
Current status of endoscopic therapy for ulcer bleeding

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This article provides an overview of the therapeutic endoscopic modalities available for the treatment of peptic ulcer bleeding. The benefits of endoscopic haemostasis have been fully demonstrated by three meta-analyses, which included most of the controlled trials published until 1992. In this review, an emphasis is placed on randomized, prospective comparative trials published during the past 20 years. Using an evidence-based medicine approach, the results of meta-analyses are translated into efficacy measures known as relative and absolute risk reductions, and number needed to treat. Single-modality treatments with injection agents such as epinephrine, sclerosants and thrombogenic substances, or with thermal therapies, are efficacious and comparable. Combination therapy involving injection and thermal techniques may offer an advantage over single-method therapy. The differences in the results between clinical trials and routine clinical practice, and among the various randomized studies, are probably related to operators' experience and variations in technique rather than to inconsistency of endoscopic haemostasis.

Key words: endoscopy [therapy]; gastrointestinal haemorrhage [therapy]; peptic ulcer haemorrhage [therapy]; haemostatic techniques [comparative studies].

Over the past two decades, endoscopy has evolved from being a diagnostic tool to being the initial therapeutic intervention of choice in acute peptic ulcer bleeding. Once initial haemostasis has been achieved, recurrent bleeding remains the single most important prognostic factor contributing to mortality in these patients. Thus, the re-bleeding rate is a very useful reference point to compare the haemostatic effect of the various endoscopic modalities. The incidence of further bleeding after endoscopic treatment is surprisingly high in some studies and is exceedingly variable among most of the trials. In this review, an attempt is made to provide summary estimates of treatment effects, drawing mainly on studies published in full form. When a single estimate of effect is not possible, an evidence-based medicine approach is taken to report the comparison of results between two endoscopic treatments.

The results are presented in terms of relative risk reduction (RRR) calculated as 1 minus the relative risk (RR); absolute risk reduction (ARR), which is the net difference in the proportion of events between two groups; and the number needed to treat (NNT), with their corresponding 95% confidence intervals (CI). The NNT is an

estimate of the number of patients that would need to be treated with the experimental therapy in order to prevent one of them developing an adverse outcome. It is calculated as the reciprocal of ARR (i.e. $1/ARR$).

If one of the limits of the 95% CI for the ARR (from which the NNT is calculated) crosses unity, the 95% CI provided for NNT includes at one extreme a number needed to benefit (NNTB), and at the other, a number needed to harm (NNTH).¹ In the latter, there is no statistically significant difference between the two interventions being compared, and the use of the experimental treatment could lead to a higher proportion in the compared event rate.

Pooled odds ratios (PORs) from meta-analyses are translated into the RRR and NNT according to the base-line risk of adverse events following the methods previously suggested.²⁻⁴ The statistical analysis was carried out using Arcus QuickStat (Research Solutions, Addison Wesley Longman Ltd) and CATmaker ver 1.0.

WHAT WE KNOW FROM ANIMAL STUDIES

A landmark article on the nature of visible vessels published by Swain et al evaluated resected specimens from 27 patients with recurrent bleeding gastric ulcers and characterized the pathological changes of the bleeding vessels.⁵ They found that the bleeding arteries had a mean external diameter of 0.7 mm, with a range of 0.1 to 1.8 mm.

The size of the vessel into which the ulceration process erodes, in addition to the extensive nature of the arteritis leading to vessel wall damage, is an important prognostic element of outcome for bleeding ulcers.⁶ Bleeding vessels of an external diameter of over 3 mm have been found in both the duodenum and the stomach in patients who died from bleeding peptic ulcers.⁷ Thus, a natural question that arises in the assessment of the different haemostatic techniques relates to the effectiveness of these endoscopic methods to secure bleeding from vessels of increasing calibre.

Experimental studies in animal models have shown that injection sclerotherapy is ineffective in bleeding vessels over 0.5 mm^{8,9}, and that ethanol is the most effective agent in canine serosal vessels of 0.5 mm in diameter.⁸ There is also a limit to the efficacy of bipolar diathermy and laser therapy; in some studies, these haemostatic methods reliably stop bleeding from vessels of 0.5 mm but have increasing difficulty sealing vessels greater than 1 mm in external diameter.¹⁰⁻¹⁴ In the canine model of gastric bleeding ulcers induced with jumbo biopsy forceps, epinephrine injection alone is not as effective as thermal or combination therapies for acute haemostasis (80% for epinephrine alone versus 100% for thermal or combination therapy).¹⁵ However, these results can not be directly extrapolated to humans since the mechanically induced lesions in this model do not resemble the high-risk lesions predictive of recurrent bleeding (a spurting bleeding or non-bleeding visible vessel [NBVV]) in clinical practice.

