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CME

Dual Therapy *Versus* Monotherapy in the Endoscopic Treatment of High-Risk Bleeding Ulcers: A Meta-Analysis of Controlled Trials

Riccardo Marmo, M.D.,[1] Gianluca Rotondano, M.D.,[2,4] Roberto Piscopo, M.D.,[3] Maria A. Bianco, M.D.,[4] Rosario D'Angella, M.D.,[1] and Livio Cipolletta, M.D.[4]

[1]*Department of Medicine, Division of Gastroenterology, Hospital L. Curto, Polla, Italy;* [2]*Division of General Surgery, Section of Gastrointestinal Endoscopy, Civil Hospital, Rocca d'Aspide, Italy;* [3]*Division of Internal Medicine, Section of Gastroenterology, Evangelic Hospital Villa Betania, Naples, Italy; and* [4]*Department of Gastroenterology and Digestive Endoscopy, Hospital Maresca, Torre del Greco, Italy*

BACKGROUND: There is no definite recommendation on the use of dual endoscopic therapy in patients with severe peptic ulcer bleeding. A systematic review and meta-analysis were performed to determine whether the use of two endoscopic hemostatic procedures improved patient outcomes compared with monotherapy.

METHODS: A search for randomized trials comparing dual therapy (*i.e.*, epinephrine injection plus other injection or thermal or mechanical method) *versus* monotherapy (injection, thermal, or mechanical alone) was performed between 1990 and 2006. Heterogeneity between studies was tested with χ^2 and explained by metaregression analysis.

RESULTS: Twenty studies (2,472 patients) met inclusion criteria. Compared with controls, dual endoscopic therapy reduces the risk of recurrent bleeding (OR [odds ratio] 0.59 [0.44–0.80], $P = 0.0001$) and the risk of emergency surgery (OR 0.66 [0.49–0.89], $P = 0.03$) and showed a trend toward a reduction in the risk of death (OR 0.68 [0.46–1.02], $P = 0.06$). Subcategory analysis showed that dual therapy was significantly superior to injection therapy alone for all the outcomes considered, but failed to demonstrate that any combination of treatments is better than either mechanical therapy alone (OR 1.04 [0.45–2.45] for rebleeding, 0.49 [0.50–4.87] for surgery, and 1.28 [0.34–4.86] for death) or thermal therapy alone (OR 0.67 [0.40–1.20] for rebleeding, 0.89 [0.45–1.76] for surgery, and 0.51 [0.24–1.10] for death).

CONCLUSIONS: Dual endoscopic therapy proved significantly superior to epinephrine injection alone, but had no advantage over thermal or mechanical monotherapy in improving the outcome of patients with high-risk peptic ulcer bleeding.

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BACKGROUND

There is conclusive evidence that endoscopic therapy is superior to conservative treatment in patients with severe peptic ulcer hemorrhage, with a significant decrease in the risk of recurrent bleeding, need for emergency surgery, and death (1–4). Available methods of endoscopic hemostasis include injection therapy with different agents, thermal coagulation, and mechanical therapy with the application of hemoclips and bands. Nowadays, we can expect to achieve primary hemostasis in over 95% of patients with actively bleeding peptic ulcers, but recurrent bleeding still occurs in 4–30% of cases (though this figure drops to less than 15% in referral centers) (5). Although epinephrine injection is sensibly less effective than other forms of endotherapy in terms of prevention of recurrent bleeding (6), it still is among the most popular endoscopic therapies because of its safety, low cost, and ease of application (7). Combined injection therapy plus thermal probe coagulation treatment is increasingly being offered as the gold standard of endoscopic hemostasis in referral centers (8). A recent meta-analysis showed that additional endoscopic treatment after epinephrine injection significantly reduces the risk of further bleeding, need for emergency surgery, and mortality regardless of which second procedure was applied (9). Nonetheless, the therapeutic gain of combined therapy over thermal or mechanical monotherapy may be less relevant because of their intrinsic higher efficacy.

The primary aim of the present study was to assess the efficacy of dual endoscopic therapy *versus* endoscopic

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monotherapy in reducing the rate of recurrent bleeding, need for surgery, and death in patients with peptic ulcer bleeding and high-risk stigmata. The secondary aim was to assess any negative outcomes in the treated patients.

MATERIALS AND METHODS

Literature Search and Identification of Primary Studies

Relevant papers were identified by searching the MEDLINE, EMBASE/Excerpta Medica, Current Contents, and Cochrane Central Trials databases through July 2006 using "peptic ulcer hemorrhage" or "peptic ulcer bleeding," "not variceal" and "endoscopic therapy," or "endoscopic treatment" and "clinical trial" as search terms. The search was restricted to human studies on adults published in English and non-English language. We also conducted a manual search of abstracts submitted to the Digestive Disease Week and United European Gastroenterology Week covering the same period. In addition, we hand-searched relevant articles published in journals, contacted companies, and researchers in the field to seek any ongoing or unpublished studies on the comparison of dual endoscopic therapy *versus* monotherapy. Articles selected in the search were reviewed separately by two of the authors (R.M. and G.R.), and those fulfilling the inclusion criteria were selected for further analysis. In addition, a fully recursive hand search of reference lists of the original studies was performed to find studies not identified by the previous searches. Papers recorded in the personal databases of the authors were also reviewed and included when appropriate.

Study Selection

Studies designed to compare the efficacy of dual endoscopic therapy *versus* any other form of endoscopic monotherapy in patients with peptic ulcer bleeding and high-risk stigmata were evaluated separately by two of the authors. The inclusion criteria were as follows: (a) Full-text articles should report the results of prospective comparative randomized trials; (b) Studies must include patients with hemorrhage from peptic ulcer disease (gastric or duodenal) with major stigmata of bleeding at the ulcer base (active bleeding, nonbleeding visible vessel, and adherent clot) (10–12); (c) Studies must include at least two branches of endoscopic treatment: dual therapy (epinephrine associated with a second hemostatic method, either another injection agent or thermal probe or mechanical hemostasis) *vs* monotherapy, *i.e.*, either epinephrine alone or thermal coagulation alone or hemoclipping alone; (d) The data on the baseline characteristics of the patients (number, age, sex, and others), inclusion and exclusion criteria, and results should allow adequate evaluation; and (e) Explicit reference had to be given for safety of the tested procedures either in the text or tables.

