STOMACH

Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis

Joseph J Y Sung, Kelvin K F Tsoi, Larry H Lai, Justin C Y Wu, James Y W Lau

....

See end of article for authors' affiliations
....

Correspondence to:
Professor Joseph J Sung, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, NT, Hong Kong; joesung@cuhk. edu.hk

Revised 30 April 2007
Accepted 8 May 2007
Published Online First 12 June 2007
....

Background: Hemoclips, injection therapy and thermocoagulation (heater probe or electrocoagulation) are the most commonly used types of endoscopic hemostasis for the control of non-variceal gastrointestinal bleeding.
Aim: To compare the efficacy of hemoclips versus injection or thermocoagulation in endoscopic hemostasis by pooling data from the literature.
Method: Publications in the English literature (MEDLINE, EMBASE and Cochrane Library) as well as abstracts in major international conferences were searched using the keywords ''hemoclips'' and ''bleeding'', and 15 trials fulfilling the search criteria were found. Outcome measures included: initial hemostasis (after endoscopic intervention); recurrent bleeding; definitive hemostasis (no recurrent bleeding until the end of follow-up); the requirement for surgical intervention; and all-cause mortality. The heterogeneity of trials was examined and the effects were pooled by meta-analysis.
Results: Of 1156 patients recruited in the 15 studies, 390 were randomly assigned to receive clips alone, 242 received clips combined with injection, 359 received injection alone, and 165 received thermocoagulation with or without injection. Definitive hemostasis was higher with hemoclips (86.5%) than injection (75.4%; RR 1.14, 95% CI 1.00–1.30), or endoscopic clips with injection (88.5%) compared with injections alone (78.1%; RR 1.13, 95% CI 1.03–1.23), leading to a reduced requirement for surgery but no difference in mortality. Compared with thermocoagulation, there was no improvement in definitive hemostasis with clips (81.5% versus 81.2%; RR 1.00, 95% CI 0.77–1.31). These estimates were robust in sensitivity analyses. There was also no difference between clips and thermocoagulation in rebleeding, the need for surgery and mortality. The reported locations of failed hemoclip applications included posterior wall of duodenal bulb, posterior wall of gastric body and lesser curve of the stomach.
Conclusion: Successful application of hemoclips is superior to injection alone but comparable to thermocoagulation in producing definitive hemostasis. There was no difference in all-cause mortality irrespective of the modalities of endoscopic treatment.

A cute non-variceal upper gastrointestinal bleeding remains a common medical problem associated with significant morbidity and mortality and healthcare resource use. Large population-based studies and collaborative databases have estimated the annual incidence of acute upper gastrointestinal bleeding at approximately 50 to 170 per 100 000 population.[1–5] The case fatality of upper gastrointestinal bleeding is approximately 5–10%, either directly caused by the bleeding episode or through decompensation in concurrent medical illnesses.[1–5]

Endoscopic therapy has generally been recommended as the first-line treatment for upper gastrointestinal bleeding as it has been shown to reduce recurrent bleeding, the need for surgery and mortality.[6] The American Society of Gastrointestinal Endoscopy guidelines stated that no single modality has been shown to be superior for treating upper gastrointestinal bleeding caused by peptic ulcer disease.[7] The United Kingdom guidelines suggested that hemoclips are particularly useful for actively bleeding large vessels, but pointed out that they may be difficult to apply to awkwardly placed ulcers.[8] The Non-variceal Upper GI Bleeding Conference Group, which consisted mostly of Canadian experts gave most discrete recommendations: (1) no single method of endoscopic injection is superior to the others; (2) no single method of endoscopic thermal coaptive therapy is superior to the others; and (3) the placement of clips is a promising endoscopic hemostasis therapy for high-risk
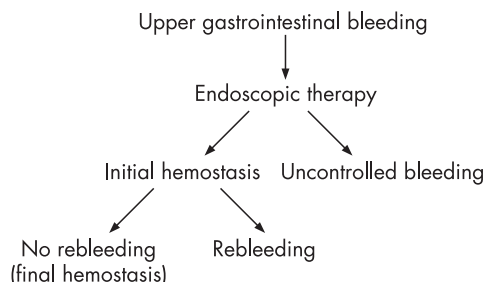
stigmata.[9] There are, however, variable successes in the literature with hemostasis using endoscopic clips, which may reflect difficulties with their placement.

Studies comparing clips with other endoscopic treatment modalities have yielded conflicting results. Most studies using clips have been limited by relatively small sample sizes and, in some cases, reporting outcomes only of patients in whom clips were successfully placed rather than performing an intention-to-treat analysis.[10–24] There are also variations in study design, entry criteria and outcome criteria. The endoscopic techniques used were also dissimilar in that some combined clips with injection (i.e. to stop bleeding first with injection therapy before applying clips), whereas others used clips alone in actively bleeding ulcers. We performed a meta-analysis based on published data to determine whether the use of endoscopic clips benefits patients with non-variceal upper gastrointestinal bleeding.

METHODS

We performed a search using the relevant keywords of ''hemoclips'' and ''peptic ulcer bleeding'' to identify randomized clinical trials in full publications of the English literature from different computerized databases: MEDLINE (1950 to January 2007), EMBASE (1980 to January 2007), and the Cochrane Centre Register of Controlled Trials (1st quarter

....

Upper gastrointestinal bleeding

Endoscopic therapy

Initial hemostasis   Uncontrolled bleeding

No rebleeding   Rebleeding
(final hemostasis)

Figure 1 A simple flowchart for peptic ulcer or Dieulafoy bleeding treatment.

2007). We also manually searched the abstracts published in major international conferences (Digestive Disease Week, United European Gastrointestinal Week and Asia Pacific Digestive Week) over the past 10 years, and scanned the articles from the bibliographies of retrieved trials.

We included all trials that randomly assigned patients to hemoclips or alternative therapies (thermocoagulations or injections) for treating non-variceal upper gastrointestinal bleeding. Randomized controlled trials were included if they met the following criteria: (1) applied endoscopic therapy only to active bleeding ulcers or ulcers with adherent blood clot or protuberant vessels (Forret I, IIa and IIb); (2) used a concurrent control group; (3) concomitant therapy was applied equally to both intervention arms; (4) diagnosis of acute bleeding from peptic ulcers or Dieulafoy lesions was made endoscopically; (5) at least one of the following outcomes was reported: initial hemostasis after first endoscopic therapy; rebleeding; definitive hemostasis, surgical intervention; mortality; and (6) it was possible to isolate data for patients with bleeding peptic ulcers. We excluded patients with the diagnosis of bleeding Mallory Weiss tear. Bleeding from a Mallory Weiss tear is often self-limiting and runs a benign course.