A randomized controlled comparison of injection, thermal and mechanical endoscopic methods in an animal model has recently been published.¹⁶ Canine mesenteric vessels were severed and randomized to haemostatic treatment with injection (adrenaline and ethanolamine), bipolar diathermy or mechanical methods (clips, bands, the sewing machine and endoloops). Neither injection therapy nor clips were effective in closing vessels of 1 mm in diameter. The success rates for vessels of up to 2 mm in diameter were 80% for bipolar diathermy and 87% for unstretched elastic bands; pre-stretched elastic bands were ineffective even on vessels of 1 mm in

size, and bipolar coagulation was completely ineffective in vessels larger than 2 mm. Only the endoloops and the sewing machine were effective in vessels of 1–4 mm in diameter; the endoloops were the only haemostatic technique that secured bleeding in vessels of 5 mm in size.

Again, although a direct extrapolation from this animal model to human clinical studies may not be appropriate, these data suggest that the most commonly used interventional endoscopic haemostatic methods may be ineffective in stopping bleeding from large vessels in ulcers. It may thus appear surprising that some trials of endoscopic intervention show a significant benefit of injection and thermal probe methods in reducing some or at least one major end-point in peptic ulcer bleeding (i.e. re-bleeding, the need for surgery, blood transfusion requirements or death).

The discrepancy between animal model studies and clinical trials may be difficult to reconcile, and although an adequate explanation can not be offered at this time, some reasons have been put forth in an attempt to explain this difference.¹⁶ The size of the bleeding artery tested in experimental studies may not reflect the diameter of the bleeding vessels in the ulcer crater responsible for most of the bleeding episodes encountered in the clinical setting. In fact, only about 20% of arteries from gastrectomy specimens had a diameter greater than 1 mm in the classic study by Swain et al.⁵ This finding may partially explain why some experimental studies have failed to show a beneficial effect of injection therapies in arresting ulcer bleeding from vessels greater than 0.5 mm in diameter whereas multiple controlled and comparative studies, as well as meta-analyses evaluating this haemostatic technique, have produced positive results.^{17,18}

What about the other haemostatic methods that show adequate control of the bleeding point in larger arteries? There might be issues of access and ulcer location (higher lesser curvature or posterior duodenal bulb) that limit the ability to deliver appropriate treatment. The necessary pressure required to induce coaptation of the blood vessels with thermal probes may not be uniformly reached during *in vivo* endoscopy. Finally, pathological changes that occur in bleeding arteries (fibrinoid necrosis and arteritis) and in the ulcer crater (the presence of scar tissue) may simply render all the endoscopic therapies difficult to use, and the animal model is less useful to extrapolate to human studies. In summary, animal models may be useful for evaluating the safety of haemostatic devices and assessing the technical and mechanical aspects of devices, but they cannot be extrapolated to predict the utility of these devices in the clinical setting.

ENDOSCOPIC INTERVENTION TRIALS

Studies in which endoscopic treatment is compared with a control

The role of endoscopic treatment in peptic ulcer bleeding is firmly established, and its benefits are clearly demonstrated in multiple trials in which some form of endoscopic intervention is compared with that used in controls managed with conventional medical treatment. Since the landmark study by Chung et al.¹⁹ in which epinephrine alone was shown to be better than control treatment, this injection substance has probably become the most frequently used agent in clinical practice.

Several trials have examined the role of alcohol alone or epinephrine plus a sclerosant agent in combination against a control treatment. Table I shows the pooled results of 10 trials published in full form. Four of the studies used alcohol alone^{20–23}, five trials used 1% polidocanol^{24–28}, and one study used 5% ethanolamine²⁹ in the

Table I. Pooled results of controlled studies evaluating alcohol alone or epinephrine plus a sclerosing agent.

Treatments compared (references)	No. of trials	Total number of patients included in analyses		Pooled risk difference (favouring treatment)	95% confidence interval	P value	P value (heterogeneity)	NNT (95% CI)
		Treated	control					
Control versus alcohol ²⁰⁻²³	4	139	140	21%	4.5-38%	0.0127	0.0325	5 (3-22)
Control versus epinephrine plus sclerosant ²⁴⁻²⁸	6	260	237	32%	21-42%	<0.0001	0.10	3 (2-5)
All therapy	10	399	377	27%	16-38%	<0.0001	0.0003	4 (3-6)

NNT = number needed to treat.

intervention arm. The overall effect is reported in terms of risk difference in the re-bleeding rate between the control treatment and the combination therapy.³⁰ An overall risk difference of 27% (95% CI 16–38%) in favour of combination therapy means that one needs to treat only four patients to avoid recurrent bleeding in one of them when compared with no endoscopic intervention. Although the *P* value for this difference is highly significant, the corresponding *P* value for the homogeneity test across the different studies is also significant.

Sources of heterogeneity in the results are related to the inclusion of different lesions and stigmata of recent bleeding (SRH) in the various trials, as well as to a variation in the definition of re-bleeding. Thus, although the pooled risk difference provides an overall estimate of the impact of treatment that is more conservative than simply averaging the re-bleeding rates from both groups and calculating the difference, caution should be exercised when interpreting these results in the presence of statistical heterogeneity.

