Thrombin – an effective treatment for gastric variceal haemorrhage

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Abstract

The optimum treatment of gastric varices has still to be defined. Lesser curve gastric varices may be treated by injection sclerotherapy, but this has a limited role in the treatment of fundal gastric varices. Surgical intervention is commonly needed but carries a high mortality in patients with advanced liver disease. This study evaluated the use of thrombin for the treatment of gastric varices in 11 consecutive patients (nine with fundal, two with high lesser curve varices), identified as having bled from this site. Bovine thrombin (1000 U/ml) was injected intravariceally (mean volume 5.5 ml, range 2–10 ml) producing initial haemostasis in all 11 cases. Varices were considered thrombosed or obliterated in all patients after a median of two injection episodes (range 1–3). After a median follow up of nine months only one patient had rebled from a gastric varix. Thrombin may represent a valuable alternative injectate for the treatment of gastric varices.

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In 20–30% of patients with suspected acute variceal haemorrhage the bleeding point is within the gastric lumen.¹ In most of those bleeding from gastric varices this will arise from isolated fundal varices.^{2,3}

Conventional sclerosants have been used to treat both lesser curve and fundal/cardia varices, with some evidence of efficacy in the first group.^{4,5} Injection sclerotherapy, however, has yielded poor results for fundal/cardia gastric varices with serious complications, including high rebleeding and death rates.^{2,4,6} Consequently surgery has been proposed as the preferred choice.^{4,5,7}

Recently alternative endoscopic techniques have been reported including the tissue adhesives *N*-butyl-2-cyanoacrylate (histoacryl) and isobutyl-2-cyanoacrylate (bucrylate), which have been applied with some success for fundal varices in uncontrolled series.^{8,9} Their use, however, requires considerable attention to detail to avoid equipment damage and may produce mucosal damage and bleeding not dissimilar to sclerosants.⁹ There are also two disturbing cases reported of cerebral embolism directly attributable to tissue adhesive injection.¹⁰ Such neurological complications are not confined to the tissue adhesives, with an isolated report of a brain abscess after injection of sclerosants,¹¹ but the worrying aspect is the serious nature of the

adverse events in the context of the limited use of the tissue adhesives.

The use of human and bovine thrombin to control variceal haemorrhage, either alone, or in combination with a sclerosing agent has been proposed.^{12,13} Initial concerns about distant and disseminated thrombosis have not been confirmed although some derangement of the clotting cascade can be detected upon detailed analysis.¹⁴

We have evaluated the use of bovine thrombin in the control of bleeding from gastric varices.

Patients and methods

All patients presenting, over the 13 month period to March 1993, with gastric varices identified as the source of bleeding at the initial or subsequent endoscopy were entered into an open trial of treatment with bovine thrombin. The site of the gastric varix was classified according to Hosking and Johnson.⁵

Bleeding was considered to have arisen from a gastric varix if it was actively bleeding at the time of initial endoscopy; there was evidence of recent bleeding (for example, a clot overlying the varix); the gastric varices were large and were associated with small oesophageal varices without stigmata of recent haemorrhage or there was no other identifiable source of blood loss.

TECHNICAL ASPECTS

Bovine thrombin (Armour Pharmaceutical Co, Illinois, USA) reconstituted to 1000 U/ml was injected intravariceally in 1 ml aliquots, using a standard sclerotherapy needle (Olympus NM-10L) through a flexible endoscope (Olympus GIF Q20), using the freehand technique. Either a direct or retroflexed approach was used as appropriate.

Thrombin injection was started at the site of haemorrhage, or in those patients who were not actively bleeding at the perceived source of bleeding or into the largest varix. In pedunculated fundal varices there was almost always one or two prominent areas to be injected. Further injections were given to cover the area of the varix, with the volume of thrombin used dependant on the size of the varix.

Treatment was repeated at one to two week intervals until the varices were considered thrombosed or obliterated.

Obliteration was judged endoscopically if the varices had either disappeared or significantly reduced in size. If doubt remained about continued patency of the varix a needle was

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TABLE I Patient characteristics

	Total	Site	
		Lesser curve	Fundus
Patients	11	2 (18%)	9 (82%)
Age (years)	Mean – 54 Range 28–81	57	48
Sex (male:female)	9:2		
Cause			
Alcohol	2 (18%)	2	0
Viral hepatitis	5 (45%)	0	5
Cryptogenic	1 (9%)	0	1
Cystic fibrosis	1 (9%)	0	1
Portal vein thrombosis	1 (9%)	0	1
Schistosomiasis	1 (9%)	0	1
Child's grade			
A	5 (56%)	0	5
B	2 (18%)	1	1
C	4 (36%)	1	3
Oesophageal varix size at treatment			
Large	4 (36%)	0	4
Small	4 (36%)	1	3
Obliterated	3 (28%)	1	2
Previous oesophageal varix treatment	10 (91%)	2	8
Previous gastric varix treatment	1 (9%)	0	1

advanced into the site of the varix and then withdrawn.