Definition of the outcome measures: in most studies, recurrent bleeding was clinically defined as the passage of fresh hematemesis or melena, or both, coupled with the development of shock or decrease in hemoglobin concentration by at least 2 g/dL after initial stabilization of 24 h or aspiration of fresh blood from nasogastric tube. Bleeding was confirmed by endoscopy in all the studies. Clinically silent bleeding observed at scheduled endoscopies was not considered for the analysis. Emergency surgery was deemed necessary for failure to control arterial bleeding (uncontrolled persistent hemorrhage) or failure to stop recurrent bleeding (retreatment failure). Few studies defined the criteria for mortality; 30-d mortality or in-hospital mortality was the most often used.

A "negative outcome" was defined as any undesired event directly induced from the application of a definite endoscopic technique, according to Fleischer *et al.* (13). Explicit reference had to be given for safety of the tested procedures (intended as presence or absence of negative outcomes) either in the text or tables. When the abstract had no clear reason for exclusion, the relative full paper was obtained and included. Where multiple reports of a single trial existed, the most recent version was obtained. We also reviewed the references of selected articles and previous clinical reviews. Data extraction was done independently by two investigators (R.M. and G.R.) using a standardized form. Decisions regarding inclusion of articles and data extraction were reached by consensus between the two reviewers. If there was disagreement, the papers were jointly evaluated to solve the inconsistency.

Data Extraction

The studies were examined with respect to the following criteria: study design (including randomization and methods of reporting adverse events); inclusion and exclusion criteria; patient characteristics (including risk assessment for bleeding and indications for endoscopic hemostasis); technical details of injection therapy (agent employed, amount injected, etc.) as well as of thermal therapy (devices, total energy delivered, pulse duration, etc.); and definition of study outcomes and their monitoring methods.

Quality Assessment

Information on objective quality-related characteristics was also collected and the quality of the studies included was assessed using 21 out of the 22 items of the CONSORT statement (14). We did not consider the items that refer to blinding because all evaluated trials were not blinded. Final quality score ranged from 0 to 21, with maximum quality studies rating 21. Results from the trial reports were reproduced where possible. The systematic review was performed according to the QUORUM statement (15).

Statistics: Quantitative Data Synthesis and Data Analysis

Statistical heterogeneity was measured by the Cochrane Q test; P values of less than 0.10 were considered significant for heterogeneity. We performed a meta-analysis of outcomes when appropriate, as well as subgroup analysis pooling data within the different subgroups of comparable treatments (injective, thermal, or mechanical). We calculated the crude and weighted odds ratios (OR) and the number needed to

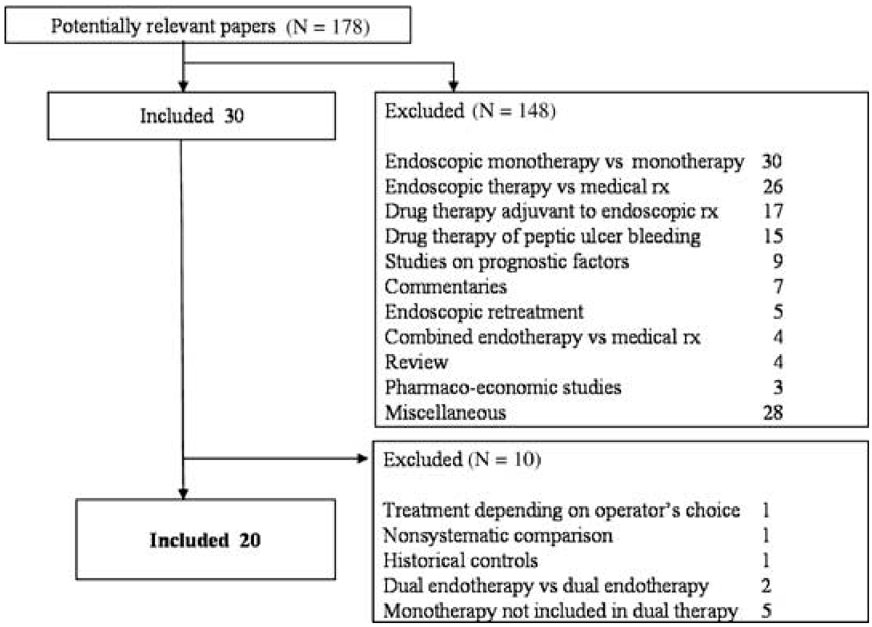

Figure 1. Trial search flow for meta-analysis.

treat (NNT) with 95% confidence intervals (CI) for each of the subgroups, as well as for all the studies included. The NNT is a measure of the therapeutic gain. It is the number of patients to treat with the experimental procedure (in this case dual endoscopic therapy) so that at least one event investigated is avoided (*e.g.*, recurrent bleeding, emergency surgery, or death). The absolute risk difference (and therefore the NNT) was done by pooling the individual risk differences after weighting each individual value by sample size of the study, as suggested in the meta-analytic procedure (16). The reciprocal was the NNT value.

A Peto fixed effects model was used unless there was significant heterogeneity, in which case a random effects model was applied. Egger's regression asymmetry test (17) was used to investigate for the presence of publication bias, defined as the number of additional nonsignificant studies that, if included in the meta-analysis, would have removed the significant meta-analysis finding.

The influence of the following factors on the trial outcome and on the heterogeneity of the analyses was assessed with metaregression analysis (16) where sufficient data were available: type of dual endoscopic treatment, publication year, quality score, frequency of active bleeding at endoscopy, and type of adjuvant pharmacotherapy (proton pump inhibitors or H_2-blockers). Analysis of data was performed using the STATA software version 8.0 (Intercooled Stata 8.2 forWindows, StataCorpLP, Houston, TX) and Meta-Analysis software (16) according to statistical tests and formulas described for performing meta-analyses in medical research. Metaregression was performed using the *MetaReg* command of the STATA software. An intention-to-treat analysis was carried out, *i.e.*, participants were analyzed in the group to which they were allocated.

