Emergency management of bleeding esophageal varices: Drugs, bands or sleep?

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BM Yan, SS Lee. Emergency management of bleeding esophageal varices: Drugs, bands or sleep? Can J Gastroenterol 2006;20(3):165-170.

Variceal bleeding is a severe complication of cirrhosis leading to significant morbidity and mortality. Treatment of acute variceal bleeding has improved dramatically since the era of the mechanical balloon tamponade. These advances include endoscopic band ligation or sclerotherapy, and vasoactive pharmacological options such as somatostatin, octreotide, vasopressin and terlipressin. Evidence from a multitude of clinical trials and meta-analyses comparing endoscopic and pharmacological treatments suggests near equivalence in efficacy for initial hemostasis, mortality and rate of rebleeding. This raises the question of whether on-call gastroenterologists should be performing emergency endoscopic treatment in the middle of the night or start pharmacological treatment and delay endoscopy until optimal patient and working conditions the next morning. The present review analyzes the available comparative data between endoscopic and pharmacological treatment options. Although the literature cannot yet definitively answer the question posed, the authors suggest that delaying endoscopic treatment until the next morning may be the most reasonable practical approach.

Key Words: *Acute variceal bleeding; Band ligation; Octreotide; Sclerotherapy; Somatostatin; Terlipressin; Vasopressin*

Le traitement d'urgence des hémorragies oesophagiennes variqueuses : les médicaments, la ligature élastique ou le sommeil?

Les hémorragies variqueuses sont une complication grave de la cirrhose, associées à une morbidité et à une mortalité importantes. Le traitement des hémorragies variqueuses aiguës s'est considérablement amélioré depuis l'arrivée de la tamponnade mécanique par ballonnet. Les progrès réalisés dans le domaine comprennent la ligature élastique endoscopique et la sclérothérapie ainsi que les médicaments à action vasomotrice comme la somatostatine, l'octréotide, la vasopressine et la terlipressine. Des données provenant de plusieurs essais cliniques et de méta-analyses et comparant les interventions endoscopiques au traitement médicamenteux semblent indiquer que les deux approches donnent des résultats quasi équivalents en ce qui concerne l'efficacité de l'hémostase initiale, la mortalité et le taux de récidive hémorragique. L'observation soulève toute la question du traitement, notamment de la conduite à tenir par les gastro-entérologues de garde : vaut-il mieux pratiquer une intervention endoscopique d'urgence au beau milieu de la nuit ou prescrire un traitement médicamenteux et reporter l'endoscopie au lendemain matin lorsque le patient est en meilleur état et les conditions de travail, plus appropriées ? Le présent article passe en revue les données disponibles comparant les interventions endoscopiques au traitement médicamenteux. Même si la documentation ne fournit pas de réponse définitive à la question, les auteurs croient que le report de l'endoscopie au lendemain matin serait peut-être la meilleure conduite à tenir.

Macbeth: I am in blood
Stepp'd in so far that; should I wade no more
Lady Macbeth: You lack the season of all natures, sleep.

–William Shakespeare, Macbeth

How prescient of the Great Bard to foresee one of the frequent dilemmas of modern gastroenterology: when the emergency room physician calls late at night with a consultation request for the acute variceal bleeder, should one go in immediately to endoscopically treat the varices or recommend vasoconstrictive drugs, return to sleep and perform the endoscopy the next morning? Indeed, recent studies have confirmed the chronobiological basis for a phenomenon that generations of on-call gastroenterologists have known about: varices rupture most often during the morning and late evening. These periods correspond to peaks in the circadian rhythm of portal pressure (1,2).

Many strides in therapy have been made in recent years resulting in improved mortality after variceal bleeding (3). In-hospital mortality from acute variceal bleeding has significantly improved from over 40% in 1980 to 14% in 2000. This is due to a combination of decreased rebleeding and bacterial infection rates. On multivariate analysis, endoscopic and antibiotic treatments were independent predictors of survival. Endoscopic therapy has gained widespread application from 6% in 1980 to 90% in 2000, of which 81% of procedures were performed in the first 24 h (3).

