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Endoscopic injection of adrenaline for actively bleeding ulcers: a randomised trial

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Abstract

A prospective randomised trial was performed to assess the efficacy of endoscopic injection of adrenaline for actively bleeding ulcers. Emergency endoscopy in 961 patients admitted for upper gastrointestinal haemorrhage identified 68 patients with actively bleeding ulcers. These 68 patients were randomised to receive either endoscopic injection of adrenaline or no endoscopic treatment. After endoscopy both groups were managed in an identical manner, and strict criteria for emergency operation were adhered to in both groups. Bleeding was initially controlled in all 34 patients assigned to the treatment group. Significantly fewer patients in the treatment group than in the control group needed emergency operations (five *v* 14, respectively). In addition, in the treatment group the median transfusion requirement was significantly less (three *v* five units of blood) and the median hospital stay shorter (six *v* eight days). No complications were observed with the injection of adrenaline, and the rate of healing of ulcers in those attending for endoscopy six weeks after discharge was similar in both groups (81% (17 out of 21 patients) in the treatment group *v* 79% (11 out of 14) in the control group).

Injection of adrenaline is effective in stopping bleeding from actively bleeding ulcers.

Introduction

Injection treatment has been used extensively to stop bleeding from haemorrhoids and oesophageal varices but the use of local injections for bleeding ulcers has received scant attention until recently. Success rates of 80-100% have been reported with alcohol,[1,2] laureth 9 (polidocanol),[3] hypertonic saline mixed with adrenaline,[4] and adrenaline followed by laureth 9.[5,6] We previously reported the use of adrenaline (diluted 1/10 000) in actively bleeding ulcers in 37 patients. Initially, success was achieved in all patients, but in five patients the ulcer rebled and three of them needed emergency operations.[7]

The results of these uncontrolled studies are impressive, but bleeding from a peptic ulcer stops spontaneously in over 80% of patients.[8] Thus any technique of haemostasis must be validated in a randomised controlled study before it can be declared clinically useful. We report such a prospective randomised trial of the endoscopic injection of adrenaline in treating actively bleeding ulcers.

Patients and methods

Emergency endoscopy—All patients admitted to this hospital with upper gastrointestinal haemorrhage had endoscopy within 24 hours after admission. Patients who were in shock or bleeding massively had endoscopy as soon as they had been resuscitated. When blood clots in the stomach obscured the view stomach lavage was carried out with an overtube system.[9] Blood clots and coffee grounds covering the base of ulcers were washed away by a modified water pump.[10]

Inclusion criteria and randomisation—All patients with actively bleeding ulcers were included. Patients excluded were those with bleeding only on contact with the endoscope, those whose visible blood vessels were not bleeding, those with blood clots covering the base of an ulcer that was not actively bleeding, and those who showed no signs of recent haemorrhage on endoscopy. Patients were randomised into control and treatment groups at endoscopy, when a sealed numbered envelope containing the treatment option, which was determined by a list of random numbers generated by a computer, was opened. Bleeding from ulcers was categorised as pulsatile (arterial spurting) or oozing (non-pulsatile bleeding that persisted after washing).

Injection—The technique of endoscopic injection of adrenaline has been described.[7] With a flexible needle injector (Olympus NM-1K) inserted through the biopsy channel of the endoscope 0·5 ml aliquots of adrenaline (1/10 000 dilution) were injected by multiple punctures into and around the bleeding point until all bleeding stopped.

Follow up—After endoscopy all patients were returned to the surgical gastroenterology ward for observation and given H_2 antagonists (cimetidine 200 mg or ranitidine 50 mg every six hours). Blood pressure and pulse were monitored hourly. Central venous pressure was monitored in patients over

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60 years of age, in those with cardiac disease, and in those who had had a massive bleed. Haemoglobin concentration was measured daily, and, if necessary, blood transfusions were given to maintain haemoglobin concentrations above 100 g/l. Endoscopy was repeated 24 hours later. Repeat injections of adrenaline were given to patients in the treatment group if active bleeding was seen.

Emergency operations—The need for emergency operation was determined by two experienced surgeons, one of whom did not give the injection treatments. Identical criteria for emergency surgery were strictly adhered to for both the treatment and the control groups. Emergency operations were performed if any one of three conditions was satisfied: (*a*) failure of blood pressure or pulse rate to stabilise after four units of blood, (*b*) a total transfusion of more than eight units of blood, or (*c*) a rebleed as shown by haematemesis or red aspirate from the nasogastric tube associated with tachycardia or hypotension, or both.

Trial indices—The treatment and control groups were compared for transfusion requirements, emergency surgery, stay in hospital, and mortality in hospital. Statistical evaluation was carried out with the χ^2 and median tests.

