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Human thrombin for the treatment of gastric and ectopic varices

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Abstract

AIM: To evaluate the efficacy of human thrombin in the treatment of bleeding gastric and ectopic varices.

METHODS: Retrospective observational study in a Tertiary Referral Centre. Between January 1999-October 2005, we identified 37 patients who were endoscopically treated with human thrombin injection therapy for bleeding gastric and ectopic varices. Patient details including age, gender and aetiology of liver disease/segmental portal hypertension were documented. The thrombin was obtained from the Scottish National Blood Transfusion Service and prepared to give a solution of 250 IU/mL which was injected via a standard injection needle. All patient case notes were reviewed and the total dose of thrombin given along with the number of endoscopy sessions was recorded. Initial haemostasis rates, rebleeding rates and mortality were catalogued along with the incidence of any immediate complications which could be attributable to the thrombin therapy. The duration of follow up was also listed. The study was conducted according to the United Kingdom research ethics guidelines.

RESULTS: Thirty-seven patients were included. 33 patients (89%) had thrombin (250 U/mL) for gastric varices, 2 (5.4%) for duodenal varices, 1 for rectal varices and 1 for gastric and rectal varices. (1) Gastric varices, an average of 15.2 mL of thrombin was used per patient. Re-bleeding occurred in 4 patients (10.8%), managed in 2 by a transjugular intrahepatic portosystemic shunt (TIPSS) (one unsuccessfully who died) and in other 2 by a distal splenorenal shunt; (2) Duodenal varices (or type 2 isolated gastric varices), an average of 12.5 mL was used per patient over 2-3 endoscopy sessions. Re-bleeding occurred in one patient, which was treated by TIPSS; and (3) Rectal varices, an average of 18.3 mL was used per patient over 3 endoscopy sessions. No re-bleeding occurred in this group.

CONCLUSION: Human thrombin is a safe, easy to use and effective therapeutic option to control haemorrhage from gastric and ectopic varices.

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Key words: Variceal haemorrhage; Ectopic Varices; Gastric varices; Portal hypertension; Thrombin

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INTRODUCTION

Haemorrhage from gastric or ectopic varices is associated with high morbidity and mortality and can account for up to one third of all cases of variceal haemorrhage[1]. In
the presence of oesophageal varices, the prevalence of
 gastric varices ranges from 15% to 100%[2,3] with the risk
 of bleeding generally regarded to range from 4%-65% 
 over the first 2 years after diagnosis[2,4]. More importantly
 it has been reported that although gastric varices are less
 likely to bleed than oesophageal varices, once they bleed,
 they tend to do so more severely and haemostasis can be
 difficult to achieve[2].

 Unlike oesophageal variceal haemorrhage, bleeding
 from gastric varices has not been extensively studied. The
 natural history of bleeding gastric varices differs from
 that of oesophageal varices and thus the precipitating
 event for gastric variceal haemorrhage remains uncertain.
 Predictive factors for oesophageal variceal haemorrhage
 such as a hepatic venous pressure gradient (HVPG) of
 > 20 mmHg[5] is not felt to be as relevant to gastric varic-
 eal bleeding and this is partly attributed to the develop-
 ment of gastrorenal shunts. Indeed we have previously
 demonstrated that a portal pressure gradient (PPG) of
 < 12 mmHg does not necessarily protect against gastric
 variceal bleeding and that a PPG < 7 mmHg is a better
 safeguard against rebleeding[6]. The variceal size, tortu-
 osity and stigmata of recent bleeding such as red signs
 however remain alarming features[7].

 Thrombin was first used for the management of gas-
 tric varices in 1947[8] and affects haemostasis by converting
 fibrinogen to a fibrin clot. It also has other influences
 on the coagulation system with one effect being the
 enhancement of local platelet aggregation. Endoscopic
 treatment with thrombin has been reported in the treat-
 ment of bleeding oesophageal, gastric and duodenal
 varices[8,9] with a low rate of rebleeding. The most recent
 study from Ramesh et al[10] reported that haemostasis was
 achieved in the acute setting in 92% patients present-
 ing with bleeding gastric varices, with only one patients
 requiring a transjugular intrahepatic portosystemic shunt
 (TIPSS) to control bleeding. The majority of these
 studies are however retrospective and include small patient
 numbers.

 The aim of this study is therefore to evaluate the use
 of human thrombin in the treatment of gastric and ec-
topic varices.