Recent guidelines (4-8) have been endorsed by the American College of Gastroenterology, which include both endoscopic and pharmacological treatments. Endoscopic treatment, mainly variceal band ligation or sclerotherapy, has proved to be effective in controlling acute variceal bleeding. A recent survey of American College of Gastroenterology members showed that 40.8% of members used band ligation, 36.3%

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TABLE 1
Endoscopic treatment options

	Band ligation	Sclerotherapy
Efficacy, %		
Initial hemostasis	80 to 100*	76 to 92
Rebleeding	6 to 30†	16 to 53
Mortality	19 at 30 days‡	35 at 30 days
Contraindications	Heavily scarred mucosa from previous treatments	Previous deep ulcerations from sclerotherapy
Complications		
Total	5%	29%
	Esophageal ulcer	Aspiration
	Bacterial peritonitis	Empyema
		ARDS
		Esophageal ulcer
		Esophageal stricture
		Perforation
		Peritonitis
		Mediastinitis
		Sepsis
Cost§	Cook (USA) multiband six shooter: $200	Tetradecyl 2 mL vial (60 mg): $5
		Marcon-Haber varices injector: $95
Comments	Expertise required	Technically easy
	Limited viewing field	Improved visualization

*Data from references 16 and 17. *OR 1.14, 95% CI 0.44 to 2.90 (versus sclerotherapy); †OR 0.52, 95% CI 0.37 to 0.74 (versus sclerotherapy); ‡OR 0.67, 95% CI 0.46 to 0.98 (versus sclerotherapy); §Calgary Health Region costs in Canadian dollars. ARDS Acute respiratory distress syndrome*

used sclerotherapy and 6.2% used both modalities emergently for variceal bleeding. Octreotide was used in only 52.6% of patients on index bleeding and vasopressin in 9.6% (7).

Multiple pharmacological options are now available (9,10). Recent studies have shown that it may be as effective as emergency endoscopic treatment and, therefore, may be appropriate as first-line treatment. It is unclear whether emergency endoscopic treatment is more effective than initial pharmacological treatment with delayed endoscopic therapy. The present review summarizes the available evidence for the initial treatment of acute variceal bleeding.

ENDOSCOPIC TREATMENT OPTIONS

Sclerotherapy versus band ligation

Endoscopic sclerotherapy (ESL) was the first available endoscopic therapy for bleeding varices (Table 1). It involves the injection of a sclerosant agent (100% ethanol, ethanolamine, polidocanol or sodium tetradecyl sulfate) into or adjacent to a varix with the goal of obliteration through irritation and thrombosis. Previous studies (11) have shown its efficacy in controlling variceal hemorrhage, reducing rebleeding and need for blood transfusions, and possibly reducing mortality. The complications related to ESL are significant, including large, deep esophageal ulcerations, strictures, mediastinitis, pleural effusions, sepsis and death.

Endoscopic variceal band ligation (EBL) is an attractive first-line therapy because of its improved efficacy and complication profile compared with ESL. Several randomized controlled trials have compared EBL with ESL in acute variceal bleeding. Gimson et al (12) reported the safety and effectiveness of EBL. In that study, 103 patients were randomly assigned to band ligation or sclerotherapy, of whom 39% and 47%, respectively, had active bleeding at index endoscopy. Both methods were equally effective in controlling initial hemorrhage (91% versus 92%). Rebleeding was significantly less in the EBL group, but other outcomes and complication rates were similar. Sarin et al (13) randomly assigned 95 patients to EBL or ESL and showed 86% versus 80% (not significant) efficacy, respectively, in initial hemostasis. The EBL group had significantly less rebleeding, development of portal hypertensive gastropathy and variceal recurrence. Lo et al (14) showed superiority of EBL versus ESL for initial control (97% versus 76%), one-month treatment failure (8% versus 30%), blood transfusions and complication rates (5% versus 29%). There was a trend toward a one-month mortality benefit (19% versus 35%, P=0.19). Laine et al (15) showed improved rebleeding rates (26% versus 44%) and decreased complications (0% versus 33%) in favour of EBL over ESL.

