Effectiveness of endoscopic treatments for colonic diverticular bleeding

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Background and Aims: Several endoscopic modalities have been used for the treatment of colonic diverticular bleeding (CDB). The aim of this study was to evaluate the effectiveness of endoscopic treatment for CDB.

Methods: We performed a systematic review and meta-analysis of the English literature. Main outcomes were initial hemostasis, early recurrent bleeding (recurrent bleeding within 30 days after endoscopic treatment), and need for transcatheter arterial embolization (TAE) or surgery. Proportions were collected from each study and were used to calculate pooled estimates. Heterogeneity was evaluated by I^2.

Results: Sixteen studies (384 patients with CDB) were included. Pooled estimates of initial hemostasis were coagulation, 1.00 (95% CI, .91-1.00) (I^2 = .0%); clipping, .99 (95% CI, .97-1.00) (I^2 = .0%); and ligation, .99 (95% CI, .95-1.00) (I^2 = .0%). Pooled estimates of early recurrent bleeding were coagulation, .21(95% CI, .01-.51) (I^2 = 61.2%); clipping, .19 (95% CI, .07-.35) (I^2 = 77.3%); and ligation, .09 (95% CI, .04-.15) (I^2 = .0%). Pooled estimates of need for TAE or surgery were coagulation, .18 (95% CI, .00-.61) (I^2 = 68.9%); clipping, .08 (95% CI, .03-.16) (I^2 = 36.8%); and ligation, .00 (95% CI, .00-.01) (I^2 = .0%). The proportion of need for TAE or surgery in the ligation group was significantly lower than that in the clipping group (P = .003) and marginally lower than in the coagulation group (P = .086). No significant difference was found between coagulation and clipping groups (P = .44).

Conclusions: Ligation therapy was more effective compared with clipping to avoid TAE or surgery. Coagulation, clipping, and ligation were equivocal in terms of effectiveness for initial hemostasis and preventing early recurrent bleeding. (Gastrointest Endosc 2018;87:58-66.)

Colonic diverticular bleeding (CDB) is the most common cause of acute lower GI bleeding, and the incidence of CDB is gradually increasing.[1-4] Although bleeding spontaneously stops in many cases of CDB, some patients require intervention to treat bleeding.[5-7] Endoscopic treatment may be required for definite diverticular bleeding with stigmata of recent hemorrhage, because the reported rate of recurrent bleeding is high if no intervention is performed.[7-10]

Several endoscopic modalities, including bipolar coagulation, epinephrine injection, clipping, ligation (endoscopic band ligation [EBL] or endoscopic detachable snare ligation), topical hemostatic agents, and over-the-scope clip (OTSC), have been used for the treatment of CDB.[7-41] Although substantial numbers of patients have experienced CDB, no randomized controlled trial comparing efficacy of endoscopic treatments for CDB has been reported to date, and there are only some reports of observational studies. In this situation a meta-analysis of existing observational studies may provide useful information regarding the selection of optimal treatment modalities.[42] Therefore, the aim of this study was to evaluate the effectiveness of endoscopic treatment for CDB in terms of initial hemostasis, early recurrent bleeding (recurrent bleeding within 30 days after initial endoscopic treatments), and need for transcatheter arterial embolization (TAE) or surgery for the management of initial bleeding or early recurrent bleeding.

Abbreviations: CDB, colonic diverticular bleeding; CI, confidence interval; EBL, endoscopic band ligation; OTSC, over-the-scope clip; TAE, transcatheter arterial embolization.

