Review article

Bleeding peptic ulcer – endoscopic and pharmacological management

S.C. Jones and A.T.R. Axon

Gastroenterology Unit, The General Infirmary, Leeds LS1 3EX, UK.

Introduction

Upper gastrointestinal (GI) bleeding is a common emergency, there is an annual incidence of 90 patients per 100,000 population, of whom approximately half are bleeding from duodenal or gastric ulcer.

In spite of greater emphasis on early diagnosis and improvements in medical, surgical and intensive care, mortality is still around 10% and has not changed significantly in the last 25 years.1-3 This lack of improvement in outcome is partly the result of a higher proportion of elderly patients in the population.4 An analysis of causes of death in 484 patients with acute upper GI bleeding showed that, in 60%, death was due to GI haemorrhage occurring incidentally during a severe medical illness, i.e. they were unavoidable4 (Table I). The majority of avoidable deaths occurred as a result of post-operative complications when surgery had been performed to terminate continuing or recurrent haemorrhage. These deaths were virtually confined to patients older than 60 years (Table II). One group has shown that in patients aged more than 60 years, early surgical intervention significantly reduced mortality – 4% versus 15% in the delayed group,6 but, as many patients in need of emergency surgery are poor surgical risks, an early surgical policy is still likely to be associated with a significant mortality from postoperative complications. Thus, if an effective low-risk haemostatic treatment was available it should reduce mortality.

There are major difficulties in assessing the effect of different treatments because of variation in cause of bleeding and the fact that the majority stop spontaneously. To document a 20% reduction in mortality with any therapy it has been estimated that 10,000 patients would need to be studied.7 Usual endpoints used in trials have therefore been rebleeding and need for emergency surgery in addition to mortality. In most trials of endoscopic methods for peptic ulcers, patients studied have been those with recent stigmata of haemorrhage – as treatment of these lesions which are at high risk of rebleeding should have the greatest impact on outcome.

What is the bleeding lesion?

It is continued bleeding or rebleeding which leads to operation or death in patients with peptic ulcer. Prospective studies have shown that endoscopic stigmata of recent haemorrhage help to predict

<table>
<thead>
<tr>
<th>Table I</th>
<th>Gastrointestinal haemorrhage – causes of death – 55 of 484 (11.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unavoidable 7%</td>
<td>malignancy</td>
</tr>
<tr>
<td>Avoidable 4.5%</td>
<td>postoperative</td>
</tr>
</tbody>
</table>

From Dronfield 19795

<table>
<thead>
<tr>
<th>Table II</th>
<th>Gastrointestinal haemorrhage – patients dying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Number</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
</tr>
<tr>
<td>30-40</td>
<td>1</td>
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<tr>
<td>40-50</td>
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<td>50-60</td>
<td>5</td>
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<tr>
<td>60-70</td>
<td>12</td>
</tr>
<tr>
<td>70-80</td>
<td>24</td>
</tr>
<tr>
<td>&gt;80</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
</tr>
</tbody>
</table>

From Dronfield 19795
which patients are likely to rebleed. One large study showed that patients with an endoscopically visible vessel in the base of the ulcer had a 57% likelihood of rebleeding, other stigmata 6%, whereas there was no rebleeding in individuals with no stig mata. Operative and post-mortem specimens show that the lesion responsible for rebleeding is an eroded artery which can usually be demonstrated in the base of the ulcer. It follows that the way to prevent avoidable deaths is to identify some method whereby the artery can be occluded, preferably permanently, at an early stage in the clinical presentation. Pharmacological methods are unlikely to be successful in providing primary haemostasis, but could be of benefit either by reducing the erosive action of gastric contents on arteries that have temporarily stopped bleeding or alternatively, by preventing fibrinolysis which might allow the artery to become permanently occluded.

Endoscopic techniques for effecting arterial occlusion

Different techniques have been used endoscopically in an attempt to occlude bleeding lesions, the most popular being thermal methods and injection. The use of tissue adhesives and the endoscopic sewing machine have not yet been adequately assessed.