Two meta-analyses of EBL and ESL have been completed. Gross et al (16) showed no significant difference between EBL and ESL for initial hemostasis (91% versus 81%, respectively). Laine and Cook (17) showed a significant benefit of EBL over ESL for reduction in rebleeding rate (OR 0.52, 95% CI 0.37 to 0.74, number needed to treat=4), overall mortality rate (OR 0.67, 95% CI 0.46 to 0.98, number needed to treat=10) and mortality due to bleeding (OR 0.49, 95% CI 0.24 to 0.996). Esophageal strictures were less frequent in EBL (OR 0.1, 95% CI 0.03 to 0.29), but no other differences in complications were found.

On the basis of equal or superior efficacy in initial hemostasis, improved rebleeding rate, decreased complication rates and possible mortality benefit, EBL should replace ESL as first-line endoscopic treatment.

Other techniques

Other viable techniques for hemostatic control include endoscopic clip or loop placement. Small, randomized trials (18,19) suggest promise with these options. These therapies may be possible first-line options if larger, randomized trials confirm their efficacy and safety. Cyanoacrylate glue injection is generally reserved for gastric variceal treatment. Previous small studies (20) have shown its effectiveness in esophageal varices; however, serious complications including distal embolization causing stroke, pulmonary embolus and mesenteric thrombosis have limited its use.

PHARMACOLOGICAL TREATMENT OPTIONS

Somatostatin and analogues

Somatostatin and its longer-acting analogues (octreotide and vapreotide) decrease portal pressure by reducing portal flow secondary to splanchnic vasoconstriction (Table 2). Results from randomized controlled trials (21,22) conflict about the efficacy of somatostatin versus placebo. A meta-analysis by Gotzsche et al (23) showed no significant benefit over placebo for hemostasis or 30-day mortality.

Octreotide has been studied extensively but no true placebo-controlled trial has been published, because all trials included adjunctive endoscopic therapy. A meta-analysis by Corley et al (24) showed improved hemorrhage control compared with

TABLE 2
Somatostatin and analogues

	Somatostatin*	Octreotide†	Vapreotide‡
Dose and duration	250 μg IV bolus then 250 μg/h infusion × 24 h to 168 h	50 μg to 100 μg IV bolus then 25 μg/h to 50 μg/h infusion × 24 h to 120 h	50 μg IV bolus then 50 μg/h x 120 h
Efficacy, %			
Initial hemostasis	60 to 92	84 to 95	69
Rebleeding	15	19 (0.46, 0.32 to 0.67)§	16 at 42 days
Mortality	9 to 38 at 42 days (1.16, 0.67 to 2.01)§	31 at 60 days (0.81, 0.48 to 1.35)§	14 at 42 days
Complications			
Total, %	6.5	26	6
Severe	Virtually none compared with placebo	Pneumonia Cardiac arrythmia Paralytic ileus Pulmonary edema	No difference in major adverse events compared with placebo
Moderate/mild	Abdominal pain	Hyperglycemia	Hyperglycemia
Diarrhea	Diarrhea Hot flushes	Abdominal cramps Abdominal pain Nausea Encephalopathy Headache Infection	
Cost¶	3 mg vial: $220.50 (wholesale cost)	50 μg ampule: $4.99 100 μg ampule: $9.42 500 μg ampule: $44.27	Not available
Comments	Conflicting RCTs No significant difference compared with placebo on meta-analysis	All trials included endoscopic treatment initially or after 48 h	All patients received endoscopic treatment in 12 h

*Data from references *21-23,33; †33,34,37; and ‡25. §RR versus placebo, 95% CI; ¶Calgary Health Region costs in Canadian dollars. IV Intravenous; RCT Randomized controlled trial*

alternative medical treatment, similar efficacy to immediate sclerotherapy and fewer major complications than with vasopressin/terlipressin. No mortality benefit was shown. Not included in the initial analysis was a large trial of octreotide versus placebo published only in abstract form. This did not show a benefit for octreotide alone but did improve the results of endoscopic therapy. Including the present study into a secondary analysis did not significantly change the conclusions.