The primary outcome of this study is definitive hemostasis defined as the successful control of bleeding after the first endoscopic therapy until the end of follow-up. Secondary outcomes include initial hemostasis (control of bleeding after the first endoscopic treatment), rebleeding (clinical evidence of recurrent bleeding after first endoscopic therapy), surgery and death from any cause (30-day mortality or "in-hospital" mortality). A flowchart outlining our outcome definitions are presented in fig 1.
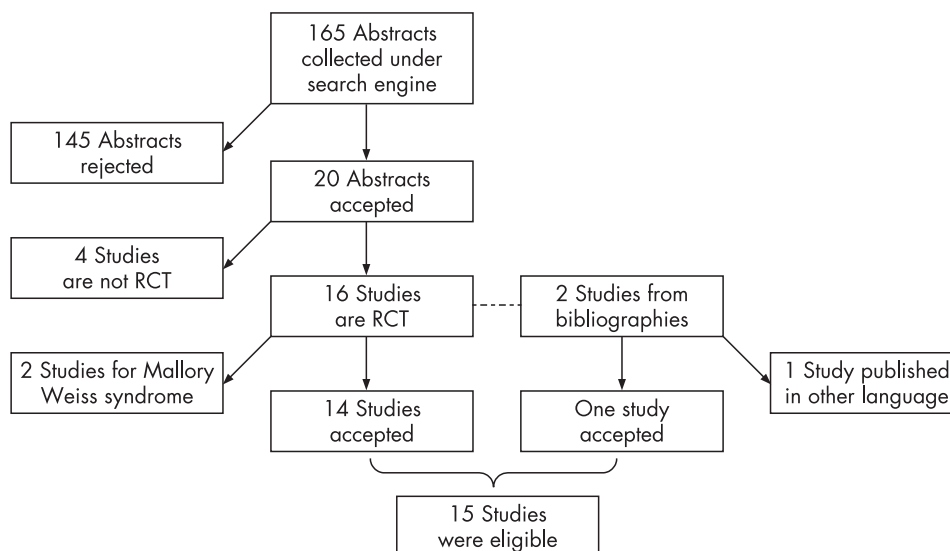
Two investigators (K.K.T., L.H.L.) independently assessed the papers generated for relevancy, and only rejected papers that fulfilled the following explicit exclusion criteria: (1) not written in English for abstract; (2) not related to bleeding peptic ulcers or Dieulafoy lesions; and (3) not concerning a clinical question regarding human subjects. We reviewed each identified trial and determined inclusion. Investigators also independently abstracted the data into a standardised data extraction form. When discrepancies were found, the third investigator (J.J.S.) would make the definitive decision for trial eligibility and data extraction.

The quality of each trial was assessed on the basis of five criteria: (1) study described as prospectively randomized; (2) randomization by concealed allocation or computer-generated allocation; (3) listing of exclusion criteria for ineligible patients; (4) clear definitions of outcomes, i.e. initial hemostasis, recurrent bleeding and definitive hemostasis; and (5) pre-defined salvage procedures when endoscopic treatment failed to control bleeding. These quality parameters have included certain "inclusion criteria" such as the use of a control group with otherwise identical concomitant therapy, and a clear definition of outcome parameters.

We performed a meta-analysis of outcomes as appropriate by combining different groups of trials and used the Mantel–Haenszel method (RevMan, version 4.2.8). Group 1 trials compared hemoclips with injections. Group 2 trials compared hemoclips with injections versus injections alone. Group 3 trials compared hemoclips with or without injections versus thermocoagulation (heater probe or electrocoagulation) with or without injections. Statistical heterogeneity was evaluated, and $p < 0.1$ was considered significant. We assessed heterogeneity with I^2, which describes the percentage of total variation across studies caused by heterogeneity rather than chance. High values of I^2 would show increasing heterogeneity. We used a fixed effects model for significant homogeneous studies. Otherwise, we applied a random effects model. All outcomes were summarized as relative risk (RR) and 95% confidence intervals. We performed one-way sensitivity analyses on study duration (< 4 weeks versus ϵ 4 weeks), adjuvant proton pump inhibitors (PPI) (yes versus no), and quality of trial (high (quality score > 3) versus low (quality score δ 3)) to test the robustness of the combined estimates.

RESULTS

We initially identified 165 articles through database searches. All abstracts were scanned and we retrieved 18 studies and two

165 Abstracts collected under search engine

145 Abstracts rejected

20 Abstracts accepted

4 Studies are not RCT

16 Studies are RCT

2 Studies from bibliographies

2 Studies for Mallory Weiss syndrome

14 Studies accepted

One study accepted

1 Study published in other language

15 Studies were eligible

Figure 2 Results of literature search. RCT, randomised controlled trial.

Table 1 Quality of randomised clinical trials to compare effectiveness of hemoclips
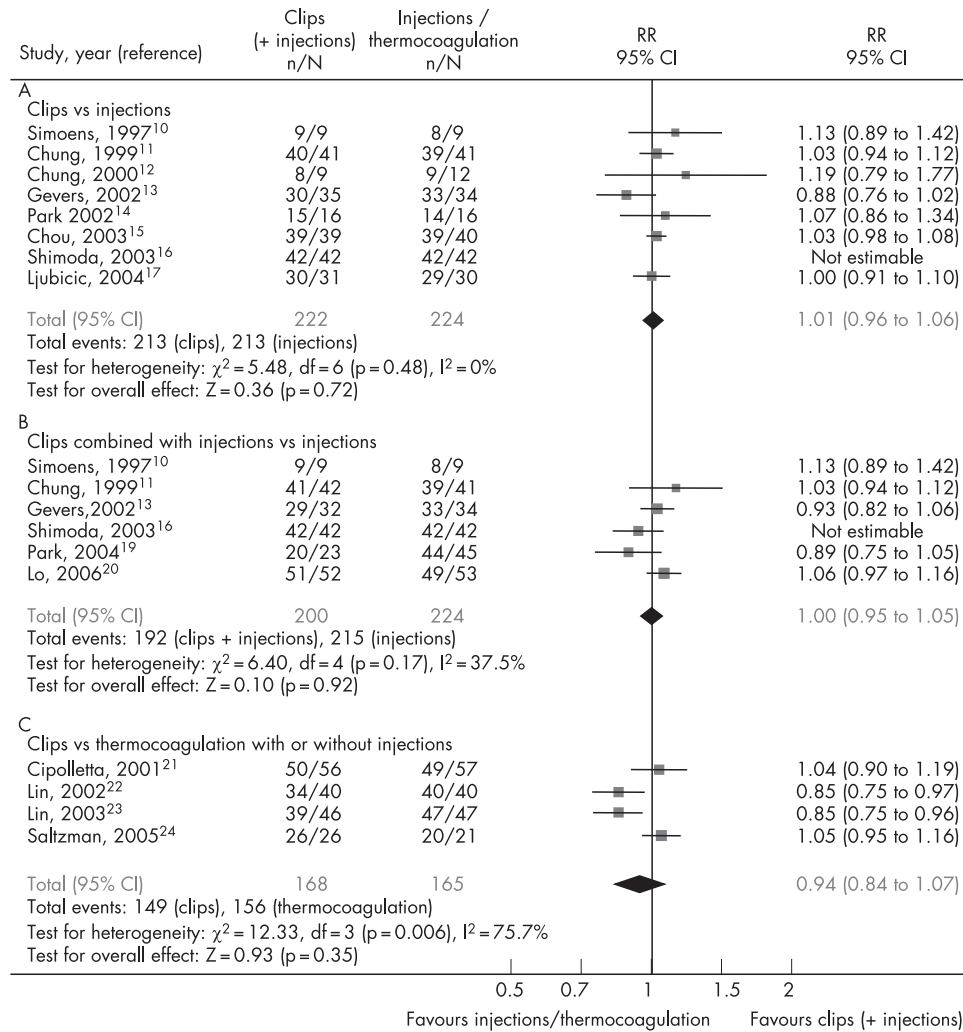
Trial	Publication type	Comparison	N	Age (mean)	Gender (male%)	Study duration (weeks)	Adjuvant PPI	Quality score (1–5)
Hemoclips versus injection								
Simoens, 1997[10]	Abstract	Hemoclips (n = 9) vs epinephrine + polidocanol (n = 9)	18	NA	NA	NA	No	1
Chung, 1999[11]	Full-text	Hemoclips (n = 41) vs hypertonic saline-epinephrine (n = 41)	82	56.2	41%	1	No	3
Chung, 2000[12]	Full-text	Hemoclips (n = 9) vs hypertonic saline-epinephrine (n = 12)	21	53.2	38%	1	No	5
Gevers, 2002[13]	Full-text	Hemoclips (n = 35) vs epinephrine + polidocanol (n = 34)	69	65.5	NA	4	No	5
Park, 2003[14]	Full-text	Hemoclips (n = 16) vs isotonic saline (n = 16)	32	61.1	38%	1	No	3
Chou, 2003[15]	Full-text	Hemoclips (n = 39) vs distilled water (n = 40)	79	64.0	39%	8	No	4
Shimoda, 2003[16]	Full-text	Hemoclips (n = 42) vs absolute ethanol (n = 42)	84	58.8	35%	8	Yes	3
Ljubicic, 2004[17]	Full-text	Hemoclips (n = 31) vs polidocanol (n = 30)	61	61.1	31%	<1	Yes	2
Hemoclips + injection versus injection								
Villanueva, 1996[18]	Abstract	Hemoclips + epinephrine (n = 42) vs epinephrine (n = 37)	79	NA	NA	NA	Yes	1
Simoens, 1997[10]	Abstract	Hemoclips + epinephrine-polidocanol (n = 9) vs epinephrine-polidocanol (n = 9)	18	NA	NA	NA	No	1
Chung, 1999[11]	Full-text	Hemoclips + hypertonic saline-epinephrine (n = 41) vs hypertonic saline-epinephrine (n = 41)	82	56.2	41%	1	No	3
Gevers, 2002[13]	Full-text	Hemoclips + epinephrine + polidocanol (n = 32) vs epinephrine + polidocanol (n = 34)	66	65.5	NA	4	No	5
Shimoda, 2003[16]	Full-text	Hemoclips + absolute ethanol (n = 42) vs absolute ethanol (n = 42)	84	58.8	35%	8	Yes	3
Park, 2004[19]	Full-text	Hemoclips + epinephrine (n = 23) vs epinephrine (n = 45)	68	62.0	43%	1	Yes	5
Lo, 2006[20]	Full-text	Hemoclips + epinephrine (n = 52) vs epinephrine (n = 53)	105	63.5	38%	8	Yes	5
Hemoclips versus thermocoagulation								
Cipolletta, 2001[21]	Full-text	Hemoclips (n = 56) vs heater probe (n = 57)	113	58.0	26%	4	Yes	5
Lin, 2002[22]	Full-text	Hemoclips (n = 40) vs heater probe (n = 40)	80	65.9	44%	2	Yes	5
Lin, 2003[23]	Full-text	Hemoclips (n = 46) vs heater probe + epinephrine (n = 47)	93	65.8	40%	2	Yes	5
Saltzman, 2005[24]	Full-text	Hemoclips (n = 26) vs bipolar electrocautery probe + epinephrine (n = 21)	47	65.1	36%	8	Yes	5