A meta-analysis published in 1992 pooled the results of laser, injection and thermal contact therapies from well-conducted randomized controlled trials (RCTs) published between 1981 and 1990, which compared different endoscopic interventions with sham treatment or medical management.¹⁸ The results of the treatment of high-risk lesions (NBVV and active bleeding) showed a significant POR in favour of endoscopic treatment for further bleeding and surgery (POR 0.23; 95% CI 0.15–0.27 and 0.26; 0.17–0.32 respectively) and barely reached statistical significance for overall mortality (POR 0.62; 95% CI 0.38–0.98). When analysed separately, none of the three endoscopic therapeutic modalities showed a significant effect on mortality for actively bleeding lesions or NBVV. There was no statistical heterogeneity of the results of trials evaluating the effect of endoscopic therapy on mortality. However, the results of treatment on re-bleeding and the need for surgery showed a variation beyond the degree of what would be expected if the true effect size were the same in each study (i.e. there was statistical heterogeneity).

Table 2 shows the results of endoscopic therapy in terms of RRR and NNT, calculated from odds ratios for re-bleeding, surgery and mortality as reported in the meta-analysis by Cook et al.¹⁸ The control event rates needed for the calculation of these figures are taken from data on outcomes of bleeding ulcers in patients randomized in prospective trials who did not receive endoscopic therapy.³¹

RRRs and NNTs are estimated for NBVV, which, in addition to active bleeding, is one of the two lesions for which there is consensus on the use of endoscopic therapy.³² The calculations assume a re-bleeding rate of around 50%, a need for surgery of 35% and a mortality rate of 11% in the control group.³¹ The pooled benefits of all the endoscopic haemostatic treatments translate into an RRR for re-bleeding of 63% and an NNT of 3. These figures suggest that endoscopic intervention with any of those haemostatic techniques results in a reduction of the re-bleeding rate from 50% to 18% for NBVV, and that only three patients need to be treated to prevent re-bleeding in one of them. Similarly, the need for surgery is reduced from 35% to 12%, and the overall mortality rate from 11% to 7%. The small effect on mortality of all the endoscopic therapies combined is expressed by the large 95% CI for NNT, which at the upper extreme requires the treatment of more than 500 patients to avoid one death. Two other meta-analyses have found an important effect of endoscopic therapy compared with conventional treatment on re-bleeding, operation and death rates, which appears to be more significant for laser therapy.^{17,33}

An analysis of the changing epidemiology of bleeding peptic ulcers may provide another perspective on this last issue. Although the overall mortality of peptic ulcer

Table 2. Relative risk reductions (RRR) and number needed to treat (NNT)* for all endoscopic haemostatic therapies.

Therapy	Further bleeding		Surgery		Mortality	
	RRR (%)	NNT (95% CI)**	RRR (%)	NNT (95% CI)**	RRR (%)	NNT (95% CI)**
Thermal	69	3 (2–3)	72	4 (3–5)	31	29 (NNTH 21 to NNTB 13)
Laser	47	4 (3–6)	32	9 (5–86)	23	40 (NNTH 18 to NNTB 15)
Injection	77	3 (2–3)	81	4 (3–4)	54	17 (NNTH 147 to NNTB 11)
All therapy	63	3 (3–3)	65	4 (4–5)	35	25 (15–510)

*Calculated using odds ratios^{2–4} from a meta-analysis of prospective controlled trials of endoscopic therapy versus no endoscopic intervention in the treatment of active bleeding and non-bleeding visible vessels.¹⁸
**CI = confidence interval; NNTH = number needed to harm; NNTB = number needed to benefit.

bleeding has remained at between 5% and 10% for the past 35 years^{32,34,35}, prevalence data shows that elderly patients with co-morbid conditions represent an increasing subgroup of patients with upper gastrointestinal haemorrhage.³⁵ Thus, the unchanged mortality despite a shift in age group may imply that a higher mortality in older patients is balanced by fewer deaths in younger subjects, or that the use of more effective endoscopic therapies has increased survival in the older age group. In addition, a difference between the endoscopic treatment benefits derived from meta-analyses to those found in actual clinical practice could be related to differences in the patients' underlying risk of adverse outcome.³⁶ In summary, there is evidence that endoscopic treatment for ulcers with active bleeding or NBVV, using either injection or thermal therapy, prevents further bleeding and decreases the need for surgery, as well as possibly reducing mortality.

Comparative trials of endoscopic intervention

Multiple endoscopic techniques have been studied for the acute haemostasis of upper gastrointestinal bleeding secondary to peptic ulcer disease. These haemostatic techniques include injection therapy with various solutions, such as epinephrine, sclerosing agents, alcohol or thrombin; thermal methods such as heater probe, bipolar or multipolar electrocoagulation and laser techniques; and mechanical devices such as hemoclips and elastic bands.

An important question in endoscopic intervention for peptic ulcer bleeding relates to determining which out of all the different haemostatic techniques currently available to the gastrointestinal endoscopist consistently renders the best results. This is a complex issue, which has not been conclusively resolved by the trials published to date.

Adding a sclerosing agent to epinephrine: does it make a difference?

Although an epinephrine injection is effective in reducing the rate of bleeding in animal studies and in clinical trials, its effect may only be temporary since it does not induce vessel thrombosis. Thus, the addition of a sclerosing agent such as polidocanol, ethanolamine or alcohol may confer an extra benefit in the acute haemostasis of upper gastrointestinal bleeding.