 MATERIALS AND METHODS

 We identified 37 consecutive patients who were treated
 with human thrombin (Scottish National Blood Transfu-
sion Service) from January 1999-October 2005 for iso-
 lated bleeding from gastric and ectopic varices. Thrombin
 was injected rather than cyanoacrylate as this was our
 Units protocol. The case notes were reviewed and total
 volume of thrombin used and the incidence of compli-
cations recorded, as was the incidence of re-bleeding or
death. Those patients with bleeding oesophageal varices
 who underwent banding of varices or any patient in
 which there was diagnostic doubt as to the aetiology of
 bleeding were excluded. The study was conducted ac-
cording to the United Kingdom research ethics guide-
lines. Following consideration by the local ethics com-
mittee, further specific ethical review and approval was
 not required, as the study was considered a retrospective
 audit using anonymised data obtained as part of usual
 patient care.

 Patient characteristics

 Twenty-eight of the patients were male (male:female ra-
tio = 28:9) with a mean age at presentation of 53.2 years
 (range: 18-83 years). The underlying aetiology was alco-
 holic liver disease in 15 patients, splenic vein thrombosis
 in 6, cryptogenic cirrhosis in 6, primary biliary cirrhosis
 in 2, chronic active hepatitis in 2, portal vein thrombosis
 in 2, primary sclerosing cholangitis in 2, α1-antitrypsin
 deficiency in 1, congenital hepatic fibrosis in 1 and hepa-
titis C in 1 patient. The Childs-Pugh grade: grade A = 5
 patients, grade B = 16 patients and grade C = 10 patients.
 Segmental portal hypertension was defined as extrahe-
patic portal hypertension in the absence of liver cirrhosis
 and was seen in 6 patients whose underlying aetiology
 was splenic vein thrombosis.

 Endoscopic therapy

 All patients had an upper gastrointestinal endoscopy/
 flexible sigmoidoscopy performed by an experienced
 operator within 12 h of presentation. Gastric variceal
 haemorrhage was defined as visible spurring or oozing
 of blood from the lesser curve or fundal vessels at the
 time of endoscopy with varices subdivided into fundal
 and non fundal. Sarin's classification for gastric varices
 was used but it was noted that it is often difficult to dif-
 ferentiate the types of fundal varices in patients who are
 actively bleeding. The gastric and duodenal varices were
 also considered to have bled if there were stigmata of
 recent bleeding such as red spots or adherent clot. Rectal
 variceal haemorrhage was defined by the presence
 of rectal varices with either adherent clot or visible active
 bleeding combined with a history of profuse fresh blood
 loss per rectum.

 In those patients with splenic vein thrombosis, an al-
ternative therapy such as splenectomy may be considered
 by some but it is important that bleeding is controlled
 and therefore all these patients underwent endoscopy and
 stabilization of bleeding prior to consideration for sple-
necomy.

 Protocol for thrombin therapy

 All patients were adequately resuscitated at the time
 of endoscopy. Human thrombin concentrate obtained
 from the Scottish National Blood Transfusion Service and
each vial was reconstituted with 5 mL of water to give
 a concentration of 250 U/mL. As thrombin was being
 used outwith its licensed use, informed written consent
 was obtained from each patient prior to endoscopy. The
 thrombin was injected directly into the varices using a
 standard injection sclerotherapy needle to a maximum

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volume of 10 mL at any one session by multiple injections. Repeat endoscopy was arranged initially for one week then at two weekly intervals until further injection was deemed unnecessary by the endoscopist as the overlying mucosa had returned to normal in which the varix appeared well covered with no stigmata of recent haemorrhage. The number of endoscopy sessions, the total volume of thrombin used and the incidence of complications were documented.

RESULTS

Thirty-three patients (89%) had thrombin for gastric varices, two (5.4%) for duodenal varices, one for rectal varices and one for gastric and rectal varices. A small number of patients in this cohort were in our original pilot study[12]. Twenty-seven patients (82%) also had oesophageal varices with 19 patients (58%) already in a banding programme. Only 3 patients were on beta-blocker therapy prior to admission. The average total volume of thrombin used per patient was 15.2 mL (range: 5-47.5 mL, combined rectal and gastric varices) over 1-7 endoscopy sessions (median 3.6 sessions).

For those patients with gastric varices, 82% were classified as gastro-oesophageal varices (GOV) type 2 with the remainder being classified as isolated gastric varices (IGV) type 1 (12 %) and type 2 (6%). In two cases where it was not absolutely clear whether they were GOV type 1 or type 2 they were included as type 2. An average of 15.2 mL of thrombin was used per patient (Figure 1). Re-bleeding occurred in four patients (10.8%), three of which bled before the 2nd endoscopy session (i.e., within 7 d of index bleed) and two of whom were managed by TIPSS. One of the TIPSS procedures was unsuccessful and the patient subsequently died after a rebleed. The two other patients were successfully treated by distal splenorenal shunt.