NA, Not available in the content of the study; PPI, proton pump inhibitor.

abstracts. We excluded four studies using non-randomized methodology and two studies recruiting Mallory Weiss syndrome with bleeding. We further identified two studies from the bibliographies of retrieved studies, but we excluded one that was published in non-English literature. The definitive analysis in this meta-analysis included 15 studies published from 1996 to 2006 (fig 2).

Among the 15 studies, eight compared the efficacy of hemoclips and injections, seven compared hemoclips with injections versus injections alone, and four compared hemoclips alone versus thermocoagulations (heater probe or electrocoagulation) with or without injections. Most studies were of high quality, with only four trials graded below 3 (table 1). A total of 1156 patients participated in these randomized trials, and the reported data

collection periods were from July 1994 to July 2004. The number of participants in individual trials ranged from 18 to 113. Four trials did not report data for gender. The remaining trials included 713 (70.0%) male patients and the mean age was 61.7 years. All trials employing endoscopic clips used Olympus hemoclips, eight injection solutions used singly or in combination were mentioned, namely epinephrine (in five studies), epinephrine-polidocanol (in three studies), hypertonic saline-epinephrine (in three studies), absolute ethanol (in two studies), isotonic saline-epinephrine, polidocanol or distilled water each in one study. In the thermocoagulation groups, bipolar electrocautery probes (Boston Scientific, Natick, Massachusetts, USA) were used in one study and heater probes (Olympus, Tokyo, Japan) were used in three studies.

Study, year (reference)	Clips (+ injections) n/N	Injections / thermocoagulation n/N	RR 95% CI	RR 95% CI
A				
Clips vs injections				
Simoens, 1997[10]	9/9	8/9		1.13 (0.89 to 1.42)
Chung, 1999[11]	40/41	39/41		1.03 (0.94 to 1.12)
Chung, 2000[12]	8/9	9/12		1.19 (0.79 to 1.77)
Gevers, 2002[13]	30/35	33/34		0.88 (0.76 to 1.02)
Park 2002[14]	15/16	14/16		1.07 (0.86 to 1.34)
Chou, 2003[15]	39/39	39/40		1.03 (0.98 to 1.08)
Shimoda, 2003[16]	42/42	42/42		Not estimable
Ljubicic, 2004[17]	30/31	29/30		1.00 (0.91 to 1.10)
Total (95% CI)	222	224		1.01 (0.96 to 1.06)
Total events: 213 (clips), 213 (injections)				
Test for heterogeneity: $\chi^2 = 5.48$, df = 6 (p = 0.48), $I^2 = 0\%$				
Test for overall effect: Z = 0.36 (p = 0.72)				
B				
Clips combined with injections vs injections				
Simoens, 1997[10]	9/9	8/9		1.13 (0.89 to 1.42)
Chung, 1999[11]	41/42	39/41		1.03 (0.94 to 1.12)
Gevers,2002[13]	29/32	33/34		0.93 (0.82 to 1.06)
Shimoda, 2003[16]	42/42	42/42		Not estimable
Park, 2004[19]	20/23	44/45		0.89 (0.75 to 1.05)
Lo, 2006[20]	51/52	49/53		1.06 (0.97 to 1.16)
Total (95% CI)	200	224		1.00 (0.95 to 1.05)
Total events: 192 (clips + injections), 215 (injections)				
Test for heterogeneity: $\chi^2 = 6.40$, df = 4 (p = 0.17), $I^2 = 37.5\%$				
Test for overall effect: Z = 0.10 (p = 0.92)				
C				
Clips vs thermocoagulation with or without injections				
Cipolletta, 2001[21]	50/56	49/57		1.04 (0.90 to 1.19)
Lin, 2002[22]	34/40	40/40		0.85 (0.75 to 0.97)
Lin, 2003[23]	39/46	47/47		0.85 (0.75 to 0.96)
Saltzman, 2005[24]	26/26	20/21		1.05 (0.95 to 1.16)
Total (95% CI)	168	165		0.94 (0.84 to 1.07)
Total events: 149 (clips), 156 (thermocoagulation)				
Test for heterogeneity: $\chi^2 = 12.33$, df = 3 (p = 0.006), $I^2 = 75.7\%$				
Test for overall effect: Z = 0.93 (p = 0.35)				

0.5 0.7   1   1.5   2
Favours injections/thermocoagulation   Favours clips (+ injections)

Figure 3 Forest plots for initial hemostasis comparison.

Clips versus injections

Eight trials were identified for the comparison of hemoclips alone with injections alone. Statistical heterogeneity was only found for the outcomes of definitive hemostasis ($I^2 = 46.6\%$, p = 0.07). No significant difference in initial hemostasis was found between hemoclips alone (95.9%) versus injection alone therapy (95.1%; RR 1.01, 95% CI 0.96 to 1.06; fig 3A). The results from a random effect model showed a marginally significantly higher probability of achieving definitive hemostasis with hemoclips (86.5%) than injection (75.4%; RR 1.14, 95% CI 1.00 to 1.30; fig 4A). Besides, hemoclips showed a significant reduction in rebleeding (9.5%) compared with injection (19.6%; RR 0.49, 95% CI 0.30 to 0.79; fig 5A) and the need for surgery (2.3% vs 7.4%; RR 0.37, 95% CI 0.15 to 0.90) in the fixed effects models (fig 6A). An insignificant difference in all-cause mortality was, however, found comparing the two modalities of treatment; pooled rates were 2.7% in the hemoclip group and 1.8% in the injection group (RR 1.45, 95% CI 0.44 to 4.74; fig 7A).