Over the past few years, five trials have examined the value of adding a sclerosant to epinephrine in comparison to that of using epinephrine alone (Table 3a).^{37–41} Two of these trials used 1% polidocanol^{38,41} in the combined treatment arm, 2 used alcohol^{37,40} and 1 used 5% ethanolamine.³⁹ The trial by Chung et al. did not report outcomes for re-bleeding, and the need for surgery is therefore used instead as a surrogate measure of re-bleeding.³⁸

The pooled risk difference, as a summary effect of the re-bleeding rate between the two groups, is 2% (95% CI –4% to 9%) in favour of combination therapy over treatment with epinephrine alone (Table 3b). Not only did the combination therapy fail to show a significant difference in the overall re-bleeding rate when compared with epinephrine, but the two complications in those five trials also occurred exclusively in the combined treatment (two perforations, one requiring a subtotal gastrectomy).^{38,41} Subgroup analysis in one of the studies showed a significant benefit in ultimate haemostasis for spurting bleeding in favour of epinephrine plus polidocanol.⁴⁰ However, the results in the subgroup of patients with spurting bleeding are not pooled because of incomplete reporting and the small number of patients available for analysis in each stratum.

Thus, the hypothetical advantages of adding a sclerosant to epinephrine have not materialized in clinical trials, and the available data in fact suggest that the addition of a sclerosing agent to the epinephrine injection does not improve the haemostasis rate achieved with epinephrine injection alone. Additionally, the complications^{42–45} associated with sclerosing agents should make one cautious about their routine use in the treatment of peptic ulcer bleeding. Therefore, epinephrine should be considered to be as effective as combination injection therapy.

Thrombin and fibrin injection

The concept of using a thrombogenic substance to arrest ulcer bleeding is attractive from a physiological standpoint. Thrombin and fibrin glue provide a natural matrix for wound healing, and their injection leads to the formation of a solid network that compresses the bleeding vessel, in contrast to the non-compact oedema and ensuing thrombosis, fibrosis, scarring and necrosis that accompany the injection of sclerosants.⁴⁶

Uncontrolled, non-randomized trials and retrospective studies of fibrin injection show a re-bleeding rate ranging from 9.4%⁴⁷ to 22%⁴⁸, and a definitive haemostasis rate of 97%.⁴⁹ A controlled study of thrombin injection showed a significant reduction in re-bleeding (40% for the control arm versus 4% for the thrombin group; $P < 0.01$).⁵⁰ A non-randomized, consecutive case series review that compared thrombin with polidocanol injection showed a similar re-bleeding rates in the two groups (15% and 18% respectively).⁵¹

Five prospective, randomized studies have compared the use of thrombin or fibrin glue with other injection modalities (Table 4).^{52–56} The RRR achieved in these trials ranges from 16% to 79%, only two trials showing a statistically significant risk reduction

Table 3a. Endoscopic trials evaluating epinephrine (Epi) versus epinephrine plus sclerosing agents.

Authors	Year	N	Lesions treated	Combination	Re-bleeding n/n (%)	
					Epinephrine	Combination
Chung et al ³⁸	1993	200	Ia	Epi + STS	16/98 (16)	14/98 (14)*
Villanueva et al ⁴¹	1993	63	Ia, Ib, IIa	Epi + polidocanol	3/29 (10)	7/32 (22)
Lin et al ⁴⁰	1993	64	Ia	Epi + alcohol	11/31 (36)	5/32 (16)
Choudari & Palmer ³⁹	1994	107	Ia, Ib	Epi + ethanolamine 5%	8/55 (14.5)	7/52 (13.5)
Chung et al ³⁷	1996	160	Ia	Epi + alcohol	9/81 (11)	6/79 (11)

*Need for surgery since re-bleeding not an outcome in this trial; STS = sodium tetradecyl sulfate.

Table 3b. Pooled risk difference of trials comparing epinephrine (Epi) versus epinephrine plus sclerosing agents.³⁷⁻⁴¹

Epi versus Epi + sclerosant	No. of trials	Total number of patients included in analyses (Treated/control)	Pooled risk difference	95% Confidence interval	P value	P value (heterogeneity)
Re-bleeding	5	293/294	2%	-4 to 9%	0.47	0.28

Table 4. Randomized trials comparing thrombin or fibrin injection against other injection therapies.

Authors	Years	Treatments compared	Re-bleeding rates	Relative risk reduction (95% CI)	Absolute risk reduction (95% CI)	NNT* (95% CI)	
Balanço et al ⁵²	1990	Epinephrine (n = 30)	Epi + thrombin (n = 29)	13 versus 7%	46% (-1.2 to 8)	6.5% (-10 to 24)	16 (NNTH 10 to NNTB 5)
Berg et al ⁵³	1994	Polidocanol (n = 25)	Fibrin glue (n = 38)	24 versus 13%	46% (-36 to 79)	9% (-7 to 28.5)	4 (NNTH 15 to NNTB 4)
Kubba et al ⁵⁴	1996	Epinephrine	Epi + thrombin (n=70)	20 versus 4.3%	79% (34 to 93)	16% (5 to 27)	7 (4 to 19)
Song et al ⁵⁵	1997	HSE** (n = 63)	Fibrin glue (n = 64)	22 versus 11%	50% (-10 to 78.5)	11% (-2 to 24)	9 (NNTH 50 to NNTB 5)
Ruutgers et al ⁵⁶	1997	Polidocanol (n = 254)	Fibrin glue single (n = 266)	23 versus 19%	16% (-17 to 40)	4% (-3 to 11)	28 (NNTH 33 to NNTB 10)
			Fibrin glue repeated (n = 270)	23 versus 15%	33.5 (5 to 54)	7.6% (1 to 14)	14 (7 to 107)

*CI = confidence intervals; NNT = number needed to treat; NNTH = number needed to harm; NNTB = number needed to benefit.