Thermal techniques produce either obliteratorive or coaptive closure. Obliteratorive closure occurs by the direct application of heat to tissue which causes dessication and shrinkage with consequent narrowing of the lumen of the artery followed by thrombosis. This mechanism is satisfactory for small arteries, but is probably less effective for medium sized and larger arteries. Coaptive closure, on the other hand, occurs when an artery is not only heated, but is compressed mechanically. The effect of this is to produce fusion of the opposing vessel walls as they are compressed, the connective tissue blending into a single sheet. In order to produce good coaptive closure, the mechanical pressure used and the amount of heat generated should be controlled; excessive heat leads to dessication of the tissue which, in turn, leads to a less secure bonding. It follows that thermal techniques, where mechanical pressure is applied (such as a heater probe) should in theory be more effective than laser therapy which produces obliteratorive closure.

The injection of adrenaline and sclerosing agents into or around the vessel produces haemostasis by spasm or thrombosis respectively. Logically, adrenaline, which produces spasm, is more likely to be successful for initial haemostasis, but may be only temporary, whereas sclerosants may fail to arrest haemorrhage initially, but, if successful, provide permanent haemostasis. A combination of these two injections has been used in a number of studies, but there is a disadvantage with sclerosants in that they may themselves cause tissue damage and give rise to complications or rebleeding.

Endoscopic techniques

(a) Heater probe this produces direct thermal coagulation by transferring heat to the tissue via a teflon coated probe. This is heated to 250°C by an inner coil and heat is transferred by conduction so that no electricity enters the tissue. The probe is held directly onto the bleeding vessel resulting in coaptive coagulation. The lesion is irrigated via the tip allowing the probe to remain in contact with the tissue.

(b) Monopolar electrocautery Electrocautery is a technique by which an electric current generates heat. Monopolar units require a metal plate to be in contact with the patient to act as the return electrode, the electrical circuit being completed by current flow through the body. Disadvantages include tissue erosion due to sparking, lack of control over tissue heating, induced bleeding due to mechanical contact, thermal complications such as perforation, and possible electrical hazards. Older (dry) probes may adhere to tissue causing clot dislodgement. Newer units (wet) permit coagulation while under continued instillation of water so that adhesion of tissue to the probe is prevented.

(c) Bi-polar or multipolar In bi-polar or multipolar units, the active and return electrodes are built into the probe tip so that no patient return electrode is required. As a bipolar electrode would be difficult to position endoscopically, a multipolar probe has been developed (BICAP) which carries 6 equally spaced microelectrodes and can contact the bleeding lesion from any direction. This unit has a 7 and 10 French probe (diameter 2.3 and 3.3 mm) and a maximum output of 50 watts. The power unit also incorporates a water pump allowing irrigation of the target area. As the tissue heats and dries, electrical resistance increases and current flow decreases. Sparking and tissue damage are minimized and deep tissue erosion avoided. The BICAP unit is portable.

(d) Microwave coagulator a monopolar electrode connected to a magnetron via a 2.7 mm coaxial cable is introduced through a biopsy channel. The electrode is inserted into the vessel and perivascular area and microwaves are then applied. The coagulated area is limited within a range of 3 mm of the inserted electrode and shows little tendency to carbonization.
(e) Laser Laser photocoagulation is achieved by conversion of light energy into thermal energy in the tissue. Currently two types of laser are suitable for the treatment of bleeding ulcers, the Argon and the Neodymium Yttrium Aluminium Garnet (Nd YAG). The Argon laser is highly absorbed by red pigments such as haemoglobin, and so causes only superficial injury especially in the presence of blood. The Nd YAG laser is poorly absorbed resulting in deep tissue penetration \(^{16}\) and is therefore theoretically advantageous when treating active bleeding from large vessels. It is not portable, and is complicated to work with and repair. During treatment the tip of the fibre is positioned approximately 10 mm away from the target and 6–8 shots of laser energy are applied in a tight ring as close to the bleeding point as possible, but avoiding it. A direct hit of the bleeding point may precipitate or aggravate arterial haemorrhage. \(^{17}\)

(For costs of equipment see Appendix 1.)