Clips combined with injections versus injections alone

Seven trials were identified for the comparison of endoscopic clips combined with injections versus injections alone. Statistical heterogeneity was not found among these trials for all outcomes (p > 0.1). No significant difference was found in initial hemostasis between hemoclips combined with injections (96.0%) versus injections alone (96.0%; RR 1.00, 95% CI 0.95 to

1.05; fig 3B). A significantly higher definitive success in hemostasis was found in endoscopic clips with injection (88.5%) than with injections alone (78.1%; RR 1.13, 95% CI 1.03 to 1.23; fig 4B). Furthermore, clips combined with injections showed a significant reduction in rebleeding (8.3% vs 18.0%; RR 0.47, 95% CI 0.28 to 0.76; fig 5B) and the need for surgery (1.3% vs 6.3%; RR 0.23, 95% CI 0.08 to 0.70; fig 6B) using the random effect model. An insignificant difference in all-cause mortality has been demonstrated comparing the two treatment modalities; the pooled rates were 2.5% in the combined hemoclip group and 1.9% in the injection group (RR 1.23, 95% CI 0.45 to 3.37; fig 7B).

Clips versus thermocoagulation with or without injection

Four trials were identified for the comparison of hemoclips versus thermocoagulation with or without injections. Statistical heterogeneities were found among the trials for the outcomes of initial hemostasis ($I^2 = 75.7\%$, p = 0.006), definitive hemostasis ($I^2 = 84.0\%$, p < 0.001), and rebleeding ($I^2 = 53.3\%$, p = 0.09). Initial hemostasis was insignificantly different between hemoclips (88.7%) and thermocoagulation (94.5%; RR 0.94, 95% CI 0.84 to 1.07; fig 3C). Definitive hemostasis of clips (81.5%) and thermocoagulation (81.2%) were comparable (RR 1.00, 95% CI 0.77 to 1.31; fig 4C). There was no difference between clips and thermocoagulation in rebleeding (7.1% vs 13.3%; RR 0.65, 95% CI 0.21 to 2.02; fig 5C),
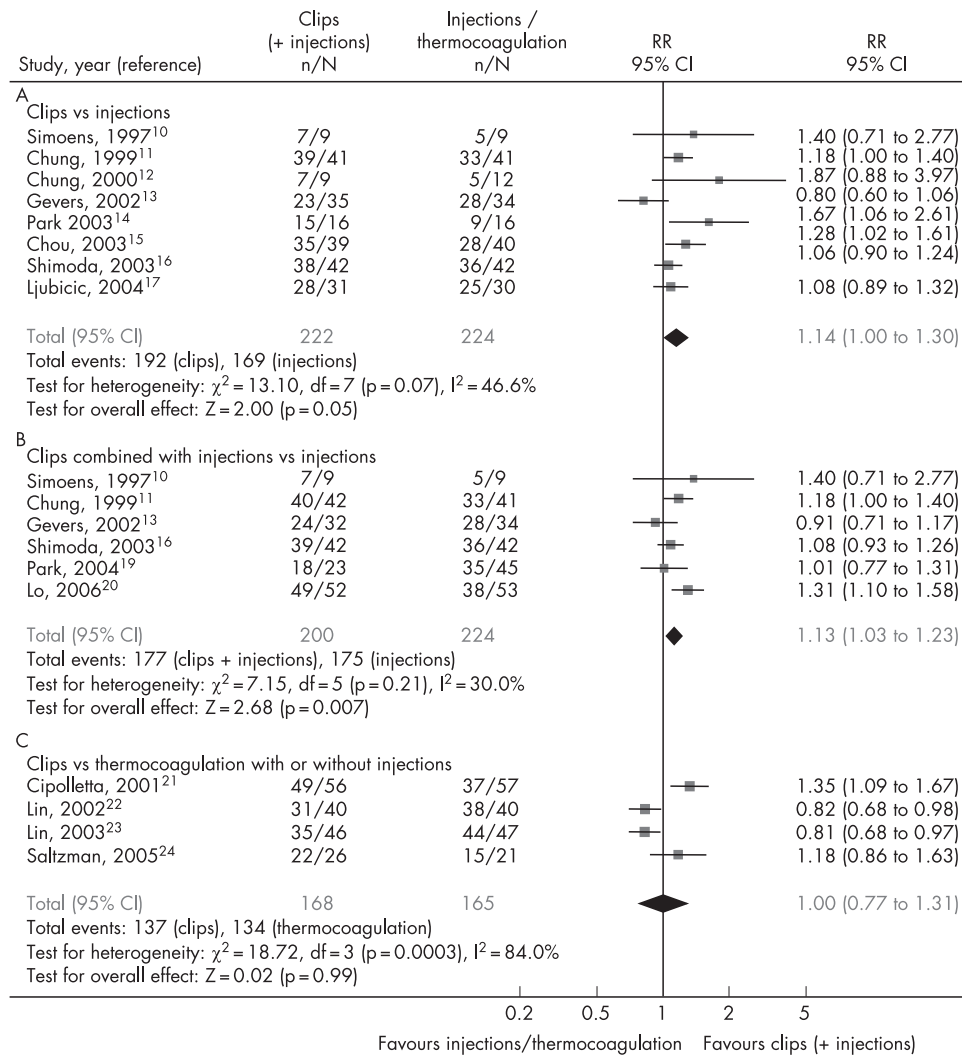
Figure 4 Forest plots for definitive hemostasis comparison.

the need for surgery (4.2% vs 4.8%; RR 0.84, 95% CI 0.32 to 2.24; fig 6C) and all-cause mortality (3.6% vs 3.6%; RR 0.96, 95% CI 0.34 to 2.76; fig 7C) in the fixed effects model.

Sensitivity analyses

One-way sensitivity analyses showed that the results on initial hemostasis, definitive hemostasis, rebleeding and the need for surgery are very consistent based on study durations, the use of adjuvant PPI, and the qualities of trials (table 2). There was no difference in the risk of mortality when comparing clips with or without injections versus injections alone. As there were only four trials comparing clips versus thermocoagulation, no sensitivity analysis was conducted.
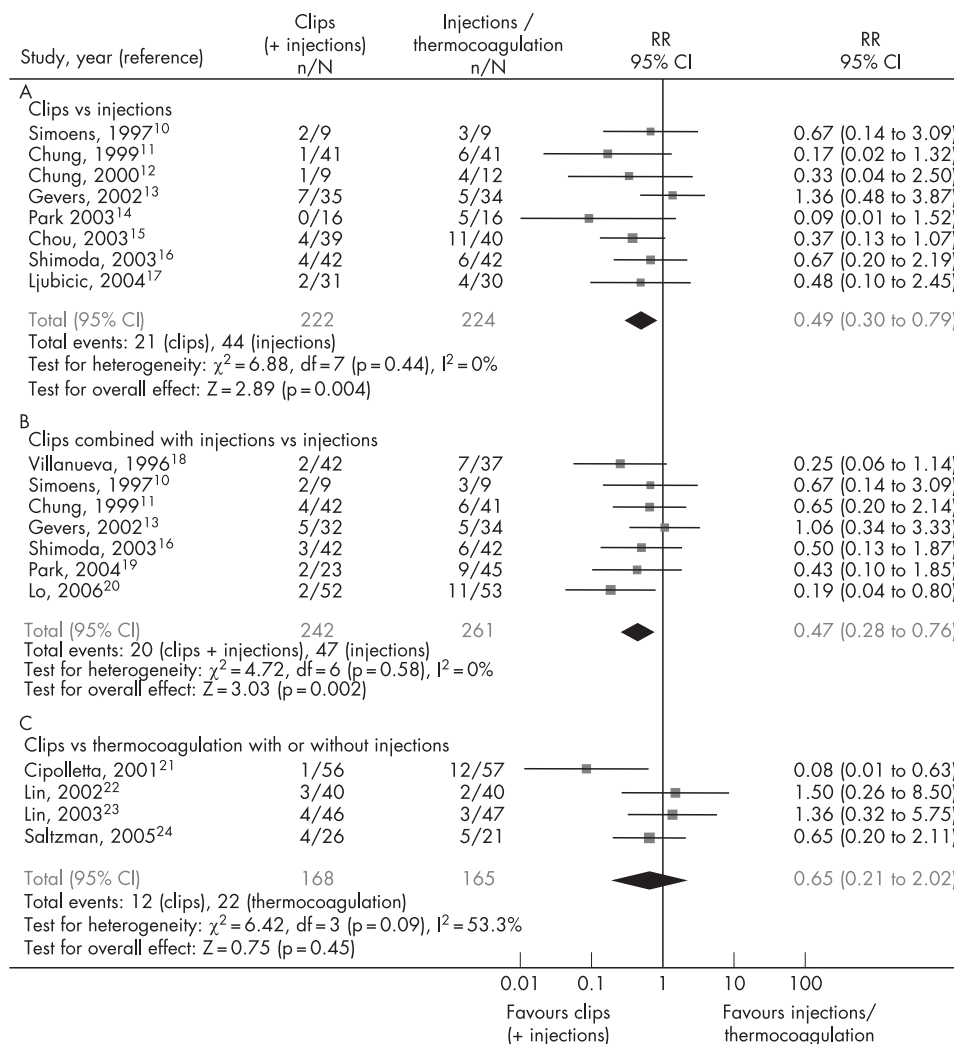
Failure of clips