**HSE, hypertonic saline epinephrine.

in re-bleeding rate.^{54,56} Kubba et al. compared epinephrine plus thrombin injection and reported significantly lower re-bleeding (4.3% versus 20%) and mortality rates (0% versus 10%) than were achieved with epinephrine alone.⁵⁴ In the large multicentre, European trial, polidocanol was compared with two different fibrin glue injection schedules: single and repeated injection.⁵⁶ Only the repeated fibrin glue injection arm demonstrated a significant risk reduction in re-bleeding rate, which translates into an NNT of 14 patients (95% CI 7-107). There was no difference in the complication and mortality rates (4–5%) between the three groups.

Thus, the available data do not convincingly show the superiority of either thrombin or fibrin injection over epinephrine or sclerosing agents. The purported benefit of a repeated application of fibrin glue or any other endoscopic therapeutic modality requires an accurate method of predicting re-bleeding based on post-treatment ulcer appearance, which is not available at present, along with a formal cost-effectiveness analysis of this strategy.

Injection versus thermal methods

Several randomized prospective trials have compared injection therapy with thermal endoscopic treatment (Table 5).^{57–66} These studies are heterogeneous with regard to the combination of injection agents used for therapy, as well as to the thermal modality and probe size employed. None of these trials show a significant difference in favour of either form of therapy in terms of re-bleeding when all the patients were analysed on an intention-to-treat basis. Subgroup analysis showed a statistical significant difference in favour of the heater probe in spurting bleeding in one study.⁵⁷ Two trials showed a significant difference in initial haemostasis in favour of heater probe treatment compared with alcohol injection^{57,67}, and one study had a higher rate of initial haemostasis for the injection group.⁵⁸ A recent meta-analysis of 12 RCTs including 1813 patients randomized to injection therapy or thermal methods found a non-significant POR for re-bleeding (1.2; 95% CI 0.91–1.55).⁶⁸ No difference was found in the need for surgery, but the mortality rate was significantly reduced in the injection group (POR 0.51; 95% CI 0.27–0.95).

It is interesting that, despite the superiority of thermal over injection methods in animal experiments of canine ulcers and mesenteric vessel bleeding, this difference has not emerged in clinical studies. Issues of portability, easiness to use and low cost make injection therapy the preferred treatment modality and the one that is likely to be used first by most endoscopists in general practice, although the results with injection therapy and thermal therapy are reasonably equivalent.

Is there any difference between the different thermal methods?

Several trials have compared electrocoagulation, heater probe and laser therapy for the treatment of peptic ulcer haemorrhage. Three trials compared electrocoagulation in the form of multipolar electrocoagulation (MPEC) or the argon plasma coagulator (APC) with heater probe treatment.^{61,69,70} Two trials compared MPEC with the Nd:YAG laser^{71,72}, two trials compared heater probe with Nd:YAG laser treatment^{73,74}, and one trial compared all three haemostatic techniques.⁷⁵ No consistent significant difference in the major end-points (re-bleeding, the need for surgery or the mortality rate) clearly emerge in favour of any one of these haemostatic techniques from these prospective studies involving over 500 patients. The average re-bleeding rates for electrocoagulation, MPEC and laser therapy were similar (23%, 20.5% and 25% respectively). The absence of

Table 5. Thermal versus injection endoscopic trials.

Authors	Year	N	Thermal	Injection	Lesions treated	Re-bleeding rate n/n (%)	
						Thermal	Injection
Lin et al ⁵⁷	1988	75	HP (10 Fr)	Alcohol	la, lb, IIa	5/41 (2.5)	6/27 (22)
Chung et al ⁵⁸	1991	132	HP (10 Fr)	Epi	la, lb	6/53 (11)	11/65 (17)
Choudari et al ⁵⁹	1992	115	HP (8 Fr)	Epi + ethanalamine	la, lb, IIa	9/57 (16)	8/58 (14)
Llach et al ⁶⁰	1996	101	HP (10 Fr)	Epi + polidocanol	la, lb, IIa, IIb	12/53 (23)	5/51 (10)
Grainek et al ⁶¹	1998	50	HP (10 Fr)	Epi + ethanol	la, lb, IIa, IIb	7/26 (27)	5/24 (21)
Laine ⁶²	1990	60	MPEC (10 Fr)	Ethanol	la, lb, IIa	2/31 (6)	3/29 (10)
Waring et al ⁶³	1991	60	MPEC (10 Fr)	Ethanol	la, lb, IIa, IIb	7/29 (25)	7/31 (23)
Panés et al ⁶⁴	1991	127	Microwave	Epi + polidocanol	la, lb, IIa, IIb	8/65 (12)	3/62 (5)
Carter & Anderson ⁶⁵	1994	44	Nd:YAG	Epi	la, lb, IIa	1/21 (5)	4/23 (17)
Pulanic et al ⁶⁶	1995	315	Nd:YAG	Polidocanol 1%	la, lb, IIa, IIb	7/146 (5)	12/145 (8)