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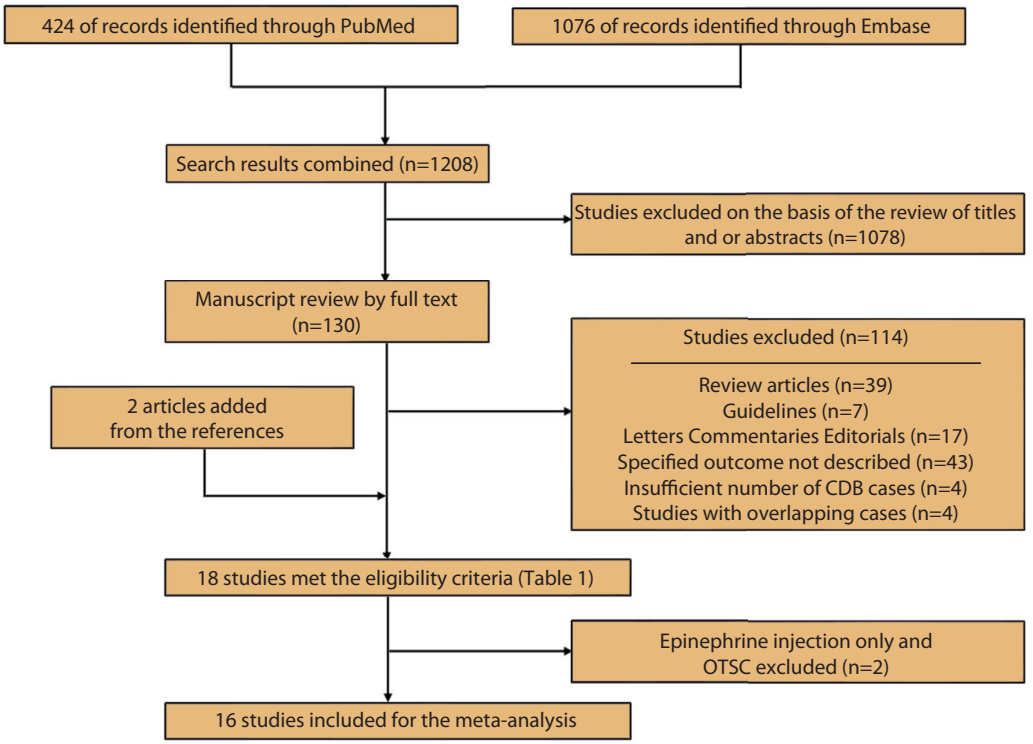

Figure 1. Flow chart of literature search according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. In the literature search 1208 articles were identified using dedicated search term in PubMed and Embase from 1995 to July 2017. After excluding 1078 articles by title and/or abstract, full text review was performed in 130 articles. Finally, the results from 16 studies were included for the meta-analysis. *CDB*, Colonic diverticular bleeding; *OTSC*, over-the-scope clip.

METHODS

Literature search

We performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[42] The literature search was performed using PubMed and EMBASE between 1995 and July 2017. Dedicated search terms were produced in discussing with librarian. Institutional review board approval was not required in this study because human subjects and patients' medical charts were not used.

Search term in PubMed was as follows: ((((“Colonic Diseases”[Mesh] OR “Colon”[Mesh] OR colon*[TIAB]) AND (diverticul*[TIAB] OR “Diverticulum”[Mesh])) AND ((“Endoscopy, Gastrointestinal”[Mesh]) OR (colonoscop*[TIAB])))) AND (“Hemorrhage”[Mesh] OR hemorrhage*[TIAB] OR bleed*[TIAB])) AND (“1995/01/01”[PDAT] : “2017/07/10”[PDAT]). Search term in EMBASE was as follows: “colon diverticulosis”/exp OR “colon diverticulosis” OR (diverticul* AND colon*) AND (hemorrhag* OR “bleeding”/exp OR bleed*) AND (“digestive endoscope”/exp OR “digestive endoscope” OR colonoscop*) NOT (“colon diverticulosis”/exp OR “colon diverticulosis” OR (diverticul* AND colon*) AND (hemorrhag* OR “bleeding”/exp OR bleed*) AND (“digestive endoscope”/exp OR “digestive endoscope” OR colonoscop*) AND “conference abstract”/it) AND [1995-2017]/py. All references of selected articles were also reviewed carefully.

Two authors (N.I. and F.O.) independently performed the study selection, data extraction, and study quality assessment. Disagreements were resolved by discussion between the 2 authors. If no agreement could be reached, it was planned that a third author would decide to obtain the consensus.

Inclusion and exclusion criteria

We included retrospective cohort studies and case series of more than 3 cases that included a description of the clinical course after endoscopic treatments (initial hemostasis, early recurrent bleeding, and/or need for TAE or surgery). Of note, randomized controlled trials comparing the effectiveness of endoscopic therapies for CDB were not found. We excluded case reports with fewer than 4 cases because it was difficult to evaluate initial hemostasis on an intention-to-treat basis.

Initially, based on review of titles and/or abstracts we excluded articles describing cases other than acute lower GI bleeding or CBD, those not written in English, and case reports. Next, we reviewed the full texts of studies meeting the above inclusion criteria. At this point studies with overlapping populations were excluded unless more-detailed information was available from the authors.