Four studies described the failure of clip application as a result of the awkward position of ulcers.[20–23] Positions described as difficult for clips were posterior wall of the duodenal bulb, posterior wall gastric body and lesser curve of the stomach. Among them, the posterior wall of the duodenal bulb was the most commonly described position.

DISCUSSION

The pooled data of 15 studies indicated that endoscopic clipping, with or without injection, is superior to endoscopic injection alone in the treatment of bleeding peptic ulcer and bleeding

Dieulafoy lesions. Clipping gives a higher rate of definitive hemostasis after a single treatment with less rebleeding and less requirement for surgery. On the other hand, comparing endo-scopic clipping with thermal therapy showed no distinct advantage. There was no demonstrable difference in hemostasis, no difference in surgery and mortality.

In this study, we have excluded Mallory Weiss syndrome, vascular ectasia, esophageal erosion and gastritis although, together they constitute up to 30% of cases of non-variceal upper gastrointestinal bleeding. Unlike peptic ulcers and Dieulafoy lesions, bleeding from these lesions is usually self-limiting and thus the efficacy of endoscopic treatment is hard to evaluate. Most studies in this meta-analysis used similar inclusion criteria for patients who had high-risk peptic ulcer or Dieulafoy lesions (i.e. either actively bleeding or showing a protuberant vessel or adherent clot). This is in line with the international guidelines.[7–9] All studies used the same endo-scopic clip, which is the hemoclip (Olympus), and that removes a potential factor of heterogeneity with different device designs. Approximately half the studies have used adjuvant PPI. This could potentially affect the outcome as high-dose PPI have been shown to reduce recurrent bleeding and reduce surgical intervention.[25 26] On the other hand, only two out of eight studies comparing endoscopic clipping with endoscopic injec-tion used adjuvant PPI. Nevertheless, there is some degree of heterogeneity introduced that necessitates the use of a random effects model in analysis. Furthermore, sensitivity analysis did

Study, year (reference)	Clips (+ injections) n/N	Injections / thermocoagulation n/N	RR 95% CI
A			
Clips vs injections			
Simoens, 1997[10]	2/9	3/9	0.67 (0.14 to 3.09)
Chung, 1999[11]	1/41	6/41	0.17 (0.02 to 1.32)
Chung, 2000[12]	1/9	4/12	0.33 (0.04 to 2.50)
Gevers, 2002[13]	7/35	5/34	1.36 (0.48 to 3.87)
Park 2003[14]	0/16	5/16	0.09 (0.01 to 1.52)
Chou, 2003[15]	4/39	11/40	0.37 (0.13 to 1.07)
Shimoda, 2003[16]	4/42	6/42	0.67 (0.20 to 2.19)
Ljubicic, 2004[17]	2/31	4/30	0.48 (0.10 to 2.45)
Total (95% CI)	222	224	0.49 (0.30 to 0.79)

Total events: 21 (clips), 44 (injections)
Test for heterogeneity: $\chi^2 = 6.88$, df = 7 (p = 0.44), $I^2 = 0\%$
Test for overall effect: Z = 2.89 (p = 0.004)

B			
Clips combined with injections vs injections			
Villanueva, 1996[18]	2/42	7/37	0.25 (0.06 to 1.14)
Simoens, 1997[10]	2/9	3/9	0.67 (0.14 to 3.09)
Chung, 1999[11]	4/42	6/41	0.65 (0.20 to 2.14)
Gevers, 2002[13]	5/32	5/34	1.06 (0.34 to 3.33)
Shimoda, 2003[16]	3/42	6/42	0.50 (0.13 to 1.87)
Park, 2004[19]	2/23	9/45	0.43 (0.10 to 1.85)
Lo, 2006[20]	2/52	11/53	0.19 (0.04 to 0.80)
Total (95% CI)	242	261	0.47 (0.28 to 0.76)

Total events: 20 (clips + injections), 47 (injections)
Test for heterogeneity: $\chi^2 = 4.72$, df = 6 (p = 0.58), $I^2 = 0\%$
Test for overall effect: Z = 3.03 (p = 0.002)

C			
Clips vs thermocoagulation with or without injections			
Cipolletta, 2001[21]	1/56	12/57	0.08 (0.01 to 0.63)
Lin, 2002[22]	3/40	2/40	1.50 (0.26 to 8.50)
Lin, 2003[23]	4/46	3/47	1.36 (0.32 to 5.75)
Saltzman, 2005[24]	4/26	5/21	0.65 (0.20 to 2.11)
Total (95% CI)	168	165	0.65 (0.21 to 2.02)

Total events: 12 (clips), 22 (thermocoagulation)
Test for heterogeneity: $\chi^2 = 6.42$, df = 3 (p = 0.09), $I^2 = 53.3\%$
Test for overall effect: Z = 0.75 (p = 0.45)

0.01 0.1 1 10 100
Favours clips (+ injections) — Favours injections/ thermocoagulation

Figure 5 Forest plots for rebleeding comparison.

not show that by removing studies with or without using adjuvant PPI, the results remain robust. All studies comparing endoscopic clipping with thermocoagulation had used adjuvant PPI, and because of the small number of trials in this category, sensitivity analysis was not performed.

The superiority of endoscopic clipping (with or without injection) over endoscopic injection alone should not be surprising, because injection leads to transient hemostasis by tamponade effects produced by the volume of fluid injected. A previous randomised controlled trial[27] and a subsequent meta-analysis of combination therapy showed improved results over injection monotherapy.[28] Endoscopic clipping producing mechanical control for bleeding vessels below the ulcer is understandably more effective than endoscopic injection in securing hemostasis in upper gastrointestinal bleeding.

There has been some debate as to whether applying injection before endoscopic clipping adds any benefit to clipping alone. Some endoscopists prefer to use clipping without injection, especially when a protruding vessel can be seen at the ulcer base. On the other hand, in a profusely bleeding ulcer, which obscures the endoscopic view, transient control of active bleeding may facilitate the precise placement of clips on the site of bleeding. Sometimes, however, injection leads to tissue edema causing difficulties in applying the clip precisely on the bleeding vessel. In the current meta-analysis, clipping with or without injection showed consistently superior results compared with injection alone. A direct comparison of

clipping versus clipping after injection is, however, not available.

Despite improvements in sustaining hemostasis by clipping or thermocoagulation leading to less rebleeding and fewer interventions with surgery, mortality has not been reduced. All-cause mortality of the three groups of pooled data ranges from 1.8% to 3.6%, and there is no indication of a reduction in the death rate. The relatively low mortality reported in these series is likely to be related to the short follow-up of some studies and the selection criteria of the studies. Nevertheless, it is an enigma that despite successful control of hemorrhage in many studies using various combinations of endoscopic and pharmacological therapies, the mortality rate remains unchanged. It is possible that, as we are treating an increasingly older population of upper gastrointestinal bleeding patients with frequent and significant comorbidities, gastrointestinal bleeding merely represents a terminal event of these very ill patients dying of cardiopulmonary decompensation and multi-organ failure.