HP = heater probe; MPEC = multipolar electrocoagulation; Epi = epinephrine.

a significant difference may be caused by the inclusion of only a small number of patients in each trial. There is an even greater chance of type II (false-negative) error in these comparative trials than in controlled studies when endoscopic therapies that are better than conventional treatment are stacked up against each other because a larger sample size is required in order to demonstrate a significant difference.

Haemorrhage from an NBVV can be precipitated or intensified by any of these endoscopic modalities. In the above trials, the precipitation or exacerbation of bleeding occurred in 15 out of 167 (9%) Nd:YAG-treated patients, 5 out of 181 (3%) for MPEC and 3 out of 191 (1.6%) for heater probes. Perforation was attributed to the heater probe in two patients and to electrocoagulation and laser therapy in one patient each.

Thus, no definitive differences appear from these comparative trials in terms of effectiveness and safety. Similar to the use of injection therapy, portability and affordability issues would make the heater probe and electrocoagulation more practical than laser treatment given the apparent therapeutic equivalence of the three haemostatic techniques.

Is combined thermal and injection therapy better than the single-treatment modality approach?

On theoretical grounds, the use of thermal therapy following injection of the bleeding point may improve the results of endoscopic treatment. After the injection of epinephrine, the bleeding field may become clearer, facilitating a forceful and precise tamponade of the haemorrhaging vessel. In this scenario, contact thermal methods such as the heater probe and MPEC may be easier to use partly because the amount of tissue sticking to the probe decreases. Treatment end-points such as flattening and cavitation of the bleeding point may be obtained with less effort and more accuracy, allowing a reduction in the total amount of energy employed and probably limiting the risk of complications.

Table 6 presents pooled estimates of response rates in terms of re-bleeding, surgery and mortality from five randomized, prospective trials in which injection therapy,

Table 6. Pooled estimate of response rates from five trials of injection therapy versus combined injection plus thermal methods.^{26,76-79}

Outcome prevented	Total number of patients	Weighted response (P) ¹ , mean ± SE ^{2,3}	
		Injection therapy	Combination therapy
Re-bleeding	500	83% ± 17%	90% ± 14%
Surgery	508	89% ± 13%	93% ± 7.5%
Mortality	509	96% ± 6%	95% ± 7%

¹In calculating the weighted mean response (the percentage of patients avoiding the undesired outcome) for each haemostatic treatment modality, the studies included are characterized by the number of subjects included (n) and the response rate (p) by those subjects.

$${}^2\text{Weighted response} = \frac{n_1 p_1 + n_2 p_2 + n_x p_x}{n_1 + n_2 + n_x}$$

$${}^3\text{SE, standard error} = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2} + \frac{p_x(1-p_x)}{n_x}}$$

consisting of epinephrine either alone or with other agents was compared with combined injection and thermal therapy.^{26,76–79} In this analysis, the results of individual studies are weighted proportionally to sample size. The results are presented as pooled outcomes of the comparison of epinephrine alone with epinephrine plus Nd:YAG laser treatment⁷⁶, epinephrine plus the heater probe⁷⁸, and epinephrine added to gold probe electrocoagulation⁷⁹, of epinephrine plus polidocanol versus epinephrine plus Nd:YAG laser²⁶, and of epinephrine followed by fibrin injection versus epinephrine plus the Nd:YAG laser.⁷⁷ The pooled results for re-bleeding ($90 \pm 14\%$ versus $83 \pm 17\%$) and need for surgery ($94 \pm 7.5\%$ versus $89 \pm 13\%$) favour the combined injection plus thermal treatment, but the mortality rates are similar. The complication rates in these trials were similar: 2.3% in the single- or dual-injection treatment group compared with 2.8% in the combined treatment group.

Individual analyses of these trials reveal patchily distributed benefits of combined injection and thermal therapy over injection therapy alone. Only one trial showed a significantly decreased re-bleeding rate in the combined (injection plus gold probe) treatment compared with injection alone (ARR 28%, 95% CI 9–47%; NNT 4, 95% CI 3–12).⁷⁹ In this study, the combined treatment was also superior to a third arm randomized to gold probe coagulation alone (ARR in re-bleeding rate 22%, 95% CI 4–40%; NNT 5, 95% CI 3–28%). Another study showed a difference in haemostasis rate after the second treatment.⁷⁶ A third trial demonstrated significant reductions in hospital stay and the need for surgery (ARR 22%, 95% CI 3.5–42%; NNT 5, 95% CI 3–29) in the subgroup of patients with spurting bleeding.⁷⁸ None showed a clear benefit in survival in favour of one form of endoscopic haemostasis.