TABLE 1. Studies of endoscopic treatments for colonic diverticular bleeding

Reference	Publication year	Study design	Description of ITT	Selection of patients	Modalities	n	Initial hemostasis	Early recurrent bleeding	Need for TAE or surgery	Late recurrent bleeding	Adverse events	Follow-up periods (mo)
Foutch et al[8]	1996	Retrospective	ITT	Consecutive	Bip	5	4 (80%)	1 (25%)	2 (40%)	0 (0%)	None	Median 18 (range, 2-36)
Jensen et al[9]	2000	Prospective	ITT	Consecutive	Bip and/or Epi	10	10 (100%)	0 (0%)	0 (0%)	0 (0%)	None	Median 30 (range, 18-49)
Bloomfeld et al[11,*]	2001	Retrospective	ITT	Consecutive	Bip and/or Epi	5	5 (100%)	2 (40%)	2 (40%)		None	
Green et al[12]	2005	Prospective	ITT	Consecutive	Bip and/or Epi	13	13 (100%)	5 (38%)			None	
Couto-worner et al[17]	2013	Retrospective	ITT	Consecutive	Clip and Epi	5	5 (100%)	1 (20%)	0 (0%)		None	
Kumar et al[18]	2011	Retrospective	N.R.	N.R.	Clip	9	9 (100%)	3 (33%)			None	
Yen et al[19]	2008	Retrospective	ITT	Consecutive	Clip and/or Epi	11	11 (100%)	0 (0%)	0 (0%)	2 (18%)	None	Median 15 (range, 1-22)
Kaltenbach et al[20]	2012	Retrospective	ITT	Consecutive	Clip and/or Epi	24	21 (88%)	0 (0%)	3 (12%)	5 (21%)	None	mean 35 (range, 1-70)
Ishii et al[21]	2012	Retrospective	ITT	Consecutive	Clip	89	87 (98%)	30 (34%)	10 (11%)		None	
Fujino et al[22]	2013	Retrospective	ITT	Consecutive	Clip	16	16 (100%)	8 (50%)	3 (19%)			
Sugiyama et al[23]	2015	Retrospective	ITT	Consecutive	Clip	23	23 (100%)	6 (26%)	5 (22%)		None	
Nagata et al[24,†]	2015	Prospective	ITT	Consecutive	Clip	18	18 (100%)	3 (17%)	0 (0%)			
Farrell et al[27]	2003	Prospective	N.R.	N.R.	EBL and/or Epi	4	4 (100%)	0 (0%)	0 (0%)	0 (0%)	None	>12
Ikeya et al[31]	2015	Retrospective	ITT	Consecutive	EBL	108	101 (94%)	15 (15%)	2 (2%)		None	
Shibata et al[32]	2014	Retrospective	ITT	Consecutive	EBL	27	27 (100%)	1 (4%)	0 (0%)	1 (4%)	None	Median 18 (range, 3-27)
Akutsu et al[35]	2015	Retrospective	ITT	Consecutive	EDSL	8	8 (100%)	1 (12%)	0 (0%)		None	
Nagata et al[24,†]	2015	Prospective	ITT	Consecutive	EBL	9	9 (100%)	1 (11%)	0 (0%)			
Bloomfeld et al[11,*]	2001	Retrospective	ITT	Consecutive	Epi	8	8 (100%)	3 (38%)	3 (38%)		None	
Ramirez et al[14]	1996	Retrospective	N.R.	N.R.	Epi	4	4 (100%)	0 (0%)	1 (25%)		None	
Wedi et al[41]	2016	Retrospective	ITT	N.R.	OTSC	6	6 (100%)	2 (33%)	0 (0%)		None	

ITT, Intention-to-treat; *N.R.*, not reported; *Bip*, bipolar coagulation; *Epi*, epinephrine injection; *Clip*, endoscopic clipping; *EBL*, endoscopic band ligation; *EDSL*, endoscopic detachable snare ligation; *OTSC*, over-the-scope clip; *TAE*, transcatheter arterial embolization.
*Two methods (bipolar coagulation and/or epinephrine injection and epinephrine injection only) were used in the study of Bloomfeld et al.
†Two methods (endoscopic clipping and endoscopic band ligation) were used in the study of Nagata et al.

We performed a meta-analysis comparing endoscopic modalities if there were more than 2 published articles evaluating the technique.

