Variable use of endoscopic haemostasis in the management of bleeding peptic ulcers

S Mahadeva, M Linch, M Hull

Background: Randomised controlled trials (RCTs) have shown that endoscopic haemostasis is beneficial for patients with a bleeding peptic ulcer. The relevance of such data to management outside of RCTs is unclear. Therefore we examined management of patients with a bleeding peptic ulcer in a UK teaching hospital.

Methods: All patients who underwent upper gastrointestinal (UGI) endoscopy for bleeding peptic ulcer between 1997 and 1999 were identified from an endoscopy database and the clinical records reviewed retrospectively.

Results: A total of 872 patients underwent UGI endoscopy for presumed acute UGI haemorrhage; 179 (21%) had an endoscopic diagnosis of bleeding peptic ulcer. Seventy nine patients had a peptic ulcer with stigmata of recent haemorrhage (SRH) but only 61 (77%) of these patients received endoscopic haemostasis (77% adrenaline, 23% combination therapy). Re-bleeding occurred in 24 patients with SRH in whom transfusion requirement was the sole predictor of re-bleeding. The re-bleeding rate among patients who received adrenaline was 25% (n=12), compared with 57% (n=8) in the combination group and 31% (n=4) in those who did not receive endoscopic haemostasis. Patients who received combination endoscopic haemostasis had an increased incidence of active bleeding (p=0.007) and an increased transfusion requirement (p=0.002). Eleven of 20 patients who re-bled had repeat endoscopic haemostasis, with 45% eventually requiring surgery.

Conclusions: Results of endoscopic management of bleeding peptic ulcers in the unit studied differ markedly from those published by specialised centres. The data reported here suggest that increased standardisation of endoscopic haemostasis is required, especially in units with provision for emergency "out-of-hours" endoscopy, performed by several individuals of different grades.

Peptic ulceration remains the commonest cause of acute upper gastrointestinal (UGI) bleeding, accounting for 30%–50% of cases. In the United Kingdom, bleeding peptic ulcer accounts for approximately 15 000 hospital admissions per year, with a district general hospital admitting one to two patients with a bleeding peptic ulcer per week. Although bleeding ceases spontaneously in at least 80% of cases, a subgroup of patients either continue to bleed or re-bleed at a later time, and this is associated with an increased mortality. Upper gastrointestinal endoscopy has not only been useful in stratifying this “high risk” group of patients, but has evolved over the last two decades into the initial therapeutic intervention of choice.

Since the landmark study by Chung et al., in which adrenaline injection of bleeding ulcers was shown to be significantly better than no treatment, multiple single centre randomised controlled trials (RCTs) have confirmed the efficacy of endoscopic haemostasis. Endoscopic haemostasis modalities that have been proved to be beneficial include either single agents (adrenaline or a sclerosant) or combination therapy (usually adrenaline/sclerosant plus a thermal modality such as heater probe application). As recurrent bleeding after initial haemostasis is the single most important prognostic factor contributing to mortality, the re-bleeding rate has been a useful reference endpoint to compare various trial results. Peptic ulcers which have an actively bleeding/spurting vessel, non-bleeding visible vessel, or adherent clot seen at initial endoscopy are known to have re-bleeding rates of 70%–95%, 30%–70%, and 30%–45% respectively. Although trials of endoscopic haemostasis have clearly demonstrated reduced re-bleeding overall, the results have been very variable. While some units have reported re-bleeding rates between 5%–10% using either single or combination therapy, others have reported re-bleeding rates as high as 40%. The different endoscopic modalities used may be an explanation for variable re-bleeding rates, although other factors such as endoscopist experience and patient co-morbidity are also likely to have contributed to variability in published outcome data.

A possible role for therapeutic endoscopy in peptic ulcer re-bleeding after initial endoscopic haemostasis has been addressed recently. Traditionally, patients who have re-bled after initial endoscopic haemostasis have been referred for immediate surgery. However Lau and colleagues recently demonstrated that 73% of patients who had repeat endoscopic haemostasis for re-bleeding after initial endoscopic haemostasis achieved long term control of bleeding and thus avoided emergency surgery. This approach was associated with fewer complications and shorter duration of hospital stay than immediate surgery after re-bleeding but there was no significant difference in mortality between the two groups.