For those two patients with duodenal varices, an average of 12.5 mL was used per patient over 2-3 endoscopy sessions. Re-bleeding occurred at day 3 in one patient which was treated successfully by TIPSS insertion.

For the patient with rectal varices, an absolute volume of 18.3 mL was used over three endoscopy sessions. No re-bleeding occurred in this group.

Only a small proportion of patients (15%) had additional therapy with vasopressor agents, the use of which did not change outcome. All patients with liver disease received five days of intravenous antibiotics as per our units protocol. In addition, true eradication of varices was rare with varices deemed visually eradicated in only two patients. No HVPG measurements were obtained in any patient as this is not our Units protocol. Overall mortality was 2.7% after median follow up of 22 mo.

Complications

No clinically significant adverse events occurred following thrombin therapy with median follow up of 22 mo.

DISCUSSION

Gastric varices are generally classified by their location in the stomach and their relationship with oesophageal varices, as proposed by Sarin et al[2]. GOV is the term used to describe gastric varices that are associated with oesophageal varices and are classified as either type 1 or type 2. IGV is used to refer to gastric varices that occur independently of oesophageal varices. It is observed that type 1 GOV (which are primarily supplied by the left gastric vein) represent 75% of all gastric varices observed. However it is generally regarded that the most serious haemorrhage occurs when type 1 IGV gastric varices (primarily supplied by the short gastric vein) bleed.

Various treatment options exist for the management of bleeding gastric varices and include endoscopic methods, TIPSS and other radiological procedures. Surgical procedures such as under running of gastric varices or devascularization procedures has previously been used but in the small studies performed have shown no great benefit and are rarely performed today.

Although there is debate regarding optimum treatment of gastric variceal haemorrhage, endoscopic therapy is an established treatment and it is currently recommended in the United Kingdom to be the first line treatment in the management of acute gastric variceal
haemorrhage\textsuperscript{[13]}. Endoscopic treatment options include standard sclerotherapy, band and snare ligation or endoscopic injection with cyanoacrylate or thrombin.

Standard sclerotherapy using ethanolamine as the sclerosing agent has been used with moderate success in the treatment of bleeding oesophageal varices but has limited success in the treatment of bleeding gastric varices. It is widely accepted that sclerotherapy for gastric varices requires significantly greater volumes of sclerosant\textsuperscript{[13]} which is thought to account for the increased number of side effects that are observed\textsuperscript{[14]}. The initial haemostasis rates obtained when using sclerotherapy have been reported to vary widely from 26\%-100\%\textsuperscript{[10-14]} which may reflect different operator ability and injection techniques. However a rebleeding rate of 60\%-90\% has been reported in most studies which is generally observed in patients with bleeding fundal varices\textsuperscript{[11,17]}. The majority of the rebleeding episodes have been reported to be related to ulceration at the injection site.

Endoscopic injection therapy with tissue adhesives such as cyanoacrylate has also been shown to be of benefit in the management of bleeding gastric varices and is becoming more popular due to the high rebleeding rates observed with sclerotherapy. A 90\% success rate in achieving initial haemostasis has been reported in a number of non randomised studies\textsuperscript{[18-20]} but Ramond et al\textsuperscript{[21]} also reported a rebleeding rate of 50\%. Several studies have also demonstrated that the use of tissue adhesives is superior to standard sclerotherapy. Oho et al\textsuperscript{[3]} have published results of a controlled but non-randomised study which demonstrated that initial control of gastric variceal bleeding and survival was significantly greater in patients treated with cyanoacrylate than standard sclerotherapy. Sarin et al\textsuperscript{[22]} have published results for a small randomised control trial which again suggested that the use of cyanoacrylate was superior to standard sclerotherapy. Complications rates between the two procedures have been reported to be similar but of course this depends primarily on the expertise available. In the hands of inexperienced operators, tissue adhesives can cause irreparable damage to the endoscope. In addition, a few centres have reported the occurrence of systemic emboli after the use of tissue adhesives to control variceal haemorrhage\textsuperscript{[23,24]}.

