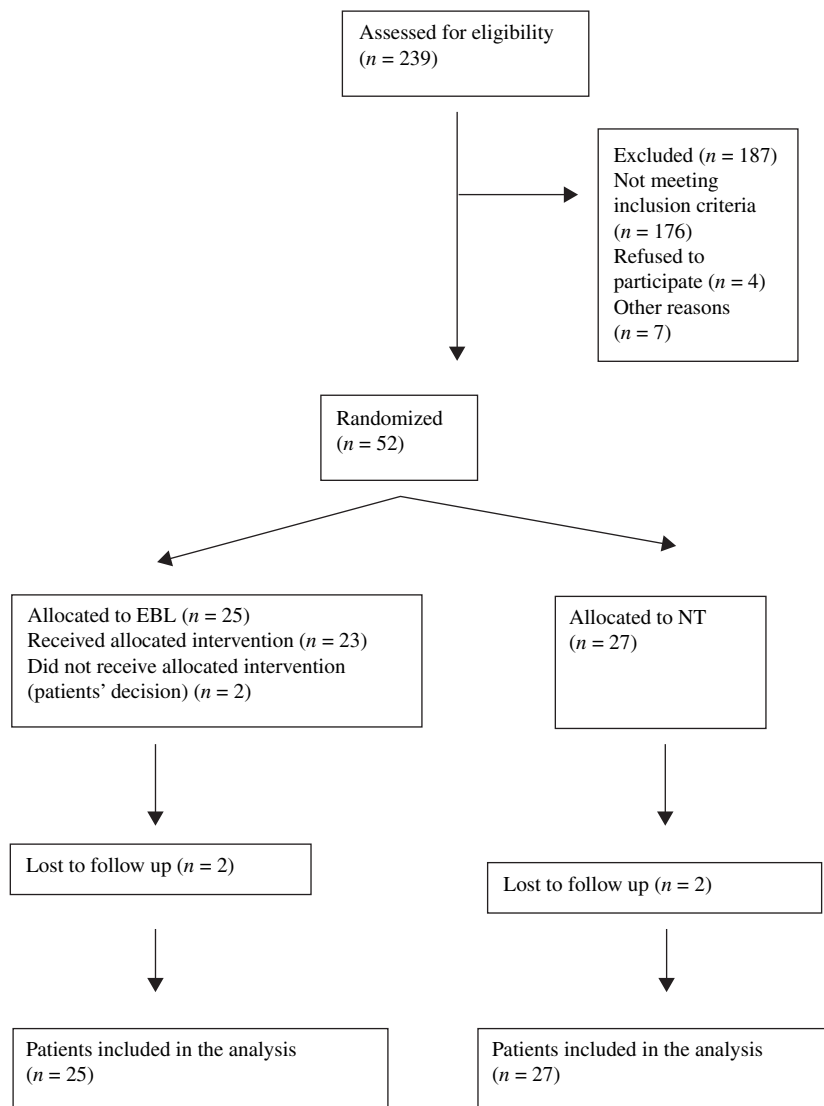


Figure 1. Flow diagram of the trial.

Polikliniki Hospital (NT group) had variceal bleeding, all the other bleeders were randomized in Evangelismos Hospital].

In the three EBL patients with variceal bleeding, the first bled during the second banding session just after the insertion of the endoscope and not following the banding suffering melaena, i.e. spontaneous variceal bleeding – transfused one unit of blood. A second variceal bleed occurred outside Greece – death occurred 14 months later. The second presented with haematemesis and melaena because of oesophageal varices confirmed at emergency endoscopy, but it was difficult to assess if there was also banding ulceration (17 days after the first banding session). He required seven units of blood and then was lost to follow-up 6 months later.

The third had haematemesis and melaena 11 days after the first banding session and had banding ulceration. He required nine units of blood; he is currently well. All three patients received sclerotherapy (the second patient with variceal bleeding was the only one requiring two sessions) combined with somatostatin;³¹ the portal gastropathy bleeders received somatostatin.^{32–34} Both the latter patients presented with only melaena and received three and one unit of blood respectively. They both subsequently bled from varices, which had recurred, the first 2 months later (refused to undergo endoscopic surveillance in the meantime and died 4 weeks after bleeding) and the second 4 months later, during continued prophylaxis with EBL (died 4 weeks later with hepatic encephalopathy).