RESULTS

Included and Excluded Studies

The preliminary search identified 178 potentially relevant papers. One hundred forty-eight of them were excluded. Detailed reasons for exclusion are outlined in Figure 1. Ten studies were then excluded from further analysis because of historical controls (18), nonsystematic comparison (19), endoscopic treatment to deliver left to operator's choice (20), both trial arms treated with dual therapy (21, 22), or because the type of endoscopic monotherapy was not included in the combined treatment protocol (23–27). Twenty studies were included in the final meta-analysis (28–47). According to the type of endoscopic treatment compared, they were divided into five subgroups.

- *Subgroup A*: Injection plus mechanical therapy compared with injection alone (four studies) (28–31);
- *Subgroup B*: Injection plus thermal therapy compared with injection alone (three studies) (32–34);
- *Subgroup C*: Injection of two agents compared with injection of a single agent (10 studies) (35–44);
- *Subgroup D*: Injection plus mechanical therapy compared with mechanical alone (three studies) (28, 30, 45);
- *Subgroup E*: Injection plus thermal therapy compared with thermal alone (three studies) (33, 46, 47).

Three studies (28, 30, 33) had multiple trial arms and were considered more than once depending on the different treatments compared.

Quality Assessment

Quality assessment was expressed as percent of the total CONSORT score (21 = 100%). The articles included ranged

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study	N	Bleeding/Nonbleeding SRH Dual	Bleeding/Nonbleeding SRH Single	Type of Endoscopic Treatment Dual	Type of Endoscopic Treatment Single	Concomitant Treatment(s)	Quality Score
Subgroup A: INJECTION + MECHANICAL *vs* INJECTION (4 trials, 362 patients)							
Chung (28)	83	21/21	14/27	HSE + HC	HSE	IV ranitidine	0.66
Park (29)	90	24/21	22/23	EPI + HC	EPI	Oral PPI; eradication if *H. pylori* +ve	0.90
Shimoda (30)	84	17/25	9/33	ETH + HC	ETH	PPI or ranitidine + antacids	0.71
Lo (31)	105	21/31	21/33	HC + EPI	EPI	IV PPI	0.77
Subgroup B: INJECTION + THERMAL *vs* INJECTION (3 trials, 376 patients)							
Chung (32)	270	136	134	HP + EPI	EPI	H_2-RA or PPI	0.76
Loizou (33)	42	5/16	3/18	Nd:Yag Laser + EPI	EPI	Ranitidine twice daily	0.66
Lin (34)	64	11/21	11/21	GP + EPI	EPI	IV PPI	0.76
Subgroup C: INJECTION + INJECTION *vs* INJECTION (10 trials, 1,075 patients)							
Balanzò (35)	64	11/21	13/19	THR + EPI	EPI	ND	0.57
Choudari (36)	107	28/24	29/26	Ethanolamine + EPI	EPI	H_2-RA	0.61
Chung (37)	196	98	98	Tetradecyl sulfate + EPI	EPI	H_2-RA	0.60
Chung (38)	160	79	81	ETH + EPI	EPI	H_2-RA and PPI	0.58
Garrido Serrano (39)	85	10/30	15/30	PODC 2% + EPI	EPI	ND	0.27
Kubba (40)	140	27/43	24/46	Thrombin + EPI	EPI	ND	0.65
Lin (41)	64	21	23	ETH + EPI	EPI	H_2-RA	0.60
Villanueva (42)	63	13/20	10/20	PODC 1% + EPI	EPI	Standard supportive therapy	0.67
Pescatore (43)	135	30/35	32/38	Fibrin glue + EPI	EPI	IV PPI; eradication if *H. pylori* +ve	0.59
Sollano (44)	61	17/12	24/8	PODC 1% + EPI	EPI	ND	0.29
Subgroup D: INJECTION + MECHANICAL *vs* MECHANICAL (3 trials, 234 patients)							
Chung (28)	83	21/21	20/21	HSE + HC	HC	IV ranitidine	0.66
Shimoda (30)	84	17/25	14/28	ETH + HC	HC	PPI or ranitidine + antacids	0.71
Gevers (45)	67	17/15	13/22	EPI + PODC + HC	HC	IV ranitidine	0.76
Subgroup E: INJECTION + THERMAL *vs* THERMAL (3 trials, 425 patients)							
Lin (34)	64	11/21	9/23	GP + EPI	GP	IV PPI	0.76
Church (46)	247	49/78	45/75	HP + THR	HP	PPI; eradication if *H. pylori* +ve	0.86
Bianco (47)	114	19/39	19/37	EPI + GP	GP	IV PPI; eradication if *H. pylori* +ve	0.71
Total	2,472						

Quality assessment is expressed as percent of the total CONSORT score (21 = 100%).
SRH = stigmata of recent hemorrhage; Bleeding stigmata = active arterial and/or oozing bleed; Nonbleeding stigmata = visible vessels and/or fresh adherent clots; HSE = hypertonic saline epinephrine; EPI = epinephrine; PODC = polidochanol; ETH = ethanol; THR = thrombin; HC = hemoclips; GP = bipolar gold probe; HP = heater probe; PPI = proton pump inhibitor; H_2-RA = histamine-2 receptor antagonists; ND: not defined.
Eradication therapy: 7-d course of antibiotics + PPI.

in quality from 27 to 90%. Individual assessment of quality is shown in Table 1. All of the studies were published as full papers.

Efficacy (Outcome Measures: Recurrent Bleeding, Surgery, and Death)

A total of 2,472 patients were evaluated, 1,233 treated with a form of dual endoscopic therapy and 1,239 controls, *i.e.*, treated with single endoscopic treatment. Numerical outcome data are summarized in Table 2. The null hypothesis of homogeneity was not rejected only for need for surgery and for mortality

A. RECURRENT BLEEDING. Overall, application of dual endoscopic therapy significantly reduces the probability of recurrent bleeding compared with controls, with a pooled OR of 0.59 (95% CI 0.44–0.80, $P = 0.0001$).