There have recently been reports of new models of endoscopic clips, including the TriClip (Cook Endoscopy, Winston-Salem, North Carolina, USA), the Resolution Clip (Boston Scientific) and the Multi-Clip (InScope, Ethicon, Cincinnati, Ohio, USA). Unlike the Endoclip (Olympus) which has two prongs opening from 6 mm to 12 mm, the TriClip opens to a maximum of 12 mm between the three prongs, the Resolution Clip has the ability to reopen and reposition the clip after closing for up to five times, and the Multi-Clip can apply four clips sequentially.[29] While we
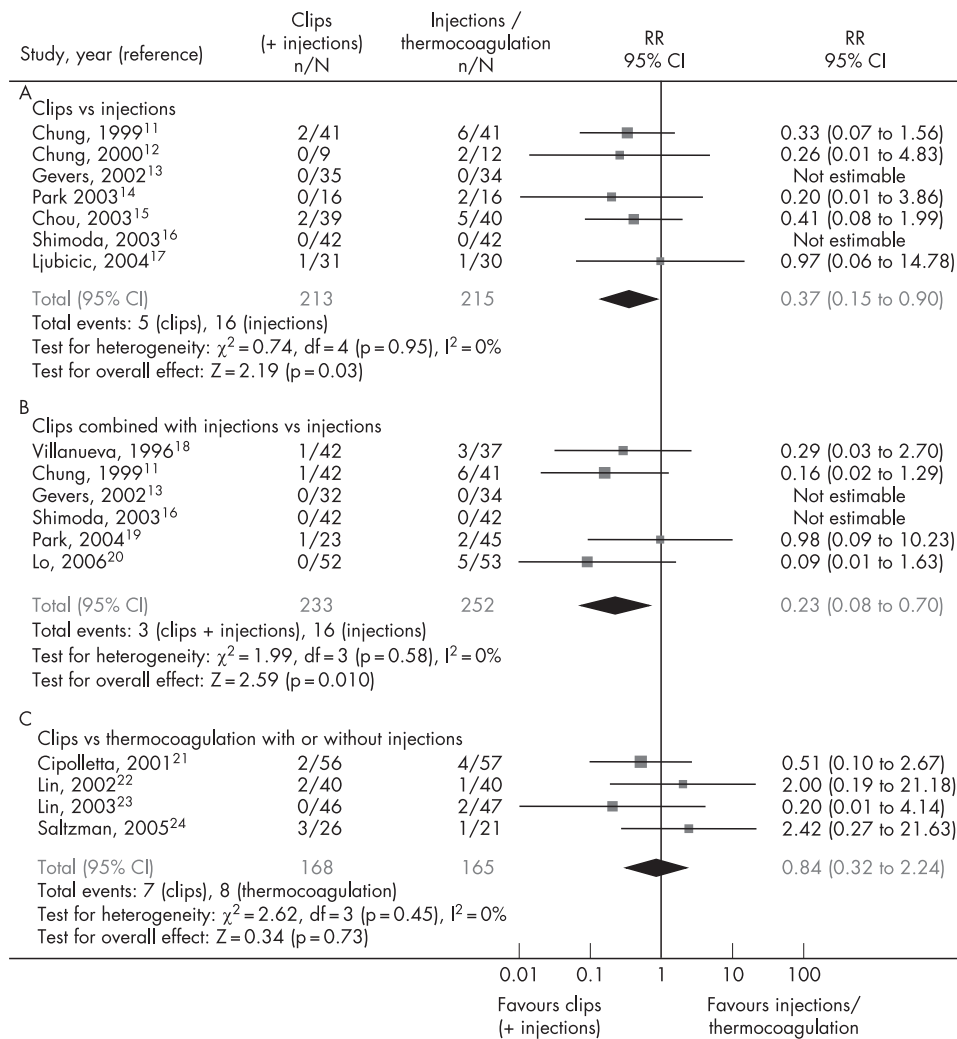
Figure 6 Forest plots for the need for surgery comparison.

are awaiting head-to-head comparison of these devices in clinical studies, animal models in the dog showed similar efficacy in clip placement and initial hemostasis.[30]

In conclusion, endoscopic clipping is superior to endoscopic injection and is comparable to thermocoagulation in securing hemostasis of bleeding peptic ulcers and Dieulafoy lesions. The choice of therapy would remain at the discretion of the endoscopist based on the nature and position of the ulcer, experience of the endoscopist and previous endoscopic therapy that the patient has received.

....

Authors' affiliations
Joseph J Y Sung, Kelvin K F Tsoi, Larry H Lai, Justin C Y Wu, James Y W Lau, Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong

Conflict of interest: none declared.