Table 1. Clinical characteristics of the two trial groups (NT, no treatment; EBL, endoscopic banding ligation)

| | NT group | EBL group |
|-------------------------------------|--------------|--------------|
| Sex (M/F) | 17/10 | 21/4 |
| Age* | 63 ± 10.27 | 60 ± 9.37 |
| Aetiology | | |
| Alcohol | 9 | 9 |
| Viral | 7 | 11 |
| Other | 11 | 5 |
| Child-Pugh | | |
| A | 8 | 9 |
| B | 7 | 6 |
| C | 12 | 10 |
| Encephalopathy | 3 | 2 |
| Ascites | 19 | 11 |
| Varices size | | |
| Small/large | 17/10 | 14/11 |
| Red spots (yes/no) | 8/19 | 9/16 |
| Gastric varices | 1 | 2 |
| PT (%) (80–110%) | 61.5 | 62.1 |
| Bilirubin* (mg/dL) | 2.4 ± 1.29 | 2.6 ± 1.76 |
| (<1.0 mg/dL) | | |
| Albumin* (g/dL) | 3.1 ± 0.52 | 3.19 ± 0.72 |
| (3.5 – 5.0 g/dL) | | |
| PLT* (150–400 × 10 ⁹ /L) | 108 ± 50 | 99 ± 52 |
| HVPG* (mmHg) | 16.7 ± 2.9 | 18.5 ± 3.5 |
| (n = 7) | | (n = 11) |
| Fup* (months) | 20.6 ± 14.64 | 18.3 ± 11.82 |

* Mean ± SD.

Table 2. Child-Pugh grade, red signs and size of varices in randomized trial groups

| | Small varices | | Large varices | |
|--------------|-----------------|----------------|-----------------|----------------|
| | EBL (n = 14) | NT (n = 17) | EBL (n = 11) | NT (n = 10) |
| Child-Pugh A | 5 | 4 | 4 | 4 |
| Child-Pugh B | 3 | 7 | 3 | 0 |
| Child-Pugh C | 6 | 6 | 4 | 6 |
| Red signs | 3 | 1 | 6 | 7 |

NT, no treatment; EBL, endoscopic banding ligation.

The two variceal bleeders in the NT group had haematemesis and maelena. One received three units of blood and the other seven units. Currently one is well and one died due to intraperitoneal bleeding 11 months later. Secondary prophylaxis with EBL was given to both.

The cumulative bleeding curve (Figure 2) shows no significant difference between the two trial groups ($P = 0.18$).

Table 3. Episodes of portal hypertensive bleeding. Relation with the size of varices and the Child-Pugh score

| Bleeding | NT group | EBL group |
|---------------|--------------------------------|--------------------------------|
| Patients | 2 | 5 |
| First episode | 2 VB* | 3 VB†, 2 PHGB‡ |
| Small varices | Bleeding: 0/17, death: 7/17 | Bleeding: 1/14, death: 3/14 |
| Large varices | Bleeding: 2/10, death: 4/10 | Bleeding: 4/11, death: 4/11 |
| Child-Pugh A | 1/8 | 2/9 |
| Child-Pugh B | 0/7 | 2/6 |
| Child-Pugh C | 1/12 | 1/10 |

NT, no treatment; EBL, endoscopic banding ligation; VB, variceal bleeding; PHGB, portal hypertensive gastropathy bleeding.

* Neither had subsequent bleeding.

† One had a subsequent variceal bleeding episode.

‡ These two patients bled after eradication of varices and then subsequently had variceal bleeding following variceal recurrence.

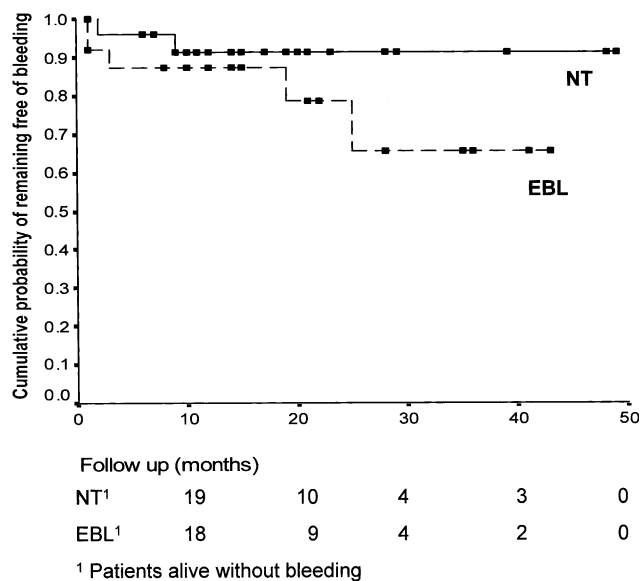


Figure 2. Cumulative proportion of portal hypertensive bleeding in the two groups of patients ($P = 0.18$).