There was significant heterogeneity between the studies ($Q = 32.2$, $P = 0.07$, I^2 31.6%). The results of the metaregression analysis to investigate heterogeneity for this outcome are shown in Table 3. The type of dual therapy employed and the posthemostasis adjuvant pharmacotherapy using proton pump inhibitors were the only two variables explaining heterogeneity of results. Neither visual examination of funnel plot (Fig. 2) nor Egger's test revealed any evidence of publication bias (coefficient –1.26, standard error 0.75, t –1.78, $P = 0.108$).

Subcategory analysis: There was a significant therapeutic gain of dual therapies over injection monotherapy. OR for recurrent bleeding in subgroup A was 0.33 (95% CI 0.17–0.63, $P = 0.006$) with a calculated NNT for this subgroup of 9 (95% CI 6–20), that is, for every nine patients treated with injection plus hemoclips, one avoids further hemorrhage compared with controls. Similar risk reduction was observed for subgroup B (OR 0.36 [95% CI 0.18–0.73], $P = 0.001$, NNT 15 [95% CI 8–66]) and for subgroup C (OR 0.65 [95% CI 0.46–0.93], $P = 0.02$, NNT 23 [95% CI 12–197]). The therapeutic advantage is lost when dual therapy is compared with either mechanical monotherapy (OR 1.04 [95%

Table 2. Numerical Outcomes Data

Study	Dual Endoscopic Treatment			Single Endoscopic Treatment		
	Rebleeding (N/Total)	Surgery (N/Total)	Death (N/Total)	Rebleeding (N/Total)	Surgery (N/Total)	Death (N/Total)
Subgroup A: INJECTION + MECHANICAL *vs* INJECTION (4 trials, 362 patients)						
Chung (28)	4/42	1/42	1/42	6/41	6/41	1/41
Park (29)	2/45	1/45	0/45	9/45	2/45	1/45
Shimoda (30)	3/42	0/42	1/42	6/42	0/42	1/42
Lo (31)	2/52	0/52	1/52	11/53	5/53	0/53
Total events	11/181	2/181	3/181	32/181	13/181	3/181
Subgroup B: INJECTION + THERMAL *vs* INJECTION (3 trials, 376 patients)						
Chung (32)	5/136	8/136	8/136	12/134	14/134	7/134
Loizou (33)	3/21	0/21	0/21	3/21	3/21	0/21
Lin (34)	2/32	1/32	1/32	11/32	5/32	3/32
Total events	10/189	9/189	9/189	26/187	22/187	10/187
Subgroup C: INJECTION + INJECTION *vs* INJECTION (10 trials, 1,075 patients)						
Balanzò (35)	2/32	5/32	0/32	4/32	4/32	0/32
Choudari (36)	7/52	4/52	0/52	8/55	4/55	1/55
Chung (37)	11/98	14/98	4/98	9/98	16/98	9/98
Chung (38)	6/79	9/79	7/79	9/81	12/81	4/81
Garrido Serrano (39)	3/40	ND	ND	12/45	ND	ND
Kubba (40)	3/70	3/70	0/70	14/70	5/70	7/70
Lin (41)	5/32	2/32	2/32	11/32	1/32	0/32
Villanueva (42)	7/33	5/33	1/33	3/30	4/30	2/30
Pescatore (43)	14/65	4/65	2/65	17/70	7/70	2/70
Sollano (44)	2/29	0/29	0/29	2/32	1/32	1/32
Total events	60/530	54/530	20/530	89/545	56/545	27/545
Subgroup D: INJECTION + MECHANICAL *vs* MECHANICAL (3 trials, 234 patients)						
Chung (28)	4/42	1/42	1/42	1/41	2/41	1/41
Shimoda (30)	3/42	0/42	1/42	4/42	0/42	3/42
Gevers (45)	5/32	ND	3/32	7/35	ND	0/35
Total events	12/116	1/84	5/116	12/118	3/83	4/118
Subgroup E: INJECTION + THERMAL *vs* THERMAL (3 trials, 425 patients)						
Lin (34)	2/32	1/32	1/32	9/32	2/32	1/32
Church (46)	19/127	16/127	8/127	17/120	13/120	14/120
Bianco (47)	5/58	1/58	1/58	8/56	4/56	3/56
Total events	26/217	18/217	10/217	34/208	19/208	18/208

CI 0.45–2.45], $P = 0.92$, NNT 50 [20 to –11]) or thermal monotherapy (OR 0.67 [95% CI 0.40–1.20], $P = 0.19$, NNT 23 [9 to –45]) (Fig. 3).

B. NEED FOR SURGERY. From a fixed-effect model, dual therapy significantly reduces the probability of needing an emergency operation compared with controls, with a pooled OR 0.66 (95% CI 0.49–0.89, $P = 0.03$).

Subcategory analysis: OR for emergency surgery in subgroup A was 0.21 (95% CI 0.07–0.60, $P = 0.003$) with a calculated NNT of 15 (9–54). A similar decrease in the risk of surgery was observed for subgroup B (OR 0.40 [95% CI 0.19–0.83], $P = 0.01$, NNT 14 [8–62]), whereas the injection of two agents did not confer any advantage over injection of a single agent (OR 0.84 [95% CI 0.55–1.28], $P = 0.43$, NNT 56 [20 to –74]). Again, the observed benefit of dual endoscopic therapy over injection monotherapy was lost when dual therapy was compared with either mechanical monotherapy (subgroup D) or thermal monotherapy (subgroup E) with no influence on the risk of surgery (OR 0.49 [95% CI 0.50–4.87], $P = 0.54$, NNT 40 [9 to –18] and OR 0.89 [95% CI

Table 3. Metaregression Analysis for Identifying the Source of Heterogeneity Among Studies

	Coeff.	Std. Err.	Z	$P > z$	95% CI
Type of dual endoscopic treatment	**0.248854**	**0.1199535**	**2.07**	**0.038**	**0.0137496** to **0.4839585**
Year of publication	0.0097915	0.0614112	0.16	0.873	−0.1105723 to 0.1301553
Quality score	−0.0063002	0.032223	−0.20	0.845	−0.0694561 to 0.0568556
Frequency of active bleeding	0.002408	0.0077121	0.31	0.755	−0.0127074 to 0.0175234
Type of adjuvant pharmacotherapy	**−0.4874415**	**0.4578999**	**−1.06**	**0.287**	**−1.384909** to **0.4100258**
_cons	−19.67402	76.79226	−0.16	0.871	−257.6869 to 218.3388

tau^2 method restricted maximum likelihood.
tau^2 estimate = 0.0172.