The relevance of outcome data for endoscopic haemostasis from specialised units in the setting of a RCT to everyday practice remains uncertain. To examine this further, we analysed endoscopic management of bleeding peptic ulcers in our institution, a large teaching hospital (1115 beds) which has operated a 24 hour emergency UGI endoscopy service for the last six years. All patients referred with acute UGI bleeding have been endoscoped either within 24 hours on the next available routine list, or immediately if the patient was unstable.

Abbreviations: RCTs, randomised controlled trials; SRH, stigmata of recent haemorrhage; UGI, upper gastrointestinal
METHODS
Data retrieval
A retrospective review of all UGI endoscopy reports on an Endoscribe Database (Astra) between 1 January 1997 and 31 December 1999 with the indications of “haematemesis” and/or “melaena” was undertaken. Patients with peptic ulcer disease as the sole cause of UGI bleeding were identified. Patients with concurrent gastro-oesophageal varices were excluded. The following information was obtained from the database: endoscopist grade—that is, registrar (1–2 years endoscopy experience), senior registrar (3–5 years endoscopy experience), or consultant (>5 years endoscopy experience), location of ulcer, presence and type of stigmata of recent haemorrhage (SRH; active bleeding, non-bleeding visible vessel, or adherent clot), type of endoscopic haemostasis (nil, adrenaline, combination therapy) performed and if primary haemostasis was achieved at the end of the procedure. Patients with peptic ulceration that did not have SRH had either a clean ulcer base or a flat pigmented spot. Difficult ulcer location, which has been associated with suboptimal endoscopic haemostasis outcome, was defined as either high lesser curve gastric ulcer or posterior wall duodenal ulcer. The time that acute UGI endoscopy was performed; “out-of-hours” (between 6 pm and 8 am the next day), at the weekend or on a routine list, was also noted.

The clinical records of patients with bleeding peptic ulcers were also reviewed. We collated information on demographic data (age and sex); evidence of re-bleeding after initial endoscopy (defined as a further episode of haematemesis and/or fresh melaena associated with hypotension—that is, systolic blood pressure <100 mm Hg); subsequent management of re-bleeding (repeat endoscopic haemostasis and/or surgery); length of stay in hospital, and eventual outcome (that is, discharge from hospital or death). Mortality was subdivided into early (<30 days) and late (>30 days). As co-morbid disease has been shown to be associated with a worse outcome after endoscopic haemostasis, this was also examined. Our classification of co-morbidity (defined as cardiovascular: known ischaemic heart disease, valvular heart disease, or congestive cardiac failure; respiratory: known chronic obstructive airways disease, pneumonia, or pulmonary embolism; renal failure—that is, on regular dialysis; cerebrovascular disease—residual deficit or recurrent transient ischaemic attacks; cancer and other) was based on a similar method used by Khuroo et al, which only included the first three disease systems. Blood transfusion requirement within 24 hours of the initial bleed was obtained from Blood Transfusion Service records.

Statistical analysis
Differences between patients receiving different endoscopic management were compared using either one way analysis of variance or the Kruskal-Wallis test. Variables which were demonstrated to be significantly different by univariate analysis were entered into a multivariate logistic regression model in order to determine independent predictors of re-bleeding. Statistical significance was assumed at a p value of 0.05.

RESULTS
Acute UGI bleeding caused by peptic ulceration
A total of 872 patients underwent UGI endoscopy for presumed acute UGI bleeding during the three year review period. Of these, 179 (21%) patients had an endoscopic diagnosis of peptic ulceration as the sole cause of an acute UGI bleed. Clinical notes were available for review in 163 (91%) cases. Seventy nine UGI endoscopies (44%) were performed “out-of-hours” or at weekends. The mean (SEM) age of the patients was 65 (1) years (range 26–96) and the male:female ratio was 2.6:1. Overall, 46% of patients fulfilled one or more co-morbid disease categories.

Endoscopic management of bleeding peptic ulcer with SRH
Of the 163 patients with a bleeding peptic ulcer who had clinical records available for review, 79 (48%) had SRH visible at initial endoscopy. Sixty one of 79 (77%) patients with SRH received endoscopic haemostasis at initial endoscopy while 18 (23%) patients did not (fig 1). Among the patients who did not receive endoscopic haemostasis, the number above each column denotes the number of patients with a particular SRH type.