Alternative haemostatic techniques

The body of published literature is much sparser for other haemostatic techniques, aside from the injection and thermal methods already discussed. Alternative techniques used to arrest ulcer bleeding include injection agents such as tissue glue (N-butyl-2-cyanoacrylate) and mechanical methods such as haemoclips and band ligation.

One randomized study that compared tissue glue with diluted epinephrine (1:10⁴) did not find significant difference between these injection agents.⁸⁰ The authors did not report any serious adverse effects in the patients injected with tissue glue, although this agent has been associated with significant complications in other reports.⁸¹

A small study compared band ligation with epinephrine injection in 20 patients with bleeding ulcers. Definitive haemostasis was achieved in all patients treated with haemoclips.⁸² There were two re-bleeding episodes in the injection group, but this difference was not statistically significant.

The use of clips is conceptually attractive for achieving definitive haemostasis when a vessel is identified in the ulcer crater. Complications should be minimized with this device since it does not cause direct damage, and thus the potential to induce enlargement of the ulcer base or cause perforation is reduced. In a comparative study, 78 patients with peptic ulcer bleeding were randomized to epinephrine injection ($n = 37$) or epinephrine injection followed by the application of haemoclips ($n = 41$).⁸³ An RRR of 74% in re-bleeding rate was noted in the combination therapy arm; there was no difference in the other outcomes measured. In 14 cases, clips could not be delivered.

A recent randomized study compared the haemoclip endoscopic method with hypertonic saline injection (HSE) and a combination of the two in 123 patients with bleeding peptic ulcer.⁸⁴ There were no major differences in initial haemostasis,

recurrent bleeding and operation and mortality rates between the three treatment arms. The authors suggest that haemoclips should be the first-choice treatment for spurting haemorrhage because the haemostasis rate for this type of bleeding was lower in the patients treated with HSE. This recommendation is not appropriate since it is based on a subgroup analysis of only two patients with type Ia lesions treated with HSE, of which one re-bleed (the point estimate has a large SE of $\pm 35\%$). The mean number of clips needed to secure haemostasis was not reported, and this information is important as there might be a possible delay in repeating haemoclip treatment if this is required because of the magnitude of acute haemorrhage.

Some other technical problems with the use of haemoclips relate to a difficult application in certain anatomical locations (the posterior wall of the proximal body of the stomach and cardia, and the posterior duodenal wall) as well as the requirement that the clip meet the bleeding lesion at the right angle.

Firm conclusions cannot be drawn from the very limited data available from controlled studies regarding the comparison of the haemostatic efficacy of these newer techniques with that of more traditional methods. More clinical studies need to be conducted using mechanical tools, including clips, bands, endoloops and the sewing machine, before a formal recommendation can be made about the role of these devices.

ENDOSCOPIC MANAGEMENT OF CLOTS

The best management approach to adherent clots still needs to be defined. The NIH Consensus Conference suggested that adherent clots without evidence of active bleeding should not be removed unless a deteriorating clinical situation mandates endoscopic therapy.³² Although the re-bleeding risk associated with these lesions is around 22%³¹, some studies using multivariate analysis have identified the adherent clot to be a high-risk lesion with an independent predictive value for re-bleeding and poor clinical outcome.⁸⁵ The variation in the re-bleeding rate depends on the definition of adherent clot, the timing of endoscopy and whether or not an attempt is made to manipulate the clot. In a prospective outcome study of patients with an ulcer clot, Laine et al. defined an adherent clot as one that resists water irrigation through a multipolar probe for 5 minutes.⁸⁶ In 26 out of 46 patients with such lesions, further bleeding occurred in 8%. In 70% of the other 20 patients, clot removal disclosed high-risk (Ia, Ib and IIa) lesions, which were treated with endoscopic therapy at index endoscopy. The re-bleeding rate in this group of patients was 7%, a figure that is clearly lower than the known risk for further bleeding if these lesions are left untreated.

Another group of investigators evaluated the natural history of tightly adherent clots, defined as blood clots that adhered to the ulcer base despite Water Pik irrigation with a setting of 10 for 10 seconds.⁸⁷ Multivariate analysis found co-morbid diseases, shock and an initial haemoglobin of less than 10 g/dl to be independent predictors of further bleeding in the quarter of patients who had such an outcome.

The issue regarding the actual benefits of the deliberate, forceful removal of clots remains an unsolved question. The safe removal of clots has been achieved by injecting epinephrine in four quadrants around the clot and guillotining off the clot with a snare; the exposed stigmata can then be thermally treated.⁸⁸ In contrast to the combined injection–thermal method, a higher re-bleeding rate has been found using either haemostatic technique alone in the treatment of clots than using conservative management.⁸⁸

In a multicentre study, 56 patients with adherent clots were randomized to the combined endoscopic approach or medical treatment.⁸⁹ The re-bleeding rate was 5% versus 34%, with an RRR in this event of 86% (95% CI 28–97%) and an NNT of 4 (3–13).