REFERENCES

1 **Blatchford O**, Davidson LA, Murray WR, et al. Acute upper gastrointestinal hemorrhage in west of Scotland: case ascertainment study. BMJ 1997;**315**:510–4.
2 **Rockall TA**, Logan RF, Devlin HB, et al. Incidence of and mortality from acute upper gastrointestinal hemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Hemorrhage. BMJ 1995;**311**:222–6.
3 **Vreeburg EM**, Snel P, de Bruijne JW, et al. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis and clinical outcome. 1997;**92**:236–243.
4 **Longstreth GF**. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol 1995;**90**:206–10.
5 **Targownik LW**, Nabalamba A. Trends in management and outcomes of acute non-variceal upper gastrointestinal bleeding: 1993–2003. Clin Gastroenterol and Hepatol 2006;**4**:1459–66.
6 **Cook DJ**, Gayatt GH, Salena BJ, et al. Endoscopic therapy for acute non-variceal hemorrhage: a meta-analysis. Gastroenterology 1992;**102**:139–48.
7 **American Society of Gastrointestinal Endoscopy**. Guideline: the role of endoscopy in acute non-variceal upper GI hemorrhage. Gastroint Endosc 2004;**60**:497–504.
8 **Palmer KR**. Non-variceal upper gastrointestinal hemorrhage: guideline. Gut 2002;**51**:1–6.
9 **Barkun A**, Bardou M, Marshall JK, for the Nonvariceal Upper GI Bleeding Conference Group. Consensus recommendation for managing patients with non-variceal upper gastrointestinal bleeding. Ann Intern Med 2003;**139**:843–57.
10 **Simoens M**, Gevers AM, Macken E, et al. A prospective randomized trial comparing three hemostasis modalities for bleeding ulcers injection therapy with epinephrine and polidocanol 1% versus hemoclip versus injection combined with hemoclip; an interim report. Gastrointest Endosc 1997;**45**:AB101.
11 **Chung IK**, Ham JS, Kim HS, et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. Gastrointest Endosc 1999;**49**:13–18.
12 **Chung IK**, Kim EJ, Lee MS, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc 2000;**52**:721–4.
13 **Gevers AM**, De Goede E, Simoens M, et al. A randomized trial comparing injection therapy with hemoclip and with injection combined with hemoclip for bleeding ulcers. Gastrointest Endosc 2002;**55**:466–9.
14 **Park CH**, Sohn YH, Lee WS, et al. The usefulness of endoscopic hemoclipping for bleeding Dieulafoy lesions. Endoscopy 2003;**35**:388–92.
15 **Chou YC**, Hsu PI, Lai KH, et al. A prospective, randomized trial of endoscopic hemoclip placement and distilled water injection for treatment of high-risk bleeding ulcers. Gastrointest Endosc 2003;**57**:324–8.
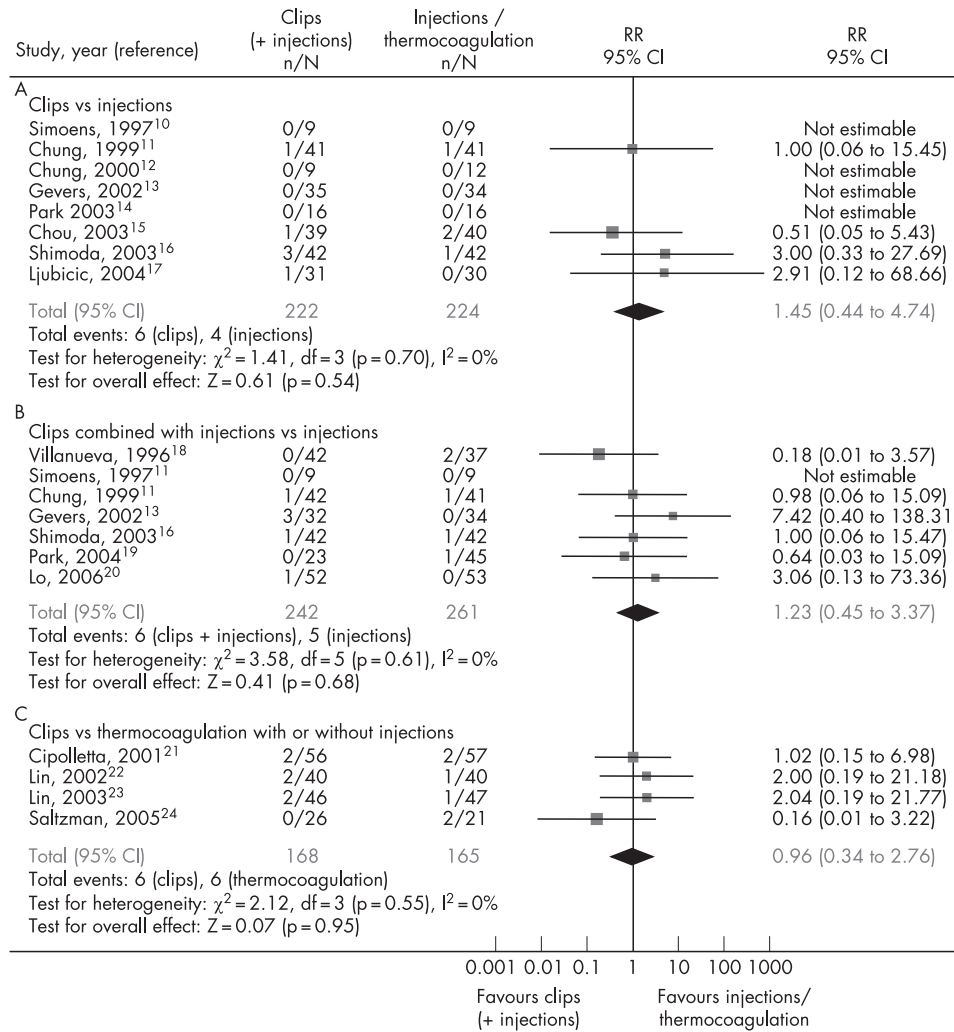
Study, year (reference)	Clips (+ injections) n/N	Injections / thermocoagulation n/N	RR 95% CI	RR 95% CI
A Clips vs injections				
Simoens, 1997[10]	0/9	0/9		Not estimable
Chung, 1999[11]	1/41	1/41		1.00 (0.06 to 15.45)
Chung, 2000[12]	0/9	0/12		Not estimable
Gevers, 2002[13]	0/35	0/34		Not estimable
Park 2003[14]	0/16	0/16		Not estimable
Chou, 2003[15]	1/39	2/40		0.51 (0.05 to 5.43)
Shimoda, 2003[16]	3/42	1/42		3.00 (0.33 to 27.69)
Ljubicic, 2004[17]	1/31	0/30		2.91 (0.12 to 68.66)
Total (95% CI)	222	224		1.45 (0.44 to 4.74)

Total events: 6 (clips), 4 (injections)
Test for heterogeneity: $\chi^2 = 1.41$, df = 3 (p = 0.70), $I^2 = 0\%$
Test for overall effect: Z = 0.61 (p = 0.54)

B Clips combined with injections vs injections				
Villanueva, 1996[18]	0/42	2/37		0.18 (0.01 to 3.57)
Simoens, 1997[11]	0/9	0/9		Not estimable
Chung, 1999[11]	1/42	1/41		0.98 (0.06 to 15.09)
Gevers, 2002[13]	3/32	0/34		7.42 (0.40 to 138.31)
Shimoda, 2003[16]	1/42	1/42		1.00 (0.06 to 15.47)
Park, 2004[19]	0/23	1/45		0.64 (0.03 to 15.09)
Lo, 2006[20]	1/52	0/53		3.06 (0.13 to 73.36)
Total (95% CI)	242	261		1.23 (0.45 to 3.37)

Total events: 6 (clips + injections), 5 (injections)
Test for heterogeneity: $\chi^2 = 3.58$, df = 5 (p = 0.61), $I^2 = 0\%$
Test for overall effect: Z = 0.41 (p = 0.68)

C Clips vs thermocoagulation with or without injections				
Cipolletta, 2001[21]	2/56	2/57		1.02 (0.15 to 6.98)
Lin, 2002[22]	2/40	1/40		2.00 (0.19 to 21.18)
Lin, 2003[23]	2/46	1/47		2.04 (0.19 to 21.77)
Saltzman, 2005[24]	0/26	2/21		0.16 (0.01 to 3.22)
Total (95% CI)	168	165		0.96 (0.34 to 2.76)

Total events: 6 (clips), 6 (thermocoagulation)
Test for heterogeneity: $\chi^2 = 2.12$, df = 3 (p = 0.55), $I^2 = 0\%$
Test for overall effect: Z = 0.07 (p = 0.95)

0.001 0.01 0.1 1 10 100 1000
Favours clips (+ injections) — Favours injections/ thermocoagulation

Figure 7 Forest plots for mortality comparison.

Table 2 Results of sensitivity analyses

	No. of trials	Combined relative risks (95% CI)				
		Initial hemostasis	Definitive hemostasis	Rebleeding	Need for surgery	Mortality
Clips versus injections						
All trials	8	1.01 (0.96 to 1.06)	1.14 (1.00 to 1.30)	0.49 (0.30 to 0.79)	0.37 (0.15 to 0.90)	1.45 (0.44 to 4.74)
Study duration						
Shorter (< 4 weeks)	4	0.99 (0.92 to 1.05)	1.07 (0.87 to 1.32)	0.59 (0.29 to 1.20)	0.39 (0.12 to 1.27)	1.64 (0.22 to 12.2)
Longer (4 weeks)	3	1.04 (0.97 to 1.11)	1.23 (0.97 to 1.56)	0.38 (0.18 to 0.80)	0.34 (0.09 to 1.35)	1.35 (0.31 to 5.89)
Adjuvant proton pump inhibitors						
Yes	2	1.00 (0.91 to 1.10)	1.07 (0.94 to 1.21)	0.59 (0.23 to 1.54)	0.97 (0.06 to 14.8)	2.97 (0.48 to 18.3)
No	6	1.01 (0.96 to 1.07)	1.21 (0.98 to 1.49)	0.46 (0.26 to 0.81)	0.33 (0.12 to 0.86)	0.68 (0.12 to 3.95)
Quality						
High (> 3)	3	0.99 (0.85 to 1.15)	1.14 (0.75 to 1.74)	0.62 (0.32 to 1.21)	0.36 (0.09 to 1.46)	0.51 (0.05 to 5.43)
Low (3)	5	1.03 (0.97 to 1.10)	1.17 (1.06 to 1.29)	0.39 (0.19 to 0.78)	0.37 (0.11 to 1.20)	2.18 (0.50 to 9.53)
Clips with injection versus injections						
All trials	7	1.00 (0.95 to 1.05)	1.13 (1.03 to 1.23)	0.47 (0.28 to 0.76)	0.23 (0.08 to 0.70)	1.23 (0.45 to 3.37)
Study duration						
Shorter (< 4 weeks)	4	0.97 (0.83 to 1.13)	1.11 (0.96 to 1.28)	0.54 (0.22 to 1.36)	0.31 (0.07 to 1.32)	0.81 (0.10 to 6.33)
Longer (4 weeks)	3	1.06 (0.97 to 1.16)	1.20 (1.07 to 1.35)	0.30 (0.11 to 0.78)	0.09 (0.01 to 1.63)	1.68 (0.23 to 12.5)
Adjuvant Proton pump inhibitors						
Yes	4	0.98 (0.82 to 1.18)	1.15 (1.03 to 1.29)	0.31 (0.16 to 0.63)	0.28 (0.07 to 1.02)	0.70 (0.19 to 2.64)
No	3	1.00 (0.93 to 1.07)	1.09 (0.94 to 1.25)	0.80 (0.39 to 1.64)	0.16 (0.02 to 1.29)	3.07 (0.05 to 18.7)
Quality						
High (> 3)	3	0.97 (0.87 to 1.09)	1.08 (0.85 to 1.37)	0.45 (0.22 to 0.93)	0.27 (0.05 to 1.35)	2.87 (0.59 to 14.1)
Low (3)	4	1.04 (0.96 to 1.13)	1.15 (1.03 to 1.29)	0.48 (0.24 to 0.94)	0.21 (0.05 to 0.94)	0.53 (0.12 to 2.39)

