

# Gut

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## Leading article

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### Endoscopic intervention in bleeding peptic ulcer

Endoscopic intervention can now be regarded as first line treatment for patients who present with major peptic ulcer haemorrhage. Randomised controlled trials have shown that a range of endoscopic treatments will stop active bleeding and reduce the risk of rebleeding. Surgery is now reserved for patients in whom endoscopic treatment fails. The best outcome depends upon close cooperation between the endoscopist and surgeon; skilled interventional endoscopists work closely with their surgical colleagues and each knows the limitations of the other.

Endoscopic therapy for bleeding ulcer improves the outcome only of high risk patients. This group comprises patients with major peptic ulcer bleeding and endoscopic stigmata of bleeding.<sup>1-4</sup> The factors which predispose to further haemorrhage include shock at presentation, anaemia, and the need for blood transfusion.<sup>8 12-14</sup> Other adverse clinical characteristics include advancing age, comorbid diseases, coagulopathy, and bleeding in patients admitted for an unrelated condition.<sup>8 12-14</sup> Large ulcers<sup>13</sup> and those located on the posterior inferior duodenal bulb or high lesser curve of the stomach<sup>15</sup> are also associated with increased risk of rebleeding.

Endoscopic stigmata are the most useful predictor of outcome but interpretation of the endoscopic appearances is often difficult because the ulcer may be obscured by a blood clot or awkwardly positioned. Most endoscopists clean the ulcer base to define the bleeding site, although this may precipitate rebleeding. Patients with an active, spurting haemorrhage have the worst prognosis; the combination of active bleeding and shock is associated with continued bleeding or rebleeding in 80% of cases. Endoscopic identification of a non-bleeding vessel varies between 6% and 48%<sup>3 5</sup>; identification of rebleeding from a visible vessel ranges even more widely, from 0% to 81%.<sup>6 7</sup> This variation is probably due to differences in endoscopic interpretation, definition of rebleeding, and to the timing of endoscopy. Some studies have related the colour of the visible vessel to outcome, but the findings are inconsistent,<sup>6 9 10</sup> probably because endoscopic interpretation tends to be subjective.<sup>11</sup> The endoscopic doppler can identify the position of the feeding artery and may predict the group of patients likely to rebleed.<sup>16-18</sup> Rebleeding is rare in the absence of a doppler signal from the ulcer base.

Patients without endoscopic stigmata and those with

only minor stigmata (irrespective of other clinical risk factors) will almost invariably recover with conservative support and should not be treated endoscopically.

#### Endoscopic techniques

##### THERMAL

##### Lasers

Photocoagulation of bleeding ulcers was first attempted using argon lasers.<sup>20 21</sup> The results were generally disappointing – partly because of the study design (many relatively low risk patients were included) but principally because the depth and intensity of tissue damage caused by the argon laser is often insufficient to induce arterial thrombosis. Animal studies subsequently showed that the ND-Yag laser would be a more appropriate thermal agent.<sup>22</sup> Obliterative coagulation is probably the most important mechanism of laser haemostasis, although oedema surrounding the vessel may be an additional factor. Most early controlled trials showed a significant treatment benefit with ND-Yag lasers.<sup>23-26</sup> Rebleeding, transfusion requirements, operation rates, and mortality were reduced. Krejs *et al.*<sup>27</sup> published a study which failed to show benefit for Nd-Yag laser treatment in a large number of randomised patients, although the most severe cases were not included and it is likely that many procedures were performed by relatively inexperienced operators.

Laser therapy for bleeding has proved safe, with low perforation rates. Bleeding is often precipitated by the treatment itself but it either stops spontaneously or can be arrested by further photocoagulation. A meta-analysis of controlled trials showed a significant reduction in the need for urgent surgery (common odds ratio (OR) 0.58 (95% confidence interval (CI) 0.38, 0.69)) and reduced mortality (common OR 0.49 (95% CI 0.30, 0.81)).<sup>28</sup> Criticisms of the laser include high capital and running costs and the difficulty of applying therapy without touching the mucosa with the laser fibre tip. Even in expert hands, 19% of patients in one study did not receive planned laser therapy because of technical difficulties.<sup>23</sup> For these reasons, and because the alternatives are at least as effective, enthusiasm for ulcer photocoagulation has waned.