Gastric variceal band ligation using ‘O’rings and detachable snares have also been used in the management of gastric variceal haemorrhage but with high rebleeding rates being observed\textsuperscript{[25]}. Yoshida et al\textsuperscript{[26,27]} have however published data on the combined use of the detachable snare and simultaneous injection sclerotherapy and O-ring ligator. In a study of 43 patients\textsuperscript{[26]}, 97\% had eradication of gastric varices with an 8\% rebleeding rate observed within a 2 year follow up period.

The optimal treatment for the management of gastric varices therefore remains uncertain but as our results suggest, a promising therapeutic option is the use of intravascular injection of thrombin. The use of thrombin in bleeding gastric or ectopic varices has only previously been reported in a handful of studies in which a variety of thrombin preparations have been used. To our knowledge, this study is currently the largest published study using human thrombin.

For the management of bleeding gastric varices, our rates of achieving initial haemostasis were in keeping with 93\% published by Datta et al\textsuperscript{[19]} and 100\% by Williams et al\textsuperscript{[10]}. Our rebleeding rate of 14\% was again in keeping with data published by Williams et al\textsuperscript{[10]} but it should however be recorded that the median follow up time in these studies varied greatly from six weeks to nine mo. It should also be documented that this rebleed rate was observed without us actively attempting to visually eradicate the varices and may suggest that continued thrombin injection to achieve visual eradication appears unnecessary. This point was emphasised when we examined the number of endoscopic sessions in which thrombin was given as initially the procedure was performed out to 7 sessions. It was only after analysis of these pilot data that rebleeding was deemed extremely rare after 3 endoscopic sessions and that eradication of gastric varices was unnecessary. It is therefore now our Units adopted policy that patients should be treated with thrombin for 3 endoscopic sessions. Overall, our mortality rate of 2.7\% highlights how effective thrombin therapy can be, but it should be recorded that these results were obtained after 5 patients who rebleed underwent further interventions: namely TIPSS or splenorenal shunt surgery.

The thrombin used in this study was obtained free of charge from Blood Transfusion Service but we have now changed to using a recombinant thrombin preparation at cost of £250 for concentration of 250 IU/mL. This is comparable to the cost of cyanoacrylate and the cost of TIPSS (at £5000).

Currently, no randomised controlled trials comparing thrombin with tissue adhesives or sclerotherapy have been performed. Interestingly however, Kojima et al\textsuperscript{[28]} have published results for 30 patients with bleeding fundal varices that underwent sclerotherapy with ethanolamine under fluoroscopic guidance with the injection site being sealed with topical thrombin glue. All participants also received intravenous vasopressin and transdermal nitroglycerin. They reported an initial haemostasis rate of 93\% with a rebleed rate of 19\% after 5 years of follow up. The efficacy of the topical thrombin is however difficult to determine and the specialized technique and equipment required for this procedure may limit its future application.

With regards to the safety of human thrombin, we did not record any complications of thrombin use and this is again in keeping with all of the previously published studies that have used human thrombin. Complications such as anaphylaxis or altered thrombogenesis that have previously been reported with the use of bovine thrombin did not occur\textsuperscript{[29]}

Although in this study we have not monitored the
effect of thrombin by any means, we have evidence that results can be further improved by assessing clot formation with other means such as endoscopic ultrasound. In conclusion, we have shown that human thrombin is a safe, easy to use and effective therapeutic option in the management of bleeding gastric and ectopic varices. Our study also suggests that continued thrombin injection to achieve visual eradication appears unnecessary. Larger randomised control trials are necessary to compare the use of human thrombin with the current available therapeutic modalities.

COMMENTS

Background
Haemorrhage from gastric or ectopic varices is associated with high morbidity and mortality and can account for up to one third of all cases of variceal haemorrhage.

Research frontiers
Unlike oesophageal variceal haemorrhage, bleeding from gastric varices has not been extensively studied. The natural history of bleeding gastric varices differs from that of oesophageal varices and thus the precipitating event for gastric variceal haemorrhage remains uncertain.

Innovations and breakthroughs
Initial haemostasis rates, rebleeding rates and mortality were catalogued along with the incidence of any immediate complications which could be attributable to the thrombin therapy. The duration of follow up was also listed. The study was conducted according to the United Kingdom research ethics guidelines.

Applications
Human thrombin is a safe, easy to use and effective therapeutic option in the management of bleeding gastric and ectopic varices.

Peer review
The results of a retrospective study concerning 37 patients, who were treated with thrombin injection for bleeding gastric or ectopic varices. Their major finding is that in patients with gastric varices this treatment is effective. The authors conclude that thrombin injection may be used to treat patients with gastric or ectopic variceal bleeding.

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