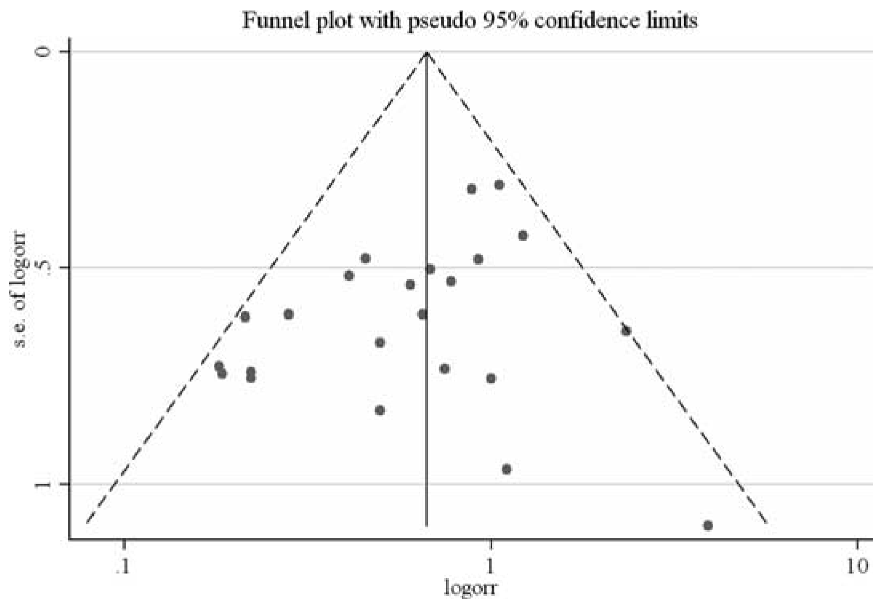

Figure 2. Funnel plot analysis comparing dual with single endoscopic therapy for recurrent bleeding. Statistical analysis confirmed no evidence of publication bias.

0.45–1.76], $P = 0.74$, NNT 44 [14 to –39], respectively) (Fig. 4).

C. DEATH. Overall, dual therapy only showed a trend toward reduced mortality compared with controls (OR 0.68 [95% CI 0.46–1.02], $P = 0.06$, NNT 93 [95% CI 41 to –337]).

Subcategory analysis: Fails to demonstrate that any combination of treatments is better than a single endotherapy in preventing death from hemorrhage in this high-risk population. Calculated OR for subgroup A was 0.99 (95% CI 0.20–4.96), $P = 0.56$, with an NNT of 1020 (43 to –43), similar to

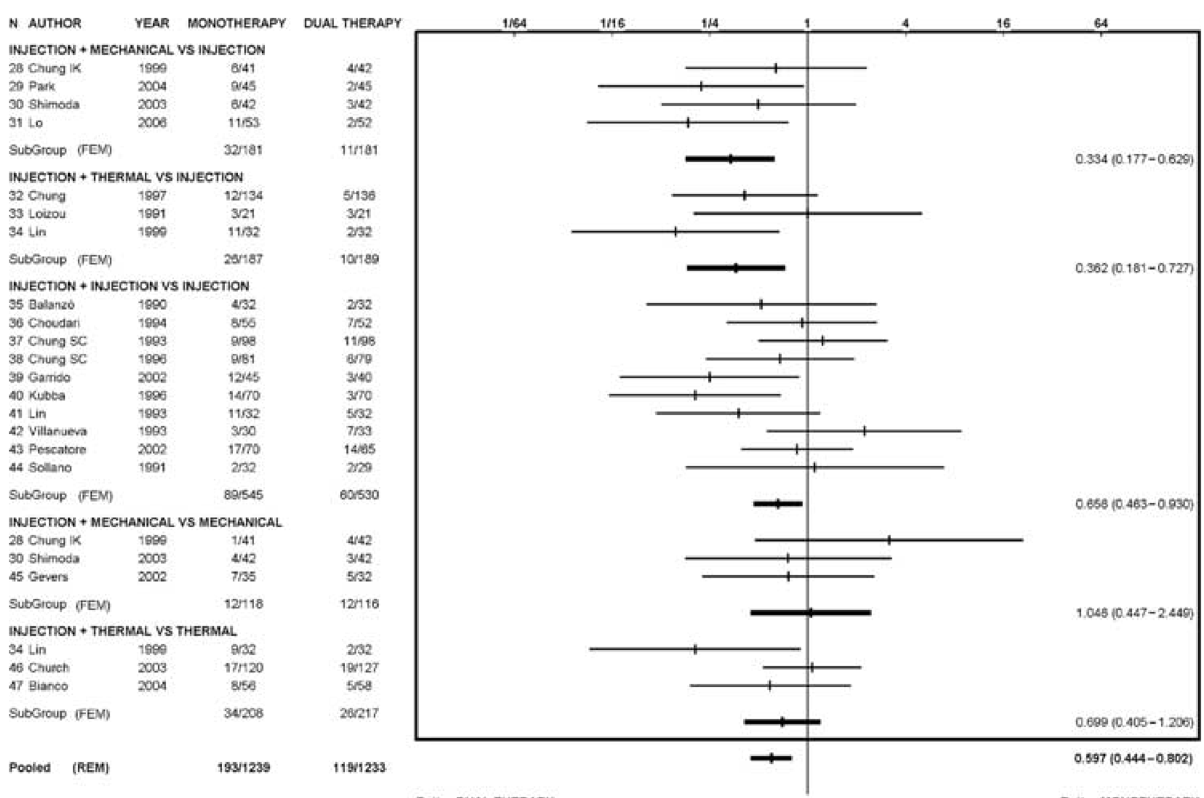

Figure 3. Meta-analysis: Efficacy of dual *versus* single endoscopic treatment. Outcome: Recurrent bleeding.