Results

From November 1985 to December 1986 961 patients had emergency endoscopy for acute gastrointestinal haemorrhage. Altogether 68 patients with actively bleeding ulcers were identified and entered into the study. Two patients who were actively bleeding at the time of endoscopy were not included because the bleeding lesion could not be seen. One of them was found to have an aorto-oesophageal fistula at autopsy, the other was found to be bleeding from a gastric varix at operation. Table I shows the clinical details of patients randomised to the treatment and control groups. The two groups were comparable in age, sex, site of ulcer, and severity of bleeding.

TABLE I—*Details of patients entered into study*

	Treatment group (n=34)	Control group (n=34)
No of men	26	26
No of women	8	8
Mean (SD) age (years)	51 (19)	54 (22)
No with gastric ulcer	10	12
No with duodenal ulcer	24	22
No with haemoglobin < 100 g/l	19	23
No in shock	11	11
No with spurting ulcer	9	10
No with oozing ulcer	25	24

Table II summarises the results of the endoscopic injection of adrenaline. Adrenaline controlled bleeding in all 34 patients in the treatment group. The volume of adrenaline used ranged from 3-14 ml (mean 6·8 ml), and no complications were observed. Two patients rebled and were operated on six and 16 hours after injection. At repeat endoscopy 24 hours later ulcers in six of the 32 remaining patients were found to be bleeding again (one spurting, five oozing), but repeat injections controlled the bleeding in all six patients. Three of the 32 patients required emergency surgery at 34, 48, and 48 hours after the initial injection. None of the 29 patients who had no active bleeding at repeat endoscopy 24 hours after the initial injection required emergency operation. In the five patients who required emergency operation the indications were haemodynamic instability after four units of blood had been transfused in one patient, transfusion of eight or more units of blood in two others, and rebleeding in the remaining two; three patients satisfied more than one criterion. The blood transfusion requirement ranged from 0-12 units (median three units, interquartile range three units).

In the control group 14 patients had emergency operations. Four had operations within six hours after endoscopy, four between six and 25 hours, two after one day, three between three and five days, and one at 10 days after endoscopy. Seven of them had operations because of haemodynamic instability after four units of blood were transfused, eight because more than eight units had been transfused, and four because of rebleeding of the ulcer; four patients satisfied more than one criterion. The blood transfusion requirement ranged from 0-25 units (median five units, interquartile range five units).

Elective operations—Two patients in each group who had had multiple episodes of bleeding underwent elective ulcer operations 7-10 days after their first endoscopy. None had shown any evidence of rebleeding before operation.

Mortality—Three patients in the treatment group died in hospital, one of heart failure on day 1, one of postoperative pneumonia on day 5, and one of renal failure on day 23. Two patients died in the control group, one of pneumonia on day 5 and the other of hepatorenal failure on day 30.

Healing of ulcers—Excluding the five patients who died and the 21 who had had operations, 42 patients were discharged from hospital taking H_2 antagonists. Seven patients did not return for follow up, but 35 (83%) returned for endoscopy six weeks after discharge. Ulcers were completely healed in 17 of the 21 patients (81%) in the treatment group and in 11 of the 14 (79%) patients in the control group.

Discussion

Despite advances in diagnosis and management the hospital mortality of upper gastrointestinal haemorrhage has remained constant at around 10%.[11-13] This may partly be explained by the increase in the proportion of elderly patients.[14] Continued bleeding or rebleeding of ulcers in hospital is associated with a sixfold to 12-fold increase in mortality.[11 15] To avoid such rebleeding early operations have been advocated for subgroups of patients selected on clinical and endoscopic grounds.[16 17] In an increasingly elderly population of patients an aggressive surgical policy may merely exchange "medical" for postoperative deaths, with no effect on overall mortality.[18]

Although emergency endoscopy has not been shown to reduce the mortality of gastrointestinal haemorrhage in randomised trials, endoscopy has become the investigation of choice in most hospitals for patients admitted with gastrointestinal bleeding. With the accurate identification of the bleeding point, haemostasis by endoscopy, which avoids the risks of general anaesthesia and operation, is clearly very attractive. Endoscopic laser photocoagulation has attracted much attention both in the lay press and in medical publications. The equipment is expensive, and difficult to use, and controlled trials have given contradictory results.[20 21] Newer thermal methods, such as bipolar electrocoagulation[22] and heat probes,[23] allow pressure to be applied to the bleeding point during coagulation to produce a better seal. Early results are promising, but further assessment is necessary.