### Electrocoagulation

Electrocoagulation devices cause arterial thrombosis by passing an electric current through the bleeding area. Monopolar units apply a ball-tipped probe, and the electrical circuit is completed through a plate attached to the patient. The technique has the drawbacks of tissue adherence, unpredictable tissue damage, and the need to frequently clean the tip. An electrical conducting fluid can be used to transmit the current mucosa (liquid monopolar coagulation), and this largely overcomes the problem of tissue adherence and improves the performance of the system. Three controlled trials have shown that active bleeding can be stopped and rebleeding rates reduced by monopolar electrocoagulation<sup>29-31</sup> but because of the unpredictable tissue injury associated with it, the device has largely been superseded by other contact methods.

Bipolar coagulation works by completing an electrical circuit between probes applied to the mucosa. The multipolar electrocoagulation pulse, known as BICAP, has three pairs of electrodes on its side and tip; electrocoagulation can be performed if any pair of electrodes are in tissue contact, and this allows tangential treatment. The amount of energy applied to the area and the degree of tissue damage is much more predictable than with monopolar units. Although early clinical trials with the BICAP were disappointing,<sup>32-33</sup> two subsequent prospective randomised controlled studies from the same author showed that the device was effective. One small clinical study showed a significant haemostatic effect in actively bleeding patients,<sup>34</sup> and the other showed reduction of rebleeding in patients with non-bleeding visible vessels.<sup>35</sup> Both studies showed a reduced need for emergency surgery, a shorter stay in hospital, and reductions in transfusion requirements and hospital costs. Bleeding can be precipitated by treatment in almost a third of cases but this usually stops with repeated applications. A particular advantage of contact probes is the ability to stop bleeding by tamponade and the best results of BICAP are associated with forceful application of the larger (3.2 mm) probe, low watt setting, and prolonged periods of coagulation.<sup>36</sup>

### Heater probe

The heater probe transmits predetermined amounts of energy to the mucosa through a Teflon coated tip. Several early uncontrolled studies showed that the heater probe was both safe and effective.<sup>37-38</sup> Subsequent randomised, controlled trials in high risk patients confirmed that treatment reduced rebleeding rates and the need for emergency surgery.<sup>39-40</sup> Optimum therapy is best administered using the 3.2 mm probe, firm tamponade, a setting of 25-30 Joules and repeated applications before the probe position is changed. The heater probe is attractive because it is relatively cheap and portable. The facility to apply forceful tamponade, its capacity to apply energy tangentially, and a powerful water jet which cleans and irrigates the area are particular advantages.

### INJECTION THERAPY

Endoscopic injection of agents into a bleeding ulcer is cheap and relatively easy. Haemostasis can be accomplished using a range of solutions, but the mechanism by which this occurs is not entirely clear. Many regimens include dilute adrenaline which causes vasoconstriction<sup>41</sup> but may also act by enhancing platelet aggregation<sup>42</sup> and by tamponade since a relatively large volume is used. In animal models, adrenaline rarely causes arterial thrombosis<sup>43-44</sup> yet in clinical trials, injections seems to prevent rebleeding. Injection of sclerosants results in tissue

necrosis, ulceration, and thrombosis<sup>43-45 52</sup> but does not cause vasoconstriction or spasm, yet some studies show benefit in active bleeding. Mechanisms of action for injection methods may be clarified if an appropriate model for peptic ulcer bleeding can be developed, yet this seems difficult to achieve. Examination of resection specimens from patients requiring surgery for ulcer haemorrhage is of little value because it is difficult to distinguish between the histological effects of chronic ulceration (which include endarteritis) and those of the injection.