Considering only the subgroup with small varices, none of 17 in the NT group bled, compared to 1 of 14 in the EBL group. In those with large varices 2 of 10 bled in the NT group compared with 4 of 11 in the EBL group (Table 3).

Obliteration of varices and variceal recurrence

Initial variceal obliteration was achieved in 20 patients: three bled from varices before eradication, two refused

continued participation. Median time to obliteration was 28 (14–101) days; median endoscopy sessions 3 (1–5); median banding sessions 2 (1–4) and median bands 5 (2–20) (mean: 7 ± 4.68) [median 4 (2–7)/session]. Oesophageal varices recurred after initial obliteration in seven (35%) patients [median 11.6 (5.4–24.4) months] and were re-obliterated [median: 1 (1–3) banding sessions]. Small varices were obliterated using median 1 (1–4) sessions and large varices median 2 (1–3) sessions; Child-Pugh grade A, median 2 (1–4), grade B, median 2 (1–3) and grade C, median 1 (1–3) sessions. Variceal recurrence occurred in 3/11 with small varices and in 4/8 with large varices.

In 23 with banding complications (Table 4) one (4%) had fever and nine (39%) had ulcers (7/14 with small varices and 2/11 with large varices). Only two of nine with banding ulcers had no bands placed during the subsequent endoscopic session. No EBL group patient developed new gastric varices.

Mortality

The Kaplan–Meier survival plots (Figure 3) show no significant difference between trial groups with 7/25 (28%) dying in the EBL and 11/27 (41%) in the non-treatment group ($P = 0.49$). The causes of death were: NT group: six liver failure, one hepatorenal syndrome, two HCC, one intraperitoneal bleeding and one infection; EBL group: three subsequent variceal bleeding, three liver failure and one hepatorenal syndrome. In the NT group, seven died (five grade C) from 17 with small varices, and four (three grade C) from 10 with large varices. In the EBL group three died (two grade C) from 14 with small varices, and four (two grade C) from 11 with large varices.

Table 4. Complications in the endoscopic banding ligation (EBL) group (23 of 25 patients)*

| Complications | EBL | | |
|---------------------|---------------|---------------|---------|
| | Small varices | Large varices | Total |
| Dysphagia (solids) | 3 (13) | 3 (13) | 6 (26) |
| Dysphagia (liquids) | 2 (8.7) | 2 (8.7) | 4 (17) |
| Heartburn | 9 (39.2) | 4 (17.4) | 13 (57) |
| Chest pain | 3 (13) | 2 (8.7) | 5 (22) |
| Fever | 0 (0) | 1 (4.4) | 1 (4) |
| Ulcers | 7 (30.5) | 2 (8.7) | 9 (39) |

Values within parenthesis are expressed as percentage.

* Two patients never received banding.

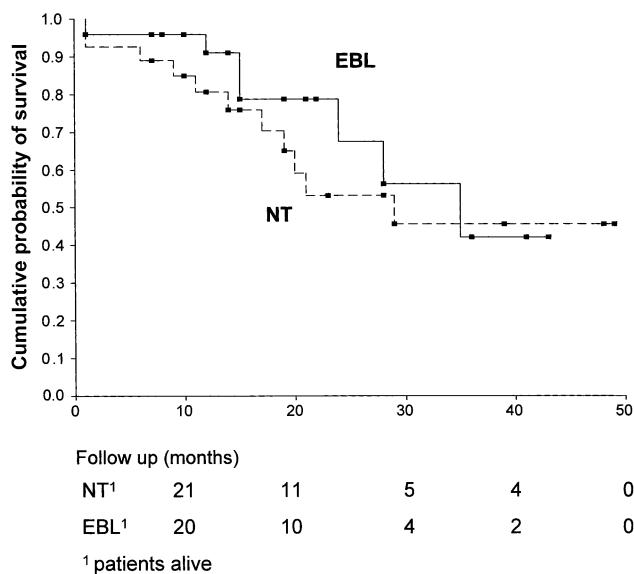


Figure 3. Survival curve in two trial groups ($P = 0.49$).