Statistical analysis

The main outcomes of interest were proportions of initial hemostasis, early recurrent bleeding, and need for

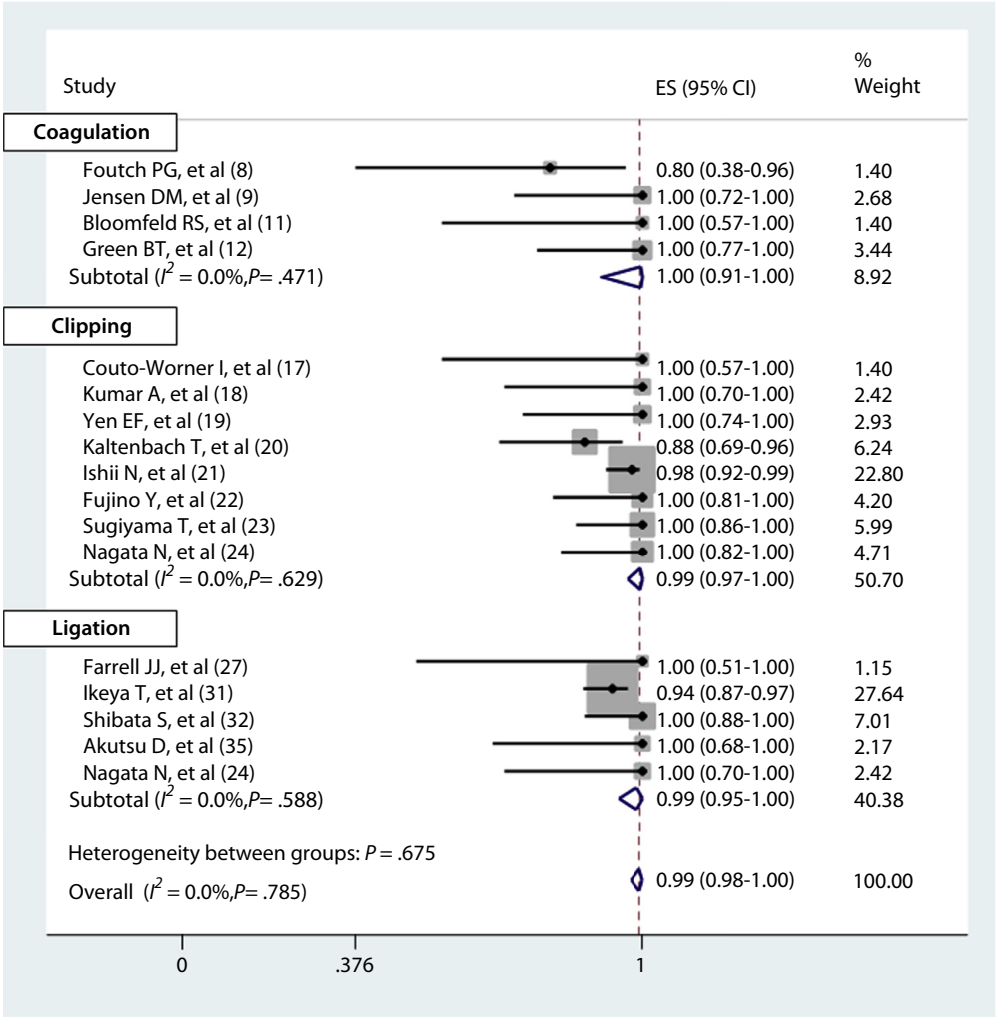

Figure 2. Forest plot of initial hemostasis proportions by the coagulation, clipping, and ligation treatment. The pooled estimate (95% confidence interval [CI]) probability of successful hemostasis of coagulation, clipping, and ligation therapy was 1.00 (95% CI, .91-1.00), .99 (95% CI, .97-1.00), and .99 (95% CI, .95-1.00), respectively. All pooled estimates were calculated by fixed effects model. The difference among 3 endoscopic treatments was not statistically significant.

TAE or surgery after endoscopic treatment. Early recurrent bleeding was defined as recurrent bleeding within 30 days after endoscopic treatment.[9]

Proportions of initial hemostasis, early recurrent bleeding, and need for TAE or surgery were collected from each study, and 95% confidence intervals (CIs) of those proportions were calculated. Meta-analyses for proportions were performed to calculate pooled estimates. Because the proportions of some studies were 0% or 100%, Freeman-Tukey double arcsine transformation and its back transformation were applied. The 95% CI of each study was calculated by score CI. Each treatment group and their overall pooled estimates were 95% Wald CIs.[43] Heterogeneity was expressed by I^2. We used fixed effect model if $I^2 < 25\%$; otherwise, we used the random effect model. The Bonferroni multiple comparisons procedure was applied to avoid Type I error in case of comparing 2 groups among 3 groups. $P < .016$ was considered to be statistically significant in multiple comparisons of 2 groups among 3 groups. Otherwise, $P < .05$ was considered to be statistically significant. All analyses were performed by *metaprop* using STATA version 14.1 (StataCorp, College Station, Tex).