<table>
<thead>
<tr>
<th>Patient characteristics, transfusion requirement, and outcome of patients who had SRH visible at initial endoscopy</th>
<th>Endoscopic haemostasis types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No endoscopic haemostasis (n=47)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>67 (33–93)</td>
</tr>
<tr>
<td>Co-morbidity (%)</td>
<td>56</td>
</tr>
<tr>
<td>Active bleeding (%)</td>
<td>6</td>
</tr>
<tr>
<td>Endoscopist grade (%)</td>
<td></td>
</tr>
<tr>
<td>Registrar</td>
<td>44</td>
</tr>
<tr>
<td>Senior registrar</td>
<td>28</td>
</tr>
<tr>
<td>Consultant</td>
<td>28</td>
</tr>
<tr>
<td>Difficult ulcer location (%)</td>
<td>28</td>
</tr>
<tr>
<td>Mean (SEM) transfusion requirement (units)</td>
<td>2.7 (0.6)</td>
</tr>
<tr>
<td>Re-bleeding rate (%)</td>
<td>31</td>
</tr>
</tbody>
</table>

One way analysis of variance. †Kruskal-Wallis test.
received initial endoscopic haemostasis, 39 (64%) cases had active bleeding or a non-bleeding visible vessel at the time of endoscopy; compared with three (17%) in the group that did not receive any initial endoscopic haemostasis (fig 1). In contrast, 15 (83%) of the patients who did not receive initial endoscopic haemostasis had adherent clot compared with 22 (36%) patients who did receive initial endoscopic haemostasis (fig 1).

**Outcome of patients receiving different endoscopic haemostasis techniques**

Of the patients who received endoscopic haemostasis, 47 (77%) had adrenaline (1:10 000 dilution) injection only while 14 had combination endoscopic haemostasis (adrenaline plus heater probe, n=12; adrenaline plus thrombin injection, n=2) (fig 2). Patient characteristics, endoscopic findings, and blood transfusion requirements are documented in table 1. Complete haemostasis was achieved at the end of the endoscopic procedure in all but two patients (96%). Twelve of 47 patients (25%) re-bleed after adrenaline endoscopic haemostasis (fig 2). In the combination endoscopic haemostasis group, 8/14 patients (57%) re-bleed after initial endoscopic haemostasis (fig 2). Univariate analysis showed that the transfusion requirement (p=0.002) and the presence of active bleeding at initial endoscopy (p=0.007) were significantly higher in the group of patients who received combination endoscopic haemostasis. A higher proportion of patients receiving combination endoscopic haemostasis had co-morbidity compared with the other two groups (table 2) but this did not reach statistical significance. Although differences in the grade of endoscopist between the three groups of patients with SRH were not statistically significant, combination endoscopic haemostasis was used more by senior registrars compared with other grades (table 1). Logistic regression analysis revealed that transfusion requirement was the only independent predictor of re-bleeding (p = 0.002). In the group of patients with SRH who did not receive initial endoscopic haemostasis, 4/18 (31%) had re-bleeding after initial diagnostic endoscopy. Only 2/84 patients who were reported to have no SRH re-bleed (which was managed surgically with one mortality).

**Management of re-bleeding after initial endoscopy**

Among the patients who re-bleed after receiving adrenaline endoscopic haemostasis, four patients had repeat endoscopic haemostasis (all combination), two died (one immediate death and the other did not have further intervention due to severe cerebrovascular disease), and six underwent surgery immediately (fig 2). Of those that re-bleed after combination endoscopic haemostasis, seven had repeat endoscopic haemostasis (all combination) and one patient had surgery immediately. Five of 11 (45%) patients who had repeat endoscopic haemostasis required salvage surgery for continued bleeding (fig 2). Nine of 11 (81%) patients who received repeat endoscopic haemostasis had co-morbidity compared with 3/7 (43%) who underwent surgery immediately for re-bleeding. The group of patients in whom repeat endoscopic haemostasis failed had 100% co-morbidity and a significantly higher mean transfusion requirement compared with those who had successful repeat endoscopic haemostasis for re-bleeding or immediate surgery (table 3). Two of 11 (18%) patients who had repeat endoscopic haemostasis suffered early mortality compared with 1/7 (14%) patients who had immediate surgery. Surgery for re-bleeding or secondary bleeding after failed endoscopic haemostasis consisted of under-running of the ulcer (n=6), under-running of the ulcer with pyloroplasty and vagotomy (n=3), excision of ulcer and vessel under-running (n=1), gastroenterostomy (n=1), and partial gastrectomy (n=1). Patients who had re-bleeding from an ulcer in a “difficult” location were more likely to be referred for immediate surgery (57%) than those whose ulcer was elsewhere (20%). The length of hospital stay after acute UGI bleeding was significantly longer in those patients who had repeat endoscopic haemostasis but eventually required surgery (table 3). However a similar duration of hospital stay was noted in those who underwent surgery or successful repeat endoscopic haemostasis for re-bleeding (table 3).