Vapreotide, another somatostatin analogue, in combination with endoscopic therapy improved hemostasis and survival compared with endoscopic treatment alone in one study (25). This drug is not yet available in North America.

Vasopressin and analogues

Vasopressin and its analogues produce systemic and splanchnic vasoconstriction, thereby reducing portal hypertension (Table 3). A meta-analysis by D'Amico et al (26) showed a significant benefit for vasopressin compared with placebo for hemostasis (OR 0.22, 95% CI 0.12 to 0.43) but no mortality benefit. Because of significant side effects including myocardial infarction, mesenteric ischemia and death, vasopressin monotherapy is not recommended.

Terlipressin, a longer-acting vasopressin analogue, decreases portal and variceal pressure with fewer side effects than vasopressin. Ioannou et al (27) completed a systematic review of terlipressin, including 20 randomized trials with 1609 patients. Compared with placebo, terlipressin reduced mortality (RR 0.66, 95% CI 0.49 to 0.88), improved hemostasis (RR 0.63, 95% CI 0.45 to 0.89) and reduced emergency procedures or rebleeding. In addition to sclerotherapy, terlipressin improved hemostasis (RR 0.75, 95% CI 0.58 to 0.96) and showed a trend toward mortality benefit (RR 0.74, 95% CI 0.53 to 1.04). No significant differences were found between terlipressin and balloon tamponade, sclerotherapy, somatostatin, octreotide or vasopressin for mortality, failure of hemostasis, rebleeding and procedures for uncontrolled bleeding. The one exception was the reduced failure of hemostasis favouring octreotide (OR 1.62, 95% CI 1.05 to 2.50). However, this finding was based on three low-quality randomized controlled trials involving 203 patients. No difference was found in adverse events compared with any group.

Activated recombinant factor VII

Correction of coagulopathy may be beneficial in those who fail conventional therapy. In a small, open-label series of eight patients with refractory variceal bleeding, a single intravenous dose of recombinant activated factor VII achieved hemostasis in all cases (28). Larger, randomized trials are required before any conclusions can be drawn about the usefulness of this expensive drug.

TABLE 3
Vasopressin and analogues

	Vasopressin*	Terlipressin†
Dose and duration	0.4 U IV bolus then 0.2 U/min to 1.0 U/min × 72 h	1 mg to 2 mg IV every 4 h × 24 h to 168 h
Efficacy, %		
Initial hemostasis	0 to 80	81 (0.66, 0.53 to 0.82)‡
Rebleeding	4.8	14 (0.99, 0.60 to 1.61)‡
Mortality	36	25 at 42 days (0.66, 0.49 to 0.88)‡
Complications		
Total, %	46 (monotherapy)	20
Severe	Death (3%)	Limb ischemia
	Cardiac ischemia/ arrhythmia	Hyponatremia
	Mesenteric ischemia	Seizure
	Limb ischemia	Cardiac ischemia/ arrhythmia
	Stroke	Congestive heart failure
	Bronchial constriction	Hypertension
Moderate/mild	Headache	Auricular fibrillation
	Abdominal pain	Abdominal pain
	Nausea/vomiting	Skin lymphangitis
	Tremor	Nausea
	Urticaria	Fever
	Diaphoresis	
Cost§	1 mL (20 U/mL): $12.55 5 mL (20 U/mL): $42.55	Not available in North America except on compassionate release
Comments	Significant side effects because monotherapy limits its use	Only pharmacological agent shown to reduce mortality compared with placebo (RRR 34%)
	Combination with nitroglycerin attenuates side effects but has not been shown to improve control of bleeding or mortality	

*Data from references *26,38-40 and †27,31; ‡RR versus placebo, 95% CI; §Calgary Health Region costs in Canadian dollars. IV Intravenous; RRR Relative risk reduction*

ENDOSCOPIC VERSUS PHARMACOLOGICAL TREATMENT

Is endoscopic treatment superior to pharmacological treatment for acute variceal bleeding (Table 4)? All published studies have compared sclerotherapy with pharmacological therapy. No studies to date have directly compared emergency variceal band ligation with pharmacological therapy.