RESULTS

Studies selected for the meta-analyses

The results of the literature search are presented in Figure 1. Six manuscripts were based on the same database (St. Luke's International Hospital, Tokyo),[21,28-31,33] and there was some overlap in cases treated with EBL or clipping. Four studies with overlapping cases were excluded.[28-30,33] For 1 study additional data were obtained from the author and the study was included.[24] Two additional studies[14,41] were excluded because there was

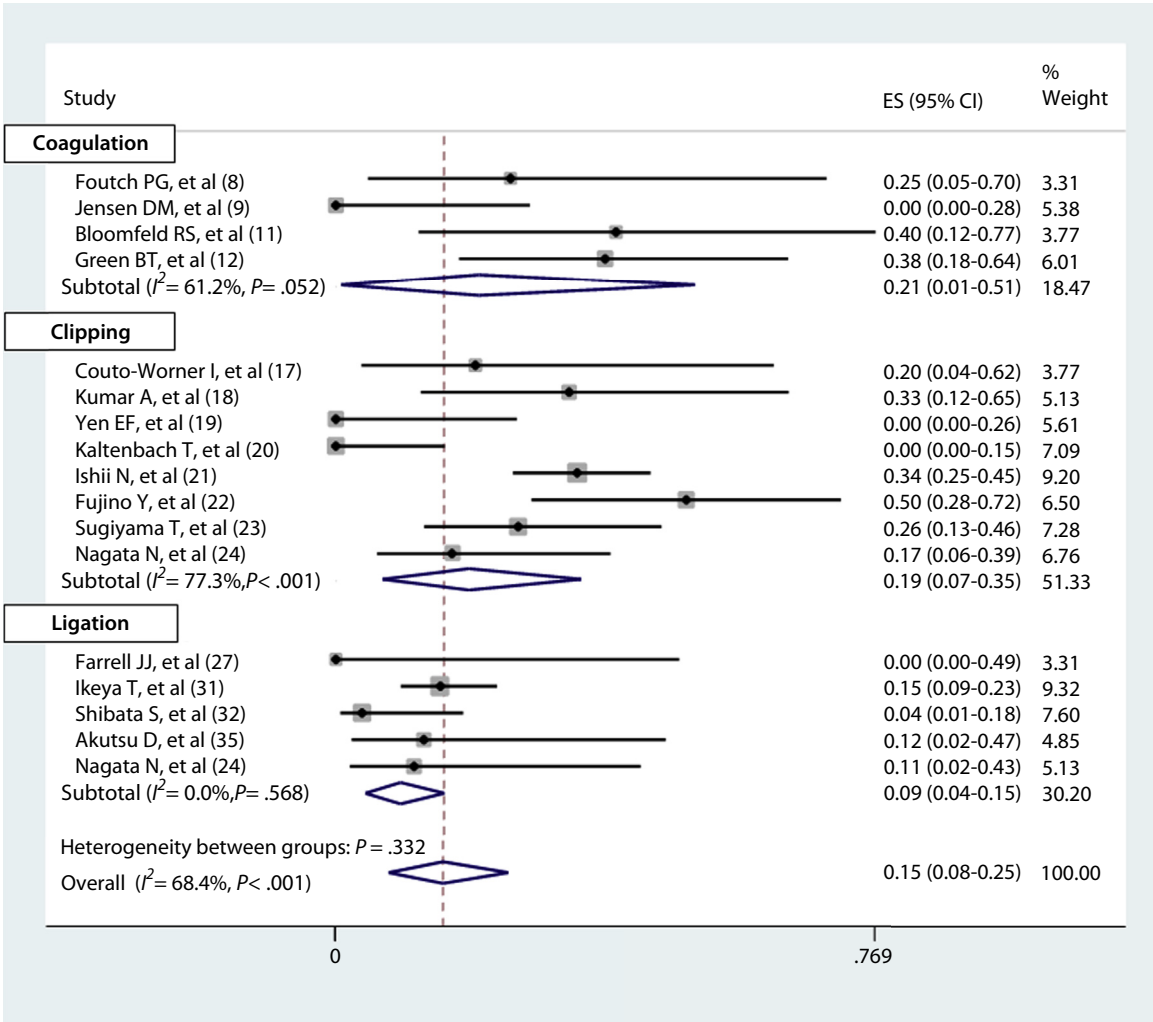

Figure 3. Forest plot of early recurrent bleeding proportions by the coagulation, clipping, and ligation treatment. The pooled estimate (95% confidence interval [CI]) probability of early recurrent bleeding after coagulation, clipping, and ligation therapy was .21 (95% CI, .01-.51), .19 (95% CI, .07-.35), and .09 (95% CI, .04-.15), respectively. Pooled estimates of coagulation and clipping were calculated by random effects model. Pooled estimate of ligation was calculated by fixed effects model. The effectiveness for preventing early recurrent bleeding was not different from each other among the 3 procedures.

only a single study available on the respective techniques, 1 using epinephrine alone and 1 using OTSC.