**Outcome of patients who did not receive endoscopic haemostasis**

In the group of patients with SRH who did not receive initial endoscopic haemostasis the outcome of the four patients that re-bleed were as follows: one suffered early mortality, two received endoscopic haemostasis (one of which required salvage surgery for continued bleeding but did not survive), and a further patient had surgery immediately.

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**Table 2 Co-morbidity of patients with SRH visible at initial endoscopy; values are number (%)**

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>No endoscopic haemostasis</th>
<th>Adrenaline</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>8 (44)</td>
<td>26 (55)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Present</td>
<td>10 (56)</td>
<td>21 (45)</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3 (17)</td>
<td>9 (19)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1 (6)</td>
<td>1 (2)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Cerebrovascular/disease</td>
<td>3 (16)</td>
<td>6 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td>2 (11)</td>
<td>3 (6)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (6)</td>
<td>0</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 2 Outcome of patients who received endoscopic haemostasis.**
Mortality of patients with bleeding peptic ulcer
The 30 day mortality rate for all patients with bleeding peptic ulcers was 11.6%. Subgroup analysis revealed 30 day mortality rates of 6% in the group of patients who received no SRH, 16.4% in the SRH group that received initial endoscopic haemostasis, and 22.2% in the SRH group who did not receive initial endoscopic haemostasis.

DISCUSSION
Use of endoscopic haemostasis for peptic ulcers with SRH
This retrospective study of the endoscopic management of bleeding peptic ulcers in a large teaching hospital has raised several important issues. Firstly, only 77% of patients with SRH at the ulcer base received endoscopic haemostasis at initial endoscopy. This was explained largely by reduced use of endoscopic haemostasis in cases with adherent clot at the ulcer base. Although endoscopic haemostasis has previously not been advocated for peptic ulcers with adherent clot alone at the base and many endoscopists are hesitant to disturb adherent clot when there is no active bleeding, recent evidence suggests otherwise. 24–26 Laine et al have shown that aggressive irrigation of adherent clots can reveal “higher risk” lesions in up to 28% of cases. 24 The final analysis from a recent multicentre study has also shown that the re-bleeding rate of patients with adherent clot at the ulcer base was significantly better after endoscopic haemostasis compared with medical treatment only (5% v 34%). 28 High interobserver variability in differentiation between a non-bleeding visible vessel and adherent clot when there is no active bleeding, recent evidence suggests otherwise. 24–26 Laine et al have shown that aggressive irrigation of adherent clots can reveal “higher risk” lesions in up to 28% of cases. 24 The final analysis from a recent multicentre study has also shown that the re-bleeding rate of patients with adherent clot at the ulcer base was significantly better after endoscopic haemostasis compared with medical treatment only (5% v 34%). 28 High interobserver variability in differentiation between a non-bleeding visible vessel and adherent clot is another reason for treating the latter endoscopically. 27–29

Variability of endoscopic haemostasis techniques
In cases where endoscopic haemostasis was applied, the type which was used was variable. The large number (n=19) and variable experience of endoscopists and the introduction of novel modalities, such as thrombin, during the review period is likely to have contributed to this lack of uniformity of endoscopic haemostasis.

Re-bleeding rates after endoscopic haemostasis
Another important point relates to the re-bleeding rate in patients who received endoscopic haemostasis. Although the re-bleeding rate after adrenaline endoscopic haemostasis (23%) was comparable to published RCT data, 24–26 the re-bleeding rate in patients who received combination endoscopic haemostasis was particularly high (57%) in comparison with data from RCTs that have randomised only patients with actively bleeding ulcers. 20,21,25,29 However, the size of the acute UGI bleed (measured by size of blood transfusion) in the unselected group of patients who received combination endoscopic haemostasis during our review period was higher than in published RCTs (reported between 3–5 units). 20,21,25,29 This may explain the high re-bleeding rate in this group of patients as size of the acute bleed (measured by presence of shock, haemodynamic instability, and transfusion requirement) has been demonstrated to be an important predictor of re-bleeding. 17,18 Another possible explanation which deserves further (prospective) study is that, outside of RCTs, combination endoscopic haemostasis may be less efficacious than adrenaline injection alone.