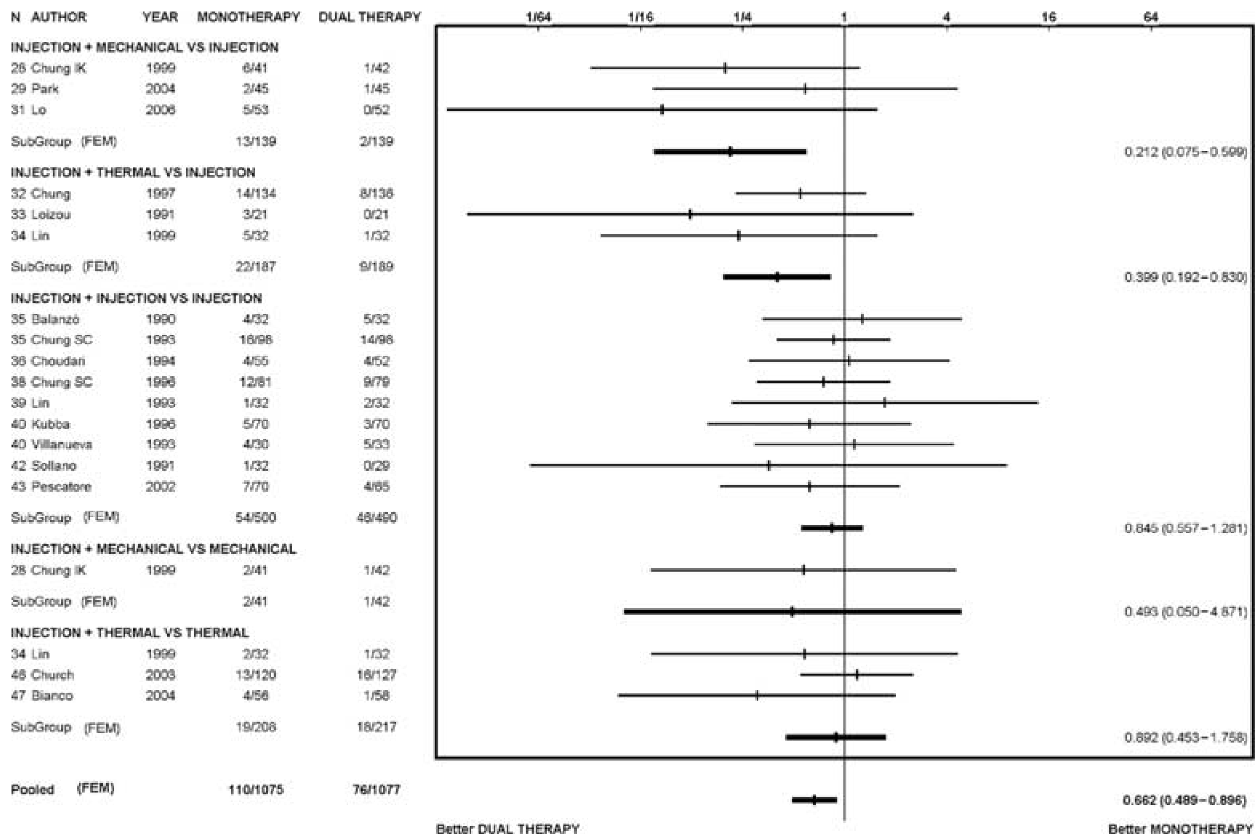

Figure 4. Meta-analysis: Efficacy of dual *versus* single endoscopic treatment. Outcome: Need for surgery.

that for subgroup B (OR 0.88 [95% CI 0.35–2.22], $P = 0.79$, NNT 176 [18 to –23]).

The risk of death seems to be somewhat reduced by the application of dual injection therapy *versus* injection monotherapy (subgroup C) (OR 0.61 [95% CI 0.33–1.14], $P = 0.12$, NNT 53 [25–402]) as well as by the application of injection plus thermal therapy *versus* thermal monotherapy (subgroup E) (OR 0.51 [95% CI 0.24–1.10], $P = 0.09$ with an NNT of 30 [13–110]). When compared with mechanical monotherapy (subgroup D), dual endoscopic treatment even increases the risk of death and seems to do more harm than benefit (OR 1.28 [95% CI 0.34–4.86], $P = 0.70$, NNT –139 [20 to –18]) (Fig. 5).

Safety

Morbidity of endoscopic treatment of such high-risk patients was acceptable, with an overall event rate of 3.5% (38 complications out of 1,069 patients treated) for dual endoscopic therapy *versus* 3.3% (35 negative outcomes out of 1,068 patients treated) for single endoscopic therapy (Table 4).

As for the specific negative outcomes directly related to the application of endoscopic hemostatic methods, the rate of induced bleeding (*i.e.*, hemorrhage precipitated in a nonbleeding lesion) was similar in both treatment arms (18 *vs* 18), whereas perforation was significantly more frequent in patients treated with dual endotherapy as compared with single endotherapy (7 *vs* 0) ($P = 0.03$). Perforations occurred mostly in patients treated with dual therapy combining injection plus thermal methods (five cases) and in two cases in patients treated with double injection therapy. No perforation was observed in patients treated with thermal monotherapy.

One patient in the dual therapy arm experienced a gastric wall necrosis following combination therapy with epinephrine plus sclerosant (polidochanol) and another one a right gastric artery thrombosis with infarction of the lesser curve of the stomach following injection of epinephrine plus sclerosant (ethanolamine oleate).