16 **Shimoda R**, Iwakiri R, Sakata H, *et al.* Evaluation of endoscopic hemostasis with metallic hemoclips for bleeding gastric ulcer: comparison with endoscopic injection of absolute ethanol in a prospective, randomized study. *Am J Gastroenterol* 2003;**98**:2198–202.

17 **Ljubicic N**. Efficacy of endoscopic clipping and long-term follow-up of bleeding Dieulafoy's lesions in the upper gastrointestinal tract. *Hepato-Gastroenterology* 2006;**53**:224–7.

18 **Villanueva C**, Balanzo J, Sabat M, *et al.* Injection therapy alone or with endoscopic hemoclip for bleeding peptic ulcer. Preliminary results of a randomized trial. *Gastrointest Endosc* 1996;**43**:361.

19 **Park CH**, Joo YE, Kim HS, *et al.* A prospective, randomized trial comparing mechanical methods of hemostasis plus epinephrine injection to epinephrine injection alone for bleeding peptic ulcer. *Gastrointest Endosc* 2004;**60**:173–9.

20 **Lo CC**, Hsu PI, Lo GH, *et al.* Comparison of hemostatic efficacy for epinephrine injection alone and injection combined with hemoclip therapy in treating high-risk bleeding ulcers. *Gastrointest Endosc* 2006;**63**:767–73.

21 **Cipolletta L**, Bianco MA, Marmo R, *et al.* Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: a prospective and randomized trial. *Gastrointest Endosc* 2001;**53**:147–51.

22 **Lin HJ**, Hsieh YH, Tseng GY, *et al.* A prospective, randomized trial of endoscopic hemoclip versus heater probe thermocoagulation for peptic ulcer bleeding. *Am J Gastroenterol* 2002;**97**:2250–4.

23 **Lin HJ**, Perng CL, Sun IC, *et al.* Endoscopic haemoclip versus heater probe thermocoagulation plus hypertonic saline-epinephrine injection for peptic ulcer bleeding. *Digest Liver Dis* 2002;**35**:898–902.

24 **Saltzman JR**, Strate LL, Di Sena V, *et al.* Prospective trial of endoscopic clips versus combination therapy in upper GI bleeding. *Am J Gastroenterol* 2005;**100**:1503–8.

25 **Lau JYW**, Sung JJY, Lee KKC, *et al.* Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000;**343**:310–16.

26 **Leontiadis GI**, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syste Rev*, 2004;CD002094.

27 **Chung SCS**, Lau JYW, Sung JJY, *et al.* Randomized comparison between adrenaline injection alone and adrenaline injection plus heater probe treatment for actively bleeding ulcers. *BMJ* 1997;**314**:1307–11.

28 **Calvet X**, Vergara M, Brullet E, *et al.* Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology* 2004;**126**:441–50.

29 **American Society of Gastrointestinal Endoscopy**. Technology status evaluation report. Endoscopic clip application devices. *Gastrointest Endosc* 2006;**63**:746–50.

30 **Jensen DM**, Machicado GA, Hirabayashi K. Randomized controlled study of three different types of hemoclips for hemostasis of bleeding canine acute gastric ulcers. *Gastrointest Endosc* 2006;**64**:768–73.

EDITOR'S QUIZ: GI SNAPSHOT ....

Robin Spiller, Editor

A huge intra-abdominal mass in a young man

Clinical presentation

A 19-year-old man presented to our department because of a 3-year history of left upper abdominal distention. He had no notable past medical history such as abdominal trauma or pancreatitis. On physical examination, a huge elastic hard mass was palpable in the left abdomen, but he did not complain of tenderness. Laboratory data on admission were unremarkable, including normal values for white blood cell count, C-reactive
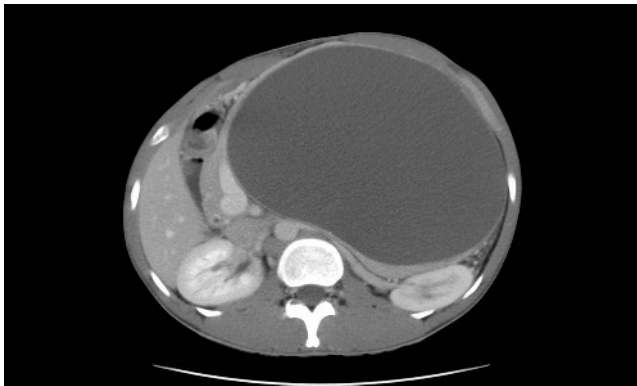

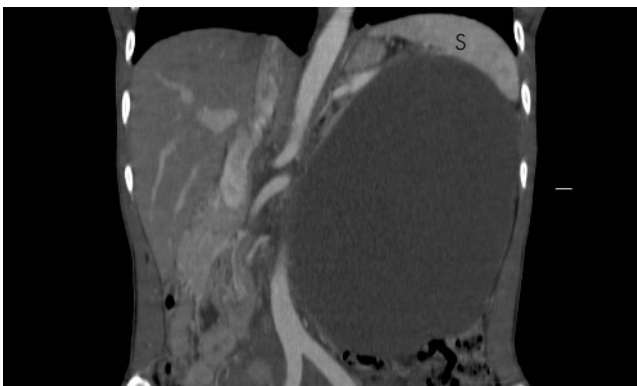**Figure 1**   Computed tomography scan on admission (axial image).

Figure 2   Computed tomography scan on admission (coronal reformatted image). S, spleen.

Figure 3   Endoscopic retrograde pancreatography reveals extravasation of the contrast medium into the cystic lesion at the tail of the pancreas.

protein, pancreatic enzymes (pancreatic amylase and lipase) and tumour markers (CEA and CA19-9). IV contrast-enhanced abdominal computed tomography showed a cystic lesion 21 cm in diameter located mainly in the left upper abdomen (fig 1, 2). A well-enhanced crescent-shaped structure was also noted adjacent to the cyst (fig 1). Endoscopic retrograde pancreatography revealed no abnormal findings apart from leakage of contrast medium into a cystic lesion at the tail of the pancreas (fig 3).

Question

What is the diagnosis of the cystic lesion?

See page 1393 for answer

T Tsujino, H Kogure, N Sasahira, H Isayama, M Tada, T Kawabe, M Omata
Department of Gastroenterology, Faculty of Medicine, University of Tokyo, Japan
M Akahane
Department of Radiology, Faculty of Medicine, University of Tokyo, Japan
K Sano, M Makuuchi
Department of Surgery, Faculty of Medicine, University of Tokyo, Japan

Correspondence to: Takeshi Tsujino, Department of Gastroenterology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; tsujinot-int@h.u-tokyo.ac.jp