Management of patients with re-bleeding after initial endoscopy
Eleven of 20 patients who re-bleed had repeat endoscopic haemostasis. Patients who received repeat endoscopic haemostasis had a higher prevalence of co-morbidity than those who underwent emergency surgery immediately. The position of the ulcer and “ease” of endoscopic haemostasis at initial endoscopy also appears to have been a factor in the decision whether to refer a patient for immediate surgery or repeat endoscopy as those cases with a difficult ulcer location are over-represented in the group who received immediate surgery. Forty five per cent of the patients who had repeat endoscopic haemostasis eventually required salvage surgery compared with 27% of patients who had repeat endoscopic haemostasis for re-bleeding in the RCT performed by Lau et al. 29 Furthermore, the failed repeat endoscopic haemostasis group had a significantly higher transfusion rate and longer inpatient stay compared with those who had immediate surgery (table 3). Although mortality rates in the immediate surgery and repeat endoscopic haemostasis groups were similar, the duration of hospital stay was longer for those patients who received repeat endoscopic haemostasis (especially if that modality failed with subsequent surgery). However, the small number of patients does not allow a definitive conclusion to be drawn. Despite reviewing endoscopic data in a large unit over a three year period, we were still not able to analyse a sufficient number of cases of re-bleeding after endoscopic haemostasis. Future analyses of patient management after initial endoscopic haemostasis are likely to require regional audit in order to generate sufficient power. Recently, it has been demonstrated that high dose intravenous acid suppression therapy reduces re-bleeding after endoscopic haemostasis of peptic ulcer.

Table 3  Patient characteristics, transfusion requirement, and outcome of patients who underwent surgery or repeat endoscopic haemostasis after re-bleeding

<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>Immediate surgery</th>
<th>Repeat endoscopic haemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Failed (n=5)</td>
<td>Successful (n=6)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>69 (47–89)</td>
<td>72 (58–81)</td>
</tr>
<tr>
<td>Co-morbidity [%]</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Active bleeding [%]</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>Endoscopist grade (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registrar</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Senior registrar</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Consultant</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Initial endoscopic haemostasis type [%]</td>
<td>86</td>
<td>40</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Combination</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>No (%) with difficult ulcer location</td>
<td>3 (57)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Mean [SEM] total transfusion (units)</td>
<td>11.5 (1.54)</td>
<td>15.8 (2.71)</td>
</tr>
<tr>
<td>Mean (SD) length of inpatient stay (days)</td>
<td>16 (3)</td>
<td>41 (21)</td>
</tr>
</tbody>
</table>
Endoscopic haemostasis and bleeding peptic ulcers

With SRH. However, during our review period (1997–99), intensive acid suppression was not used after endoscopic haemostasis for bleeding peptic ulcer at St James’s University Hospital.

Our data have revealed a lower proportion of patients with a diagnosis of bleeding peptic ulcer than previous published reports of audits of acute UGI bleeding. One reason for this may have been bias due to the retrospective nature of the study. A more likely explanation is the less stringent criteria for evidence of gastrointestinal bleeding that was applied in this study when compared with the published literature. Only cases of witnessed haematoma or melaena, by medical or nursing staff, were analysed in previous studies. Our study included all cases of haematoma and/or melaena, both witnessed and self-reported, for which the attending medical team had requested UGI endoscopy. Therefore, our series is likely to have included a number of cases with less or no pathology and lowered the proportion of peptic ulcers presenting as an acute UGI bleed.

The results presented here have implications for the British Society of Gastroenterology working party report on provision of endoscopy services which has recently been published. Our study suggests that specific guidelines for emergency endoscopic management should be incorporated in order to minimise variability of practice, especially for units where provision of emergency UGI endoscopy is dependent on multiple endoscopists. Our unit now uses a specific protocol for management of patients with a bleeding ulcer which incorporates specific guidelines on endoscopic haemostasis technique. However, the need for surgery or repeat endoscopic haemostasis is still left to individual gastroenterologists and surgeons in collaboration.

In conclusion, this study has demonstrated variability of endoscopic management of patients with bleeding peptic ulcer and higher re-bleeding rates after endoscopic haemostasis compared with those reported in RCTs. Although an increase in bleed severity and co-morbidity may account for higher re-bleeding rates, variability in operator experience and haemostatic techniques are also likely to be contributory.

ACKNOWLEDGEMENTS

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