Removing the clots that can be easily washed away with water irrigation and treating the underlying stigmata is safe and associated with a better result. On the other hand, the outcome of the forceful removal of clots is variable and associated with an unpredicted clinical course. Thus, despite the findings of the multicentre study⁸⁹ – from which the full report is eagerly awaited – the current available data do not support a systematic policy of attempting forcefully to remove ulcer clots. Perhaps the presence of poor prognostic signs, such as those found in multivariate analysis, can select out a subgroup of patients who would benefit from the removal of clots, which should only be done with discretion and a readiness to render immediate therapy.

AFTER THE FIRST RE-BLEEDING EPISODE, SHOULD IT BE REPEAT ENDOSCOPY OR SURGICAL INTERVENTION?

Re-bleeding occurs in 10–20% of patients after initially successful haemostasis. In most of the randomized trials to date, surgery has been reserved as a rescue procedure for endoscopic failure or evaluated as one of the treatment endpoints after endoscopic haemostasis.

A recent published trial from Hong Kong compared surgical intervention ($n = 44$) as a primary intervention with endoscopic treatment ($n = 48$) for patients with recurrent bleeding after initially successful endoscopic therapy.⁹⁰ There was no difference in the overall mortality rate (18% versus 10%), although the patients randomized to surgery had a higher complication rate than the patients in the endoscopic re-treatment arm (36% versus 15%). Mortality is high when surgery is undertaken after a second re-bleeding episode, as demonstrated by the 50% mortality rate in this study in the patients assigned to endoscopy who underwent a ‘salvage’ surgical procedure for that reason. Thus, the clinical challenge remains how to identify accurately those patients who are at risk of endoscopic treatment failure and refer them for early surgery.

In several studies, multivariate analyses have consistently identified shock and ulcer size greater than 2 cm as independent risk factors for the failure of initial endoscopic therapy and endoscopic re-treatment after recurrent bleeding.^{90–92} In light of the available data, re-bleeding patients who are fit surgical candidates and have poor prognostic factors should be considered for definitive surgery, which should prevent the risks that result from repeated but unsuccessful endoscopic attempts.

Second-look endoscopy and prophylactic re-treatment has been proposed as an alternative strategy to reduce re-bleeding and the need for surgery. The results of randomized trials have been conflicting. In one study, the rate of permanent haemostasis was significantly better in the group of patients randomized to prophylactic epinephrine injection than in the control group.⁹³ Another trial found a trend toward a better result in the group of patients who received second-look endoscopy and re-treatment with epinephrine injection.⁹⁴ In a recent study, 105 patients initially treated with epinephrine followed by fibrin/thrombin injection were randomized to second-look endoscopy ($n = 52$) within 24 hours or observation.⁹⁵ Forrest Ia, Ib or IIa lesions were re-treated with the same regimen. Programmed routine endoscopy did not have any influence on re-bleeding or any other outcome

parameter. In a fourth trial, 40 high-risk patients (defined as having a Baylor score of over 5) were randomized to routine scheduled endoscopy the next day and re-treatment with the heater probe versus no re-treatment.⁹⁶ Pre-emptive endoscopy and re-treatment had a significant impact on the re-bleeding rate, leading to an RRR of 100%, an ARR of 24% and an NNT of 4 compared with the group of patients not re-treated. A difference in patient selection may account for the divergent results between this last study and some of the others, essentially because the latter study included a subgroup of patients at high risk of re-bleeding after successful endoscopic therapy, while the other studies included all-comers. Whether such an approach based on re-bleeding risk stratification will systematically reduce the rate of adverse events associated with further bleeding still remains to be determined in larger, prospective trials.

CONCLUSIONS

Ten years have passed since the author of a sober review on methodology of therapeutic endoscopy emphasized the importance of several issues in this area⁹⁷:

1. the need for well-designed controlled and comparative trials evaluating new haemostatic techniques before they are blindly adopted by practising physicians;
2. the standardization of a nosology concerning the terms necessary to communicate the results of these trials, especially as they relate to the objective measurement of outcomes that reflect the efficacy of endoscopic haemostasis;
3. the definition of the natural history of SRH;
4. the inclusion of large sample sizes to avoid type II errors, these being preferably within a multicentre framework so that the applicability of haemostatic techniques can be tested in the hands of a wide array of endoscopists.

The first three goals have been largely realized, but, except for isolated efforts⁵⁶, the need for large trials with enough power to detect real differences in hard end-points such as mortality remains to be fulfilled. A hope that this limitation can be overcome is provided by the work being carried out by the Clinical Outcomes Research Initiative (CORI project).⁹⁸

Although many questions remain to be answered, remarkable advances have been made in the therapeutic endoscopy of bleeding ulcers. Significant benefits in terms of a reduction in re-bleeding and in the need for emergency surgery have been shown with most haemostatic techniques. Future investigation is needed to quantify the safety and clinical efficacy of new techniques such as haemoclips, endoloops, endoscopic suturing and APC. Newer haemostatic modalities such as cryotherapy⁹⁹ should be brought into the clinical arena in an attempt to improve upon the results already obtained, and more studies on outcomes research^{61,100} are necessary to establish the cost-effectiveness of the various haemostatic techniques.

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