Associated oesophageal varices were treated at the follow up endoscopies using endoscopic banding ligation, which was repeated until the oesophageal varices had been obliterated.

Results

Forty two patients presented with variceal bleeding, over the 13 month period to March 1993. In 11 (26%) this was considered to have arisen from gastric varices.

Table I details the patient characteristics. The patients had a mean age of 54 years and were predominantly male (nine male, two female). Five (45%) had liver disease that was viral in origin. Five (45%) were Child's grade A, two (18%) Child's grade B, and four (36%) were Child's grade C.

Ten (91%) of the patients had previously had sclerotherapy for oesophageal varices, and one (9%) had previously had ethanolamine oleate injected into a fundal gastric varix, which had been identified as the site of haemorrhage. At the time of presentation oesophageal varices were still present in eight (73%), being assessed as large in half of these patients (Table I).

At the index bleed four (36%) patients were actively bleeding, three from fundal gastric varices and one from lesser curve gastric varices. Seven (63%) had spontaneously stopped bleeding (six had bled from fundal/greater curve varices and one from lesser curve varices). In one of the patients who was actively bleeding views of the fundus were obscured by an adherent blood clot, but it was clear that bleeding had originated from fundal varices at the subsequent endoscopy.

TABLE II Treatment details

	Total	Site	
		Lesser curve	Fundus
Patients	11	2	9
No of injection episodes	20	5	15
Mean volume thrombin used (ml)	5.5	5.9	5
Range (ml)	2–10	4–10	2–10

Haemostasis for the presenting episode was achieved in all patients with a single session of thrombin injection. The patients had a total of 20 injection sessions with a median of two injections (range 1–3) per patient to achieve obliteration. The mean volume of thrombin injected was 5.5 ml (5500 U/ml) per session (Table II).

REBLEEDING

Rebleeding during the same admission occurred in one patient from a friable gastro-oesophageal junction distant from the treated gastric varix. Late rebleeding (follow up 6–13 months, median 9 months), occurred in two patients. One rebled from oesophageal varices and the other rebled from lesser curve gastric varices during the preterminal phase of severe alcoholic hepatitis (Table III).

COMPLICATIONS

Apart from rebleeding no clinically significant major/minor complications attributable to bovine thrombin injection were recorded.

Discussion

The treatment of gastric varices remains controversial⁷ but our results suggest that thrombin is an effective treatment for the short and medium term control of bleeding from gastric varices.

Thrombin proved straightforward to inject in the acute setting, and requires few injection sessions (median 2; range 1–3) to achieve luminal obliteration. It is, however, acknowledged that only four of our patients could be identified as actively bleeding at the time of the initial endoscopy. One of these patients was not identified as having bled from fundal gastric varices at the initial endoscopy because of limited views of the fundus. This problem is well reported in patients bleeding from gastric varices,¹⁵ and represents an important limitation to accurate diagnosis and direction of treatment.

The safety of intravarix bovine thrombin has been suggested in other reports and in particular there is no evidence to support thrombosis distant from the site of injection.¹³

One important advantage of this approach is the absence of any mucosal damage and ulceration after the injection that is characteristic of sclerosants¹⁶ and tissue adhesives.⁹ This permitted the use of multiple injections to thrombose the varices. Although rebleeding resulting from mucosal damage is reported to be uncommon and easily controlled after the use of tissue adhesives⁹ the use of thrombin removes one of the important causes of rebleeding after previous endoscopic treatment.¹⁷

The longterm efficacy of thrombin is unknown but our results show effective control of bleeding up to 13 months after the initial injection session without evidence, in those patients who had a subsequent endoscopy, of varix recurrence.

TABLE III *Rebleeding details*

	Total	Site	
		Lesser curve	Fundus
Early rebleed (before discharge)	1	0	1*
Late rebleed (after discharge)	2	2*	0

*Two patients rebled from sites distant from gastric varices—one early rebled from a friable gastro-oesophageal junction and one late rebled from oesophageal varices.

Overall thrombin seems to be a safe and simple agent to use for controlling active gastric variceal bleeding as well as providing longer term protection against rebleeding. There would seem to be advantages for the use of thrombin compared with sclerosants as well as the tissue adhesives both of which produce mucosal damage. There is the additional problem of the toxicity of the tissue adhesives.¹⁰

The ability, however, to attain adequate vision (particularly for fundal variceal bleeding) will remain a limitation for any endoscopic treatment. In such circumstances failure of the endoscopic approach should be recognised with recourse to surgery or perhaps transjugular intrahepatic portal systemic shunts.¹⁸

The data presented in this paper have previously been presented, in abstract form, at the British Society of Gastroenterology (*Gut* 1993; 34 (suppl 1): S48).

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