DISCUSSION

In this randomized study we evaluated EBL prevention of first portal hypertensive bleeding in cirrhotics intolerant or with contraindications to β -blockers. Compared with the previous seven randomized trials of EBL vs. NT, our study (52 patients) is the second smallest (as we stopped the trial), but it had 42% Child-Pugh grade C patients –the highest proportion amongst all 16 primary prevention trials using ligation [median: 26% (11.8–38%)]. The small sample size means there is lack of precision because of reduced statistical power. The median 15 (1–49) months follow-up was similar to the 16 studies [median: 14 (12–34.4)]. Although the variceal bleeding rate in our EBL group was 12%, comparable to other trials (mean $11.3 \pm 8.5\%$), the overall bleeding rate was 20% because of portal hypertensive bleeding in two patients after variceal eradication. The latter may be due to the large proportion of Child C patients as EBL may be more effective in patients with good liver function.¹³ Moreover at least two, and possibly three variceal bleeding episodes in the ligation group were iatrogenic, with two bleeding before variceal eradication and one during endoscopy. This raises concerns for the safety of ligation for primary prophylaxis of variceal bleeding.

Only 9 of 16^{10, 12, 14, 16, 17, 20, 22, 23, 25} randomized studies report information on bleeding during the procedure or related to ulcer formation.

Figure 4. Meta-analysis plot of trials of banding ligation of oesophageal varices vs. no therapy. Portal hypertensive bleeding (NT, no treatment; EBL, endoscopic band ligation). Data are expressed as OR (95% CI) in a log scale.

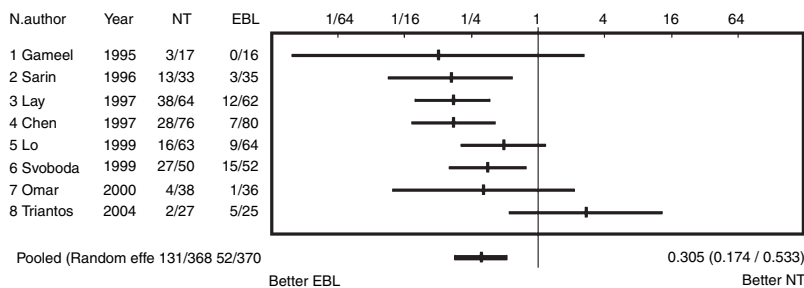
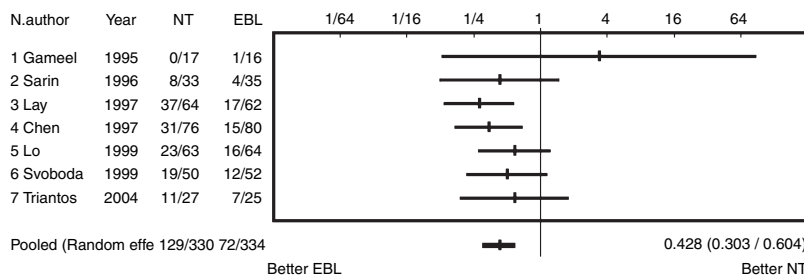


Figure 5. Meta-analysis plot of trials of banding ligation of oesophageal varices vs. no therapy. Survival (NT, no treatment; EBL, endoscopic band ligation). Data are expressed as OR (95% CI) in a log scale.



Our results underscore these observations. In these nine studies, four^{12, 17, 20, 22} reported no bleeding due to procedures or ulcers, whereas five reported 26–100% amongst those who bled.^{10, 14, 16, 23, 25} In the most recent trial,¹⁰ three of five bleeding episodes related to banding were severe (one life-threatening; two fatal).

In our trial the mortality rate was not significantly different, with no deaths related to first bleeding, despite the higher proportion of grade C patients whereas in previous trials bleeding related deaths occurred in up to 60% (EBL) and up to 80% (NT/propranolol).

