PROPHYLACTIC CLIP PLACEMENT DURING POLYPECTOMY DOES NOT REDUCE THE RISK OF DELAYED BLEEDING: A SYSTEMATIC REVIEW AND META-ANALYSIS

By

Tarun Rai

Submitted to the graduate degree program in Clinical Research and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science

_____

Chairperson Dr. Edward Ellerbeck, MD, MPH

_____

Dr. Prateek Sharma, MD

_____

Dr. Ajay Bansal, MD

Date Defended: 04/28/2016

The Thesis Committee for Tarun Rai
certifies that this is the approved version of the following thesis:

PROPHYLACTIC CLIP PLACEMENT DURING POLYPECTOMY DOES NOT REDUCE THE RISK OF DELAYED BLEEDING: A SYSTEMATIC REVIEW AND META-ANALYSIS

_____
Chairperson Dr. Edward Ellerbeck, MD, MPH

_____
Dr. Prateek Sharma, MD

_____
Dr. Ajay Bansal, MD

Date approved: 5/12/16

Abstract

Background: Delayed gastrointestinal bleeding is a known complication of snare polypectomy during colonoscopy. Published data on prophylactic clip placement are scarce with conflicting results.

Aim: To determine the effect of prophylactic clip placement on delayed post polypectomy bleeding.

Methods: Three independent reviewers conducted a search of MEDLINE/PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, and recent abstracts from major conference proceedings using the following MeSH search terms: "polyp", "bleeding", "colonoscopy" and "clips". Randomized and non-randomized studies that compared prophylactic clip placement with no clip placement were included. Pooled estimates of delayed post polypectomy bleeding, perforation and overall complications were analyzed by calculating odds ratio (OR) along with 95% confidence interval (CI). Random and fixed effects models were used as appropriate. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency.

Results: Initial search revealed 418 studies; of which 26 studies were reviewed. Eleven studies (including 4 randomized controlled trials) met the inclusion/exclusion criteria. The final analysis included 10,910 polypectomies in 13,308 patients. The