Most patients presenting with upper gastrointestinal bleeding are admitted to district general hospitals. Those whose ulcers continue to bleed are unlikely to be fit for transfer to a specialised unit. To lower the mortality associated with bleeding peptic ulcers an endoscopic procedure should be readily available in most hospitals and be technically easy to perform. Endoscopic injections require no specialised equipment, and the technique is comparatively easy to master. The successful use of injection treatment for non-variceal bleeding has been reported by several groups. Although the results with sclerosants in uncontrolled clinical studies are impressive, the ulcerogenic potential of these substances is worrying; ulcers have been shown to grow bigger and healing to be retarded with large

TABLE II—*Results of endoscopic injection of adrenaline by group and type of bleeding from ulcer*

	Treatment group			Control group			
	Spurting ulcer (n=9)	Oozing ulcer (n=25)	Total (n=34)	Spurting ulcer (n=10)	Oozing ulcer (n=24)	Total (n=34)	Significance (p value)
Median No (range) of units of blood transfused	4 (1-8)	3 (0-12)	3 (0-12)	6 (3-10)	4 (0-25)	5 (0-25)	<0·05
No having emergency operation	3	2	5	7	7	14	<0·02
Median (range) stay in hospital (days)	6 (3-13)	5 (2-27)	6 (2-27)	8·5 (4-18)	8 (3-108)	8 (3-108)	<0·005
No of deaths		3	3		2	2	NS

volumes of laureth 9,[3] and in another study one patient died of a perforated ulcer when alcohol was used.[1]

In clinical trials on gastrointestinal bleeding various end points can be used to determine the success or otherwise of treatment.[24] The most unequivocal end point is death. With modern management in a specialised unit the mortality from bleeding ulcers is under 10%. In most patients the cause of death is a coexisting irreversible medical condition rather than bleeding. In our study five out of 68 patients died, giving a mortality of 7%. It is unlikely that a difference in mortality can be shown in a trial of reasonable size. Other end points include rates of rebleeding, transfusion requirements, need for emergency operation, and length of stay in hospital. Rebleeding may be difficult to define clinically as it is difficult to distinguish from continued bleeding. Although haematemesis associated with hypovolaemic shock leaves no doubt that active bleeding has occurred, diagnosing a smaller rebleed may be equivocal. Melaena may be passed days after the bleeding episode. A fall in haemoglobin concentration may be due to haemodilution. Transfusion requirements and emergency operations are also determinants that are influenced by clinical judgment, and the time spent in hospital may be affected by unrelated social factors.

Our trial was not conducted blind. To avoid bias and difficulties in interpretation unequivocal criteria for transfusion and operation were drawn up and strictly adhered to. Rebleeding was not one of the end points because it is difficult to diagnose. Instead, unequivocal rebleeding (haematemesis and shock) was included as one of the criteria for emergency operation.

The results of our randomised controlled study confirm our earlier experience that injection of adrenaline is effective and safe.[7] Initial haemostasis was achieved in all 34 patients in the treatment group. No complications were observed; ulcers did not extend on repeat endoscopy at 24 hours and the rates of healing in the control and treatment groups were identical. The treatment group required significantly less blood, needed fewer emergency operations, and had a shorter stay in hospital than the control group.

The mechanism by which injection treatment stops bleeding is conjectural. The effect of the volume of injected material may be important.[25] We showed that submucosal injection of adrenaline reduced the rate of bleeding from experimental gastric ulcers in dogs, whereas the inert carrier substance had no effect.[26] The pharmacological action of adrenaline is probably important in promoting haemostasis.

We did not find any local or systemic complication attributable to the injection of adrenaline either in the present trial or in our earlier pilot study. Catecholamines have a significant first pass extraction by the liver.[27] Submucosal injection of adrenaline into the stomach or the duodenum is less likely to cause cardiovascular side effects than systemically injected adrenaline. Tissue necrosis from local ischaemia remains a theoretical risk, but we did not observe any extension of the ulcer on repeat endoscopy or any delay in the healing of ulcers in our patients. There are no data on the maximum safe dose. As a general rule we recommend a maximum dose of up to 10 ml. In one of our patients 14 ml was injected with no untoward effect.

Data on the natural course of an actively bleeding ulcer are scanty because most patients with active bleeding either have endoscopic haemostasis or are referred for emergency operation. Scrutiny of our control group throws some light on the natural course of actively bleeding lesions seen at endoscopy. In our control group of 34 patients with active bleeding, 41% (70% of patients with spurting vessels and 29% of those with oozing ulcers) required emergency operation. Although active bleeding seen at endoscopy does not mandate immediate surgery, it does identify a group at high risk in whom future studies on endoscopic haemostasis should be concentrated.

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