A Cochrane meta-analysis by D'Amico and colleagues (29) has addressed this issue. Fifteen studies were included: one compared sclerotherapy with vasopressin plus nitroglycerin, one with terlipressin, five with somatostatin and eight with octreotide. Sclerotherapy was not superior to terlipressin, somatostatin or octreotide for any outcome. Sclerotherapy was superior to vasopressin for control of bleeding and was associated with more adverse events than somatostatin. Combining all trials irrespective of control treatment did not result in any difference for failure of hemostasis, mortality or adverse events.

TABLE 4
Summary of endoscopic versus pharmacological treatment

	EBL (%)	ESL (%)	SMS (%)	OCT (%)	VP (%)	TLP (%)
Initial hemostasis	80–100	76–92	60–92	84–95	60–80	80
Rebleeding	6–30	16–53	15	19	4.8	14
Mortality	19	35	9–38	31	36	25

EBL Endoscopic band ligation; ESL Endoscopic sclerotherapy; OCT Octreotide; SMS Somatostatin; TLP Terlipressin; VP Vasopressin

The authors concluded that emergency sclerotherapy should not be first-line treatment for variceal bleeding and might be useful only in pharmacological failures.

Gross et al (16) concluded in a meta-analysis that band ligation appeared to be the most effective treatment and significantly more successful than pharmacological treatment for hemostasis (91% versus 61% to 83%). Banding was not statistically better than sclerotherapy. Sclerotherapy was not statistically better than pharmacological therapy.

Further studies of band ligation versus pharmacological treatment, both individually and in combination, need to be completed to definitively answer the question of optimal therapy.

COMBINATION ENDOSCOPIC AND PHARMACOLOGICAL TREATMENT

Banares et al (30) assessed the role of endoscopic plus pharmacological treatment versus endoscopic treatment alone for acute variceal bleeding. Eight studies with 939 patients were included in this meta-analysis. Sclerotherapy and band ligation were included with somatostatin, octreotide or vasopressin. Initial (RR 1.12, 95% CI 1.02 to 1.23) and day 5 hemostasis (RR 1.28, 95% CI 1.18 to 1.39) favoured combination therapy. Mortality was not significantly different (RR 0.73, 95% CI 0.45 to 1.18).

The combination of terlipressin with sclerotherapy is also superior to sclerotherapy alone for initial hemostasis, number of emergency procedures required and rebleeding (27). There was a trend toward a mortality benefit for combination therapy (RR 0.74, 95% CI 0.53 to 1.04). No trials have assessed combination endoscopic and pharmacological treatment versus pharmacological therapy alone.

DELAYED ENDOSCOPIC THERAPY: CAN OR SHOULD WE WAIT?

As asked in the introduction, should definitive endoscopic variceal eradication be done emergently, or delayed and completed electively? Targeted therapy is intuitively more effective if done with a clear, bloodless field of view in a hemodynamically stable patient. To date, however, the literature does not allow a definitive conclusion on this issue. In part, this is due to a heterogeneous definition of 'emergency' endoscopy. In the study by Lo et al (14), 42 of 71 patients had emergency endoscopy within 6 h of admission and all others within 12 h. Emergency endoscopy by Laine et al (15), however, was within 24 h of admission (of note, with no vasoconstrictive medical treatment). Gimson et al and (12) and Sarin et al (13) did not specify their time to endoscopy. Mean time to endoscopic treatment has not been specified by any of these studies. In the terlipressin versus sclerotherapy study (31), time to random assignment and sclerotherapy was 6 h. The meta-analysis by Gross et al (16) had times to endoscopy ranging from less than 3 h to less than 24 h after admission. In the European acute bleeding oesophageal

variceal episodes study (32), sclerotherapy was performed within 8 h of presentation and was significantly easier to perform after somatostatin. Studies with octreotide by Hadengue (33) and Sung et al (34) delayed sclerotherapy for 48 h with no difference in control of bleeding or mortality. It is difficult, therefore, to define what entails 'emergency'. Endoscopy less than 6 h from admission may be an appropriate definition of 'emergency', less than 48 h as 'urgent' and more than 48 h as 'elective'.