Many endoscopists inject dilute adrenaline, either alone<sup>46-47</sup> or in combination with sclerosants<sup>48-51</sup> around and sometimes into the bleeding point. Other investigators have used sclerosants such as polidocanol<sup>52</sup> and absolute alcohol<sup>53-54</sup> without adrenaline. The rationale for a combined approach is that adrenaline causes vasoconstriction and stops active bleeding and the sclerosant leads to a vigorous inflammatory response causing endarteritis, arterial thrombosis, and prevention of rebleeding. Whether this actually happens in humans is unknown.

Although several groups have shown that the prognosis of bleeding peptic ulcer is improved by injection treatment, the most convincing data relate to reduction in rebleeding rates and the need for emergency surgery rather than mortality. The ideal regimen is unclear. We and the Hong Kong group believe that adrenaline is as good as any other agent or combination of agents.<sup>55-56</sup> Other investigators consider that adrenaline should be followed by a sclerosant agent such as polidocanol,<sup>57</sup> and that absolute alcohol is at least as effective as any other treatment.<sup>58-59</sup> Finally, Lin *et al*<sup>60</sup> reported that normal saline, 3% NaCl, 50% glucose/water and pure alcohol, were all comparable.

Unfortunately the inclusion criteria and the end points differ between trials and it is difficult to determine which regimen is best. All regimens seem effective and safe. Complications are unusual and perforation is rare. Sclerosants can, however, cause ulcer extension, perforation, and stomach necrosis,<sup>61-63</sup> and because we believe that they confer no additional benefit to injection with adrenaline alone, our policy is to avoid them.<sup>55</sup>

Approximately 8-10% of ulcers are inaccessible to injection treatment. Repeat injection is safe and most endoscopists now tend to reinject if there is evidence of rebleeding. The Hong Kong group routinely perform repeat endoscopy in all patients 24 hours after the initial injection and retreat the 10-20% of patients who continue to bleed.<sup>46-64</sup> A recent randomised trial examined the value of 'second look' endoscopy. The trend towards a better outcome in the group who had repeat endoscopy did not reach statistical significance.<sup>65</sup> Our own policy is only to repeat endoscopy electively in patients in whom therapy has been suboptimal.

### Comparison of endoscopic haemostatic treatment regimens

Trials comparing the various endoscopic therapies<sup>25-40 57 64 66-71</sup> suggest that the BICAP, heater probe, and injection therapy are all as safe and effective as each other. The approach of adrenaline injection followed by a thermal method is logical, although clinical trials do not convincingly show that this is better than a single modality.<sup>57 73 74</sup>

### Other novel approaches

Endoscopic haemostasis can be achieved with metal clips,<sup>75</sup> clamps,<sup>76</sup> rubber band ligation,<sup>76</sup> and sewing.<sup>77</sup> These mechanical methods may be technically difficult, however, and none are yet established in clinical practice.

## Failures of endoscopic therapy and when to operate?

We cannot predict which patients will fail endoscopic therapy. Our own data suggest that patients who present with anaemia, shock on admission, and active arterial bleeding from a posterior duodenal ulcer are at highest risk of failing endoscopic therapy (injection or heater probe).<sup>78</sup> This is perhaps not surprising since this group of patients had the worst prognosis without endoscopic treatment. It has been reported that patients who bleed from large posterior duodenal ulcers<sup>79 80</sup> and those with comorbid disease<sup>79</sup> have the highest rate of failing endoscopic injection therapy.

To date there is no study comparing surgical and endoscopic control of bleeding. Most endoscopic studies consider that the need for surgery represents treatment failure. Alternatively, it can be argued that endoscopic control of bleeding facilitates safe, early elective surgery. A successful outcome may depend upon a combination of endoscopic and surgical approaches. Like so much in gastroenterology, good management is a team approach.

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