Eighteen studies fulfilled the eligibility criteria: literature with 4 or more cases that included a description of clinical courses after endoscopic treatments (Fig. 1, Table 1).[8,9,11,12,14,17-24,27,31,32,35,41] Bipolar coagulation and/or epinephrine injection and epinephrine injection only were reported in the study by Bloomfeld et al[11] in which the number of patients treated in the study was 5 and 8, respectively. Two methods (endoscopic clipping and EBL) were used in the study by Nagata et al.[24]

The number of the studies of epinephrine injection only or OTSC were not more than 2; hence, we did not calculate pooled estimates.[14,41] A total of 16 studies were included in our meta-analysis, and initial hemostasis and early recurrent bleeding were analyzed in these 16 studies (Table 1): 4 studies in the coagulation group,[8,9,11,12] 8 in the clipping group,[17-24] and 5 in the ligation group.[24,27,31,32,35] Need for TAE or surgery were evaluated in 14 studies (Table 1): 3 studies in the coagulation group,[8,9,11] 7 in the clipping group,[17,19-24] and 5 in the ligation group.[24,27,31,32,35]

We evaluated the quality of studies based on whether patient selection was consecutive and whether the probability of initial hemostasis was assessed on an intention-to-treat basis. A total of 14 of 16 studies met these quality criteria (Table 1).[8,9,11,12,17,19-24,31,32,35]

Initial hemostasis

The forest plot of initial hemostasis in the coagulation, clipping, and ligation groups is depicted in Figure 2. The proportions of initial hemostasis ranged from .80 to 1.00. The pooled estimates of initial hemostasis in each group were as follows: coagulation group, 1.00 (95% CI, .91-1.00) (I^2 = .0%); clipping group, .99 (95% CI, .97-1.00) (I^2 = .0%); and ligation group, .99 (95% CI, .95-1.00)