The only study to directly address timing was by Shemesh et al (35), who analyzed whether emergency sclerotherapy was more effective than stabilization and elective sclerotherapy. Eighty-four patients with active variceal bleeding were randomly assigned to emergency sclerotherapy (within 6 h of presentation) or delayed (24 h to 48 h from presentation) depending on time of presentation. Those presenting from Sunday to Friday between 08:00 and 20:00 received emergency sclerotherapy. All others were delayed and received balloon tamponade and vasopressin, with sclerotherapy performed 24 h to 48 h after presentation. Emergency therapy stopped all acute bleeding and resulted in decreased rebleeding in hospital (4.7% versus 17.1%, P=0.027) and by one year (7.0% versus 17.1%, P=0.027). There was an insignificant trend showing improved mortality in hospital and at one, three and five years after follow-up in the emergency sclerotherapy group. Total mortality was 33% in the emergency group and 44% in the delayed group (P=not significant). The study would have been improved with a true randomized protocol rather than with a selection of a treatment group based on weekday and diurnal timing.

Given the similar efficacy for hemostatic control and mortality between pharmacological therapy and ESL, it seems reasonable to delay endoscopic treatment until optimal conditions or pharmacological failure occurs. Early endoscopic variceal banding may prove to be superior to pharmacological treatment, but direct comparison has not been evaluated.

LIMITATIONS

There are several limitations to the present review, because comparisons among studies are problematic. Differences in patient population (Child-Pugh class, etiology of cirrhosis, etc) may affect mortality data. Definitions for initial hemostasis range from 15 min to 72 h (16), which therefore affects definitions of rebleeding. Efficacy data for hemostasis must, therefore, be analyzed carefully and may not be directly comparable. Fortunately, more recent studies of variceal bleeding usually use consensus definitions of parameters such as hemostasis and rebleeding, thanks to the ongoing Baveno consensus conferences (36). Dose and duration of pharmacological agents vary among studies, which also may affect rebleeding rates, complication rates and mortality data. Excellent meta-analyses are available for octreotide, terlipressin and comparisons with sclerotherapy; however, pharmacological treatment and band ligation have not been directly compared. Therefore, while band ligation may appear to be superior to other methods of treatment, this conclusion is still premature. No studies to date have examined the cost-effectiveness of emergency endoscopic treatments.

CONCLUSION

If expertise is available, emergency band ligation is possibly the most effective first-line therapy for hemostatic control of acute variceal bleeding. Pharmacological therapy with terlipressin or octreotide should be initiated in all acute variceal bleeding and is appropriate first-line monotherapy in centres where band ligation is not available. Terlipressin is the only pharmacological agent shown to have mortality benefit, both alone and in combination with endoscopic treatment, but its availability in Canada is by compassionate-release protocol only. ESL is no better than pharmacological treatment and, given its potential complications, should not be used as first-line treatment. Combination endoscopic and pharmacological therapy improves initial hemostasis and early rebleeding rates but has not shown improved mortality compared with monotherapies.

Timing of definitive endoscopic treatment has not been clearly defined. Delaying endoscopic treatment may make it easier to perform in a clear, bloodless field, especially for band ligation. Current data suggest no difference in control of hemorrhage or mortality in the setting of pharmacological therapy if endoscopic treatment is delayed up to 48 h. Therefore, to the probable delight of gastroenterologists on call, we recommend that emergency endoscopic treatment (less than 6 h from presentation) be reserved for continuing bleeding resistant to initial pharmacological treatment. Cost effectiveness analyses of emergency endoscopic treatment may allow more definitive practice recommendations.

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