In the meta-analysis (Figures 4 and 5) comparing banding vs. NT, including our trial there was no statistical heterogeneity for either mortality or bleeding. The funnel plot for mortality (Figure 6) showed asymmetry ($P = 0.04$), suggesting that studies with a worse mortality are likely not to have been published.

We used the same banding technique previously described, achieving a similar average interval to variceal obliteration.^{14, 16, 20, 25} A trend was seen to more recurrence with large varices (4/8 large vs. 3/11 small varices); perhaps large varices require more surveillance after eradication.

Fewer bands were used to obliterate varices (median: 7) compared with other studies,^{10, 14, 16} despite small varices requiring a similar average number as large varices. The latter may explain why postbanding ulcers were more frequent with small than large varices; more surrounding variceal mucosa is drawn up into the banding device.

In the other 16 studies eradication was between 80 and 100%; mean sessions to obliteration were two to four, mean time to obliteration was between 29 and 75 days, mean number of bands was 8.6–10.8. Variceal recurrence was 20–75%, recurring between a mean of 3.7–11.2 months. The mean number of banding sessions after recurrence was between 1.2 and 1.4, and new gastric varices occurred between 1 and 12%.

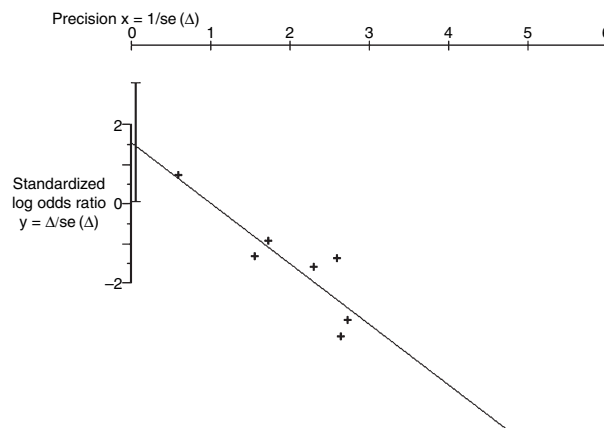


Figure 6. Funnel plot of the standardized estimates of log odds ratios for survival (y -axis) and precision (x -axis) of the randomized studies ($\alpha = 1.56$, 95% CI = 0.06–3.05, $P = 0.04$)⁺.
⁺In the absence of publication bias, the intercept of the regression line should be at zero, with the 95% confidence interval straddling the zero mark. If the 95% CI does not straddle zero, publication bias is very likely.

No patient with small varices had variceal bleeding with ligation, but one bled from portal hypertensive gastropathy (EBL group). The other patients who bled all had large varices, five with variceal bleeding (three EBL, two NT) and one with portal gastropathy (EBL). May be bleeding induced by ligation is more likely with large varices but this cannot be proved by our study. Banding did not cause bleeding in patients with small varices, who had a similar severity of liver disease as those randomized to NT – this could have occurred by chance.

Only 5 of 16 trials comment specifically on bleeding from portal gastropathy and/or gastric varices despite the report that rapid variceal eradication¹³ may lead to portal hypertensive gastropathy. Bleeding during ligation studies should consider all sources of portal hypertensive bleeding as a primary end point; it is not clear if this has always been the case.

In our study variceal ligation caused bleeding. Indeed the bleeding rate in the ligation group was so much higher than expected (whereas it was not increased in the NT group), that the trial was stopped, considering that two and may be all three variceal bleeding episodes were iatrogenic. Too large a sample size would have been required to evaluate the estimated differences in bleeding if maintaining the expected bleeding rate of 24% in the non-treated group, even if no further excess bleeding was to occur in the ligation group. Another study¹⁰ was recently stopped prematurely as there was no difference in bleeding rates between banding and propranolol after randomization of half the estimated number of patients (too large sample size would have been needed to achieve statistically significant differences).

However, once obliteration was achieved, no variceal bleeding episodes were observed and mortality was similar in the two groups. This is the first study showing that variceal ligation for primary prevention of variceal bleeding may not be as safe as has been previously thought, similar to sclerotherapy in primary prophylactic trials. We suspect banding-induced bleeding is under-reported and we would urge other investigators who may have data from unpublished trials to place data in the literature.

ACKNOWLEDGEMENTS

Dr C. K. Triantos received a scholarship from the Hellenic Association for the Study of the Liver (2003).

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