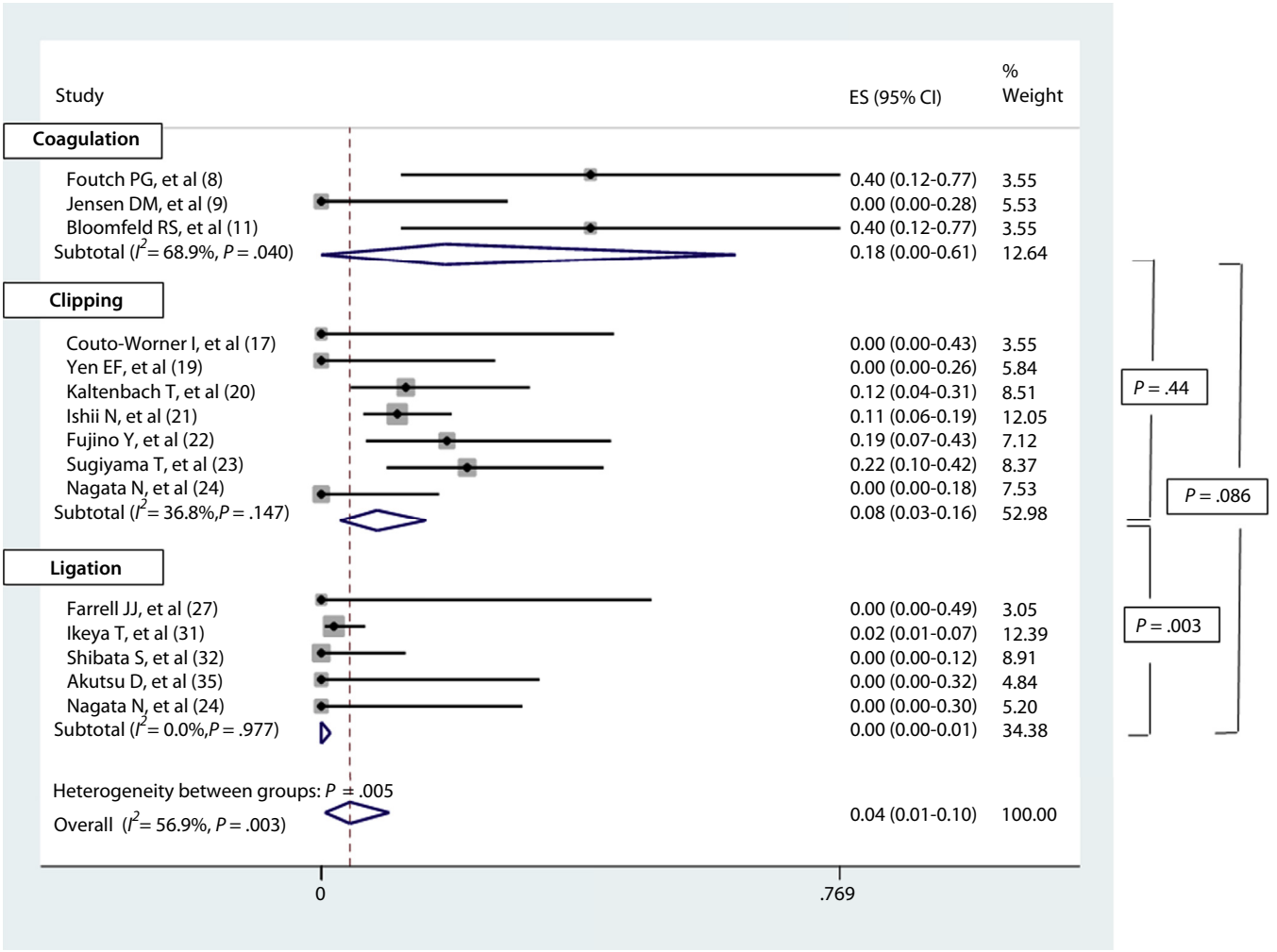

Figure 4. Forest plot of the proportions of need for TAE or surgery after the coagulation, clipping and ligation treatment. The pooled estimate (95% confidence interval [CI]) probability of having TAE or surgery after coagulation, clipping, and ligation was .18 (95% CI, .00-.61), .08 (95% CI, .03-.16), and .00 (95% CI, .00-.01), respectively. Ligation therapy was more effective than clipping to avoid TAE or surgery.

(I^2 = .0%). The heterogeneity test among 3 groups was not significant (P = .68).

Early recurrent bleeding

The forest plot of early recurrent bleeding in the coagulation, clipping, and ligation groups is depicted in Figure 3. The proportions of early recurrent bleeding ranged from 0 to .50. The pooled estimates of early recurrent bleeding were as follows: coagulation group, .21 (95% CI, .01-.51) (I^2 = 61.2%); clipping group, .19 (95% CI, .07-.35) (I^2 = 77.3%); and ligation group, .09 (95% CI, .04-.15) (I^2 = .0%). The heterogeneity test among 3 groups was not significant (P = .33).

Need for TAE or surgery

The forest plot of need for TAE or surgery in the coagulation, clipping, and ligation groups is depicted in Figure 4. The proportions of need for TAE or surgery ranged from 0 to .40. The pooled estimates of need for TAE or surgery were as follows: coagulation group, .18 (95% CI, .00-.61) (I^2 = 68.9%); clipping group, .08 (95% CI, .03-.16) (I^2 = 36.8%); and ligation group, .00 (95% CI, .00-.01) (I^2 = .0%). The heterogeneity test among 3 groups was significant (P = .005).

The proportion of need for TAE or surgery in the ligation group was significantly lower than that in the clipping group (P = .003), and lower than that in the coagulation group, albeit without statistical significance (P = .086). No significant difference was found between the coagulation and clipping groups (P = .44).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of endoscopic treatments for CDB; we compared endoscopic bipolar coagulation, clipping, and ligation-based treatments in terms of initial

hemostasis, early recurrent bleeding, and need for TAE or surgery. Although the proportions of initial hemostasis and early recurrent bleeding were not significantly different among the 3 groups, the proportion requiring TAE or surgery in the ligation group was marginally lower than that in the coagulation group ($P = .086$) and was significantly lower than that in the clipping group ($P = .003$).