DISCUSSION

In patient with peptic ulcer bleeding and high-risk stigmata, endoscopic treatment is superior to conservative management in the control of active bleeding and prevention of recurrent hemorrhage (1, 2, 5, 6). Endoscopic hemostasis improves the benefit outcome of these patients, significantly decreasing both recurrent bleeding (OR 0.39) and mortality (OR 0.31) (48).

Nearly two decades of research in endoscopic therapy have allowed for the evolution of techniques, to the point where primary hemostasis in over 95% of patients with actively bleeding peptic ulcers is expected. However, endoscopic control of severe hemorrhage is not an easy task and adequate training and competency are required. In most experienced centers, recurrent bleeding still occurs in 8–10% of such patients and

Table 4. Safety of Therapeutic Procedures (Negative Outcomes of the Tested Treatments)

Study	Dual Endoscopic Treatment	Single Endoscopic Treatment
Subgroup A: INJECTION + MECHANICAL *vs* INJECTION (4 trials, 362 patients)		
Chung (28)	0	1 induced bleeding
Park (29)	ND	ND
Shimoda (30)	1 pulmonary failure and osteomyelitis	1 hepatic failure (liver cirrhosis)
Lo (31)	0	0
Subgroup B: INJECTION + THERMAL vs. INJECTION (3 trials, 376 patients)		
Chung (32)	2 perforations	0
Loizou (33)	2 induced bleeding	1 induced bleeding
Lin (34)	0	0
Subgroup C: INJECTION + INJECTION *vs* INJECTION (10 trials, 1,075 patients)		
Balanzò (35)	No relevant	No relevant
Choudari (36)	No significant complications	No significant complications
Chung (37)	1 infarction of the lesser curvature (right gastric artery thrombosis) 1 hepato-renal syndrome in cirrhosis	1 liver failure; 2 heart failure; 1 chest infection
Chung (38)	ND	ND
Garrido Serrano (39)	ND	ND
Kubba (40)	0	0
Lin (41)	0	0
Villanueva (42)	1 perforation	0
Pescatore (43)	1 pneumonitis; 1 perforation	2 pneumonitis; 1 stroke; 1 induced bleeding
Sollano (44)	1 mucosal necrosis	0
Subgroup D: INJECTION + MECHANICAL *vs* MECHANICAL (3 trials, 234 patients)		
Chung (28)	0	0
Shimoda (30)	1 pulmonary failure and osteomyelitis	1 rupture of abdominal aortic aneurysm; 1 multiorgan failure; 1 hepatic failure (metastases from lung cancer)
Gevers (45)	1 septic arthritis	0
Subgroup E: INJECTION + THERMAL *vs* THERMAL (3 trials, 425 patients)		
Lin (34)	0	0
Church (46)	2 induced bleeding; 3 perforations; 2 myocardial infarction; 2 stroke; 1 deep vein thrombosis	1 induced bleeding; 1 myocardial infarction; 1 stroke
Bianco (47)	1 sepsis; 14 induced bleeding	1 myocardial infarction; 1 multiorgan failure; 16 induced bleeding

ND = not declared.

5–10% die (5). Many treatment methods have been investigated, both alone and in combination, but statistically significant differences are difficult to demonstrate because of low event rates and inadequate study sizes. Moreover, few studies report outcomes of endotherapy as a subgroup analysis, thus preventing us from the possibility to assess whether there is a markedly more efficacious method of endoscopic treatment in these extremely high-risk patients.

The rationale of combination therapies is to further improve the results obtained with individual treatments. Dual therapy combining injection of epinephrine plus coaptive coagulation is increasingly being offered as the "gold standard" of endoscopic treatment of high-risk bleeding ulcers in referral centers (8). Moreover, a recent meta-analysis provided evidence that, compared with injection therapy alone, "two is better than one." In fact, the addition of a second endoscopic treatment following epinephrine injection improved outcome in high-risk bleeding ulcers, reducing recurrent bleeding (OR 0.53), need for emergency surgery (OR 0.64), and mortality (OR 0.51) (9). Nonetheless, the higher initial efficacy of thermal and mechanical methods of endoscopic hemostasis raise the question as to the real therapeutic gain of dual therapy over thermal or mechanical monotherapy. The few controlled data available seem to indicate that dual therapy is not superior to thermal coagulation alone (46), except in the subgroup of patients with active arterial bleeding, in whom it assures a higher rate of initial hemostasis (47).

The present meta-analysis adds substantial contribution to the body of evidence, showing that within combined endoscopic treatments there are different degrees of efficacy and safety. In particular, the superiority of dual therapy, *i.e.*, injection of epinephrine plus something else, is definitely proven against injection therapy alone, with a substantial reduction in the risk of rebleeding and surgery and a trend toward reduced mortality. Although not significant, such a numerical advantage in terms of death prevention may still be important, bearing in mind that mortality in high-risk bleeders is usually related to comorbidities, independently of the endoscopic treatment delivered. As expected, any superiority of dual treatment is lost when single thermal or mechanical therapy is the control arm. In this case, the addition of injection therapy confers no further clinical advantage. We acknowledge that the number of studies and total patients are relatively small, and the possibility that a difference in favor of dual therapy *versus* thermal or mechanical monotherapies might be identified with more studies and patients cannot be