Studies using thermal techniques

Numerous trials have been performed using thermal techniques. Many of them are difficult to interpret and not all have been controlled. It is technically difficult to design studies which cannot be criticized. The mortality rate from bleeding peptic ulcer is low, so large numbers of patients must be recruited to give meaningful results. This problem can be overcome to some extent if patient selection is made on the basis of endoscopic stigmata and if the endpoint is taken as rebleeding or surgery rather than death. A meta analysis of photocoagulation techniques has been undertaken. \(^{18}\) In this particular study nearly 1500 patients were assessed. Laser therapy improved rebleeding, operation and death rate significantly compared with no treatment. Electrococagulation in a smaller number of patients showed an improvement for rebleeding and operation, but the figures for death were not significant. These data confirm the general impression given by a large number of studies that thermal techniques are probably useful. The choice of which technique to use, however, is more difficult.

Laser therapy has been available for a longer period than most other techniques and has been subjected to a larger number of trials. \(^{19–47}\) The Argon laser is less effective than the Nd:YAG laser. However, the problems with laser therapy are that the technique itself is more difficult, access to the bleeding point is a greater problem, and special training and support is necessary. The cost of the equipment is so much more than other forms of thermal treatment that unless the results of the technique are superior there can be no justification for purchasing it for this purpose. In practice, where the laser has been compared with other forms of endoscopic treatment it has performed little better. A recent review, \(^{48}\) comparing different studies, concluded that laser therapy of arterial bleeding did not seem to be as effective as electrocoagulation or injection.

The heater probe \(^{49–54}\) monopolar \(^{53–64}\) and bipolar \(^{65–77}\) appear from the literature to be equally effective. The heater probe has been written about with the greatest enthusiasm, it is relatively simple, easily portable, there is no electrical contact with the patient, and the amount of energy supplied with each pulse can be accurately pre-set, reducing the risk of perforation. It can be applied tangentially, and since it remains in contact can remain on target during respiratory movement. The theoretical ability to apply pressure on the bleeding vessel may provide a coaptive seal which may be more effective.

(f) Injection Injectable substances fall into two main groups – vasoconstrictors and sclerosants, which may be used alone or in combination. Sclerosants such as ethanol cause dehydration which induces tissue contraction, blood coagulation, and necrosis of the vessel with subsequent fibrosis of the surrounding tissue. \(^{78}\) The only vasoconstrictor which has been evaluated in trials is adrenaline which is thought to act by inducing vasoconstriction and platelet aggregation which combine to encourage thrombosis of the bleeding vessel. \(^{79}\)

A number of trials of injection therapy have been carried out. \(^{80–98}\) Significant benefit has been shown in some controlled studies. \(^{90–92}\) Hypertonic saline and ethanol, and pure ethanol injection gave good initial haemostasis in several uncontrolled trials. \(^{80,81,83,86,87}\) Similar success has been shown for polidocanol alone \(^{99}\) and after preinjection with adrenaline. \(^{85,100}\) It is unclear which injection is the best. Adrenaline alone seems to be effective and does not carry the risk of ulcer extension and perforation occasionally seen with other sclerosants.

The heater probe may be superior to injection with pure alcohol in patients with spurting haemorrhage. \(^{99}\) Some of the treatment failures with injection in this paper were difficult to approach en face with the needle, there was no such problem in applying the heat probe tangentially. Adrenaline + polidocanol performed better than adrenaline + laser in one study. \(^{97}\)

(g) Application of tissue adhesives Application of clotting factors such as thrombin and fibrinogen solutions have not been shown conclusively to be effective although further studies are needed. \(^{3}\) Other tissue adhesives such as cyanoacrylate polymers were ineffective in a controlled study. \(^{101}\)
(h) **Haemoclips** these were originally developed by Hayashi et al.\(^1\)\(^\text{02}\) They were of two types, one being detachable and another connected to a long polythene tube for peroral indwelling use. The clips were modified by Hachisu et al.\(^1\)\(^\text{03}\) and the clipping manoeuvre was greatly simplified. Initial haemostasis was achieved in 24 out of 27 bleeding episodes (88.9%) with a rebleeding rate of 16.7%. Clips, once planted, stayed longer than 24 days, average 9.4 days. Treated lesions included gastric ulcers, duodenal ulcers, and stomal ulcers.

**Pharmacological treatment**

The pharmacological agents which have been used to reduce mortality from peptic ulcer treatment include H\(_2\) receptor antagonists, omeprazole, tranexamic acid, prostaglandins and somatostatin.