Anatomic features of colonic bleeding diverticula need to be considered when endoscopic modalities are applied for the treatment of CDB. Colonic diverticula lack the muscular layer, and three fourths of CDB arise from the vasa recta at the base of colonic diverticula.[44] Therefore, there are more opportunities to apply hemostasis to bleeding sites at the dome of colonic diverticula than at the neck. Furthermore, the risk of perforation may need to be considered if coagulation therapy is used for the hemostasis of bleeding from the vasa recta at the dome of the colonic diverticula. It may be difficult to sufficiently coagulate ruptured vasa recta at the dome because of the risk of perforation, which might contribute to the higher proportions of early recurrent bleeding and need for TAE or surgery in the coagulation group, although significance was not found compared with other modalities.

Tissue injuries resulting from clipping are less than those of other endoscopic modalities, and clipping has been used for the treatment of CDB.[15-24] The rate of early recurrent bleeding was assumed to be low if hemoclips could be directly deployed to the bleeding site.[19,20] However, when a direct placement of hemoclips to the bleeding site at the dome was difficult, indirect placement in a zipper fashion was sometimes performed.[21] This may not have sufficiently occluded the ruptured vasa recta. This might contribute to early recurrent bleeding after initial clipping therapy and the higher proportion of need for TAE or surgery. Furthermore, despite presumed reduced tissue injury with clipping compared with other modalities, sepsis was reported after clipping.[25] Cautious deployment of hemoclips is required, especially to the muscle-deficient dome location.

EBL has been reported as a safe and effective endoscopic treatment for the hemostasis of CDB, and the number of studies of EBL for CDB treatment is increasing.[24,26-33] Recently, endoscopic detachable snare ligation has been used in the treatment of CDB instead of EBL because reinsertion of the colonoscope is not required.[35,36] Ruptured vasa recta at the dome or at the neck of the diverticula can be occluded using the ligation therapy. However, it is considered difficult to treat CDB with an orifice that is too small or a dome that is too large using ligation techniques,[30] which explains why the initial hemostasis of ligation therapy was not perfect.

Although a significant difference was not found in early recurrent bleeding among the 3 modalities, the proportion requiring TAE or surgery in the ligation group was significantly lower than that in the clipping group ($P = .003$) and lower than that in the coagulation group, albeit without statistical significance ($P = .086$). Once ligation was completed as the initial therapy, the hemostatic effect of ligation may last for a longer period and recurrent bleeding risk may be attenuated. As a result, need for TAE or surgery might be lower in the ligation group than in the coagulation and clipping groups, although the need for TAE or surgery is determined by the gastroenterologists' judgement and by the bleeding behavior. In addition, because the banded sites are gradually replaced with granulation tissues and the banded diverticula resolve, late recurrent bleeding from the same banded diverticula can be prevented using ligation therapy.[30,33,45] Further studies are required to evaluate late recurrent bleeding among several modalities. On the other hand, delayed perforation after EBL was reported in a patient with CDB who had been treated with steroid and aspirin for 22 years for Takayasu arteritis.[34] Ligation therapy may not be indicated in patients with CDB in which wound healing is inhibited because of steroid therapy. In addition, uncomplicated diverticulitis 1 day after EBL for CDB was reported, which could be managed conservatively.[46] Colonic diverticulitis might be one of the adverse events after EBL for CDB.

Our study has several limitations and strengths. First, we included only observational studies, most of which were retrospective, because prospective randomized studies were not available. Second, although the initial hemostasis, early recurrent bleeding after initial hemostasis, and need for TAE or surgery among 3 endoscopic modalities (coagulation, clipping, and ligation) were compared in the present study, the effectiveness of epinephrine injection only, topical hemostatic agents, and OTSC were not evaluated for the meta-analysis because few studies of these modalities fulfilled the inclusion criteria for the meta-analysis. Third, outcomes other than initial hemostasis, early recurrent bleeding, and need for TAE or surgery were not evaluated in the present study. For example, procedure time was not compared and may be longer with band ligation compared with coagulation and clipping therapies because reinsertion of the endoscope is necessary. In addition, our results have not been adjusted with possible confounding factors such as antithrombotic drug use. Fourth, most studies of ligation therapy have come from Asia, and it is possible that the success may be different in the West because the distribution of diverticula is different.[47,48] Nonetheless, given the lack of available prospective and randomized studies in this area, valuable information regarding treatment modalities for CDB can be derived from this meta-analysis of observational studies.

In conclusion, ligation therapy was more effective than coagulation therapy or clipping in terms of the proportion of surgical treatment and TAE, whereas ligation

therapy was equally effective to coagulation and clipping in terms of initial hemostasis and early recurrent bleeding. These findings need to be confirmed by a multicenter randomized trial.

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