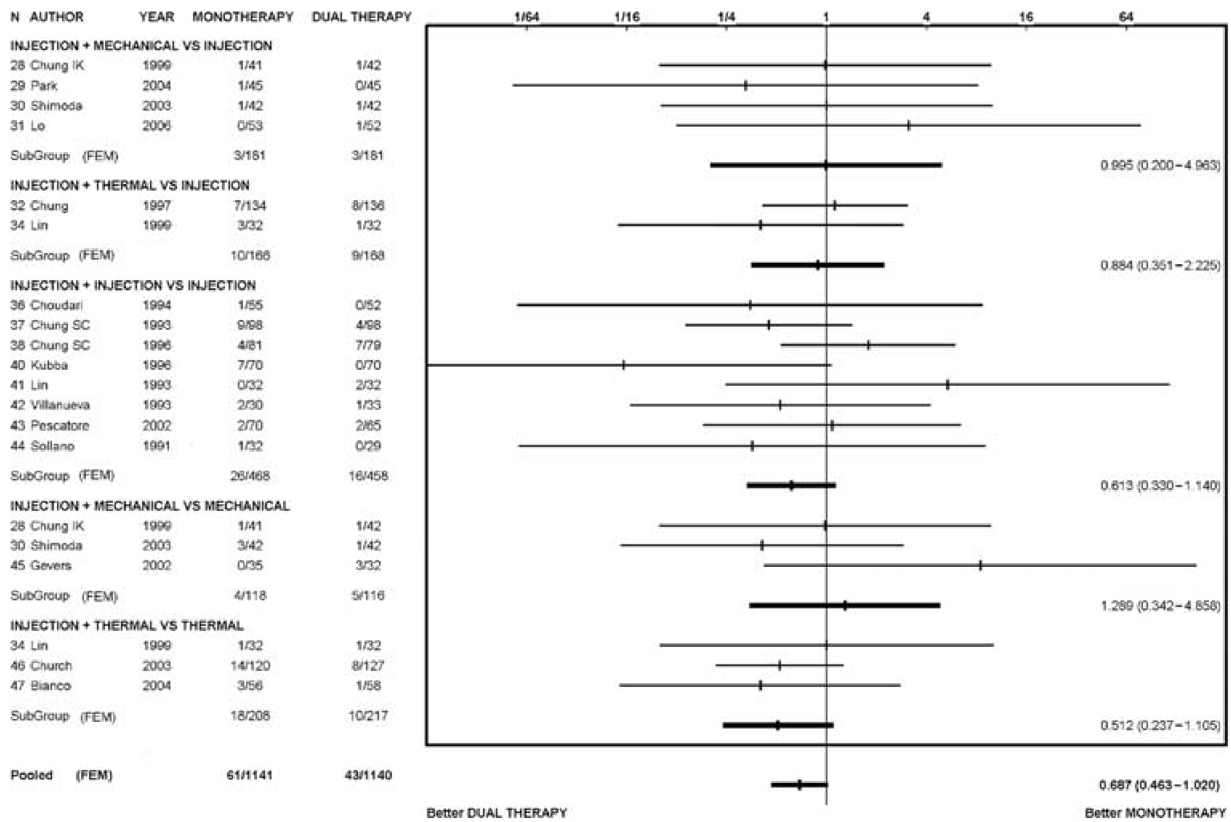

Figure 5. Meta-analysis: Efficacy of dual *versus* single endoscopic treatment. Outcome: Death.

ruled out. For the comparison with thermal therapy alone, difference in outcomes is estimated to be about 2–3%, so future studies showing an advantage for dual therapy may well redefine this subject. For the time being, the routine use of dual therapy (with its attendant risks) cannot be recommended. This "gray zone" definitely deserves further research. As for mechanical therapy alone, instead, the observed difference is so irrelevant that adding injection would likely not change the outcomes whatsoever.

Our data fail to demonstrate any superiority of dual therapies over thermal coaptation alone or over properly placed hemoclips alone. We believe that this is relevant to American practice, where bipolar coagulation was developed and widely adopted. U.S. practice seems to be more adherent to the recently published recommendations not to use injection therapy alone in high-risk bleeders but only as a first step before the application of another form of more definitive therapy (5, 49), a recommendation strengthened by the results of our meta-analysis. Nonetheless, epinephrine injection is still very popular in the treatment of peptic ulcer bleeding in clinical practice (50, 51). Endoscopists throughout the world should adopt more extensive thermal coagulation, which is demonstrated to be the most effective single endoscopic method of securing hemostasis. Clips are as effective as thermal coaptation but their use is somewhat burdened by the limited applicability and the high technical expertise required.

Although generally safe, endoscopic treatment of severe ulcer bleeding is not free of the risk of serious adverse outcomes. Dual endoscopic therapy appears more frequently burdened with the risk of perforation when a combined injective plus contact coaptation protocol is employed (with a sevenfold increase in the chance of perforation). Therefore, expertise and clinical judgment must be applied before recommending the combined injection plus thermal approach as the gold standard for all patients with severe ulcer bleeding.

Dual endoscopic therapy is not superior to either thermal coagulation or hemoclip application alone. Hence, if a single therapy is to be delivered, this should be thermal coagulation or, if applicable, mechanical hemostasis. It is therefore highly advisable that every endoscopist becomes proficient with at least one method of thermal coagulation treatment.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Endoscopic therapy of high-risk bleeding ulcers improves outcome of patients, reducing recurrent bleeding, surgery, and mortality.
- Combined therapy using epinephrine injection plus thermal coagulation is increasingly being offered as the gold standard of endotherapy in referral centers.
- There is evidence that dual endoscopic therapy (injection plus something else) is superior to injection therapy alone in high-risk lesions.

What Is New Here

- This systematic review and meta-analysis demonstrates that, although superior to injection therapy alone, dual endoscopic therapy is *not* better than either thermal monotherapy or hemoclipping alone in such patients.
- Single endoscopic treatment by means of thermal probes or clips is as effective as dual treatments and probably safer.
- Routine application of combined endoscopic therapy (injection plus coaptation or injection plus clips) cannot be routinely recommended.

Reprint requests and correspondence: Riccardo Marmo, M.D., Via Sottobraida 32, 84037 Sant'Arsenio (SA), Italy.
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CONFLICT OF INTEREST

Guarantor of the article: Riccardo Marmo, MD
Specific author contributions: Conceptual design: Riccardo Marmo, Gianluca Rotondano
Data retreival: Riccardo Marmo, Gianluca Rotondano, Rosario D'Angella
Data analysis: Riccardo Marmo, Gianluca Rotondano
Revision of the draft: Livio Cipolletta, Maria A. Bianco, Roberto Piscopo
Handwriting of paper: Gianluca Rotondano
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