**Acid reducing drugs**

A meta-analysis of trials assessing H\(_2\) receptor antagonists\(^1\)\(^\text{04}\) (Table III) assessed 2,500 patients in 27 trials. There was a reduction of 30% in mortality which just reached statistical significance. There was a trend towards reduction of rebleeding and need for surgery, but the authors of the meta analysis are very cautious in their interpretation of the results and feel that larger studies comprising at least 10,000 patients are needed to confirm a useful role for these agents. More recently preliminary results of a trial using omeprazole have been published.\(^1\)\(^\text{05}\) Over 1,000 patients were studied, but no improvement in rebleeding, transfusion, operation or death rate could be demonstrated.

**Antifibrinolytics**

A meta-analysis of the use of tranexamic acid in over 1,000 patients has produced more hopeful results.\(^1\)\(^\text{06}\) In this analysis rebleeding was reduced by 20–30%, surgery by 30–40%, and the death rate came down by 40%, the results of surgery and death reached statistical significance at the 0.05 level. Tranexamic acid is not a drug which has been used extensively by gastroenterologists, but the results of these studies suggest that it merits greater interest.

**Prostaglandins and somatostatin**

Controlled trials using prostaglandins have failed to show any benefit.\(^1\)\(^\text{07}\),\(^1\)\(^\text{08}\) In both studies anaprostil was tested against placebo in 219 patients. Somatostatin has also been studied.\(^1\)\(^\text{09}\) In this study, fewer in the treated group required surgery and the results did reach statistical significance. Similar results were found in another study.\(^1\)\(^\text{10}\) Other trials have compared somatostatin with H\(_2\) receptor antagonists. Some showed significant improvement,\(^1\)\(^\text{11–113}\) others no difference.\(^1\)\(^\text{14–116}\) Somatostatin may therefore have a beneficial effect and merits further study.

**Conclusion**

No unequivocal statement concerning the use of endoscopic or pharmacological methods in gastrointestinal haemorrhage is possible. The subject is a difficult one, many results are inconsistent and difficult to interpret. At the present time there does seem to be reasonable evidence to suggest that endoscopic therapy using thermal techniques or injection do probably reduce the incidence of rebleeding and the need for surgery. This, in theory, may reduce mortality, but has not been shown convincingly. There is little evidence to suggest that the use of pharmacological drugs influences mortality to a greater extent although studies with somatostatin and tranexamic acid merit further work. Another approach which has not been subjected to critical analysis is the possible advantages which may be gained from treating patients in specialized bleeding units managed by experienced gastroenterological teams of physicians and surgeons. This approach is even more difficult to assess prospectively in randomized studies. However, figures of mortality from gastrointestinal haemorrhage vary widely from centre to centre and a more specialized approach to the subject might lead to a fall in the number of avoidable deaths which at present amounts to somewhere in the region of 5% of all admissions with gastrointestinal haemorrhage.

**Table III** Gastrointestinal haemorrhage – meta analysis

<table>
<thead>
<tr>
<th>Reduction %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>10</td>
</tr>
<tr>
<td>Surgery</td>
<td>20</td>
</tr>
<tr>
<td>Death</td>
<td>30</td>
</tr>
</tbody>
</table>

Collins and Langman 1985\(^1\)\(^\text{04},\) n.s. – not significant.
References


44. Mathewson, K., Swain, C.P., Bland, M., Kirkham, J.S., Bown, S.G. & Northfield, T.C. Randomised comparison of NdYAG laser (L), heater probe (HP) and no endoscopic therapy (C) for bleeding peptic ulcer. Gut 1987, 28: A1352.


Appendix

Endoscopic techniques – equipment costs (approx.) excluding VAT

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat probe</td>
<td>6,730</td>
</tr>
<tr>
<td>Monopolar electrocautery</td>
<td>4,000</td>
</tr>
<tr>
<td>Multipolar probe (BICAP)</td>
<td>3,950</td>
</tr>
<tr>
<td>(7 and 10 French probe)</td>
<td>175</td>
</tr>
<tr>
<td>Microwave coagulator</td>
<td></td>
</tr>
<tr>
<td>NdYAG laser</td>
<td>75,500</td>
</tr>
<tr>
<td>Argon laser</td>
<td></td>
</tr>
</tbody>
</table>
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doi: 10.1136/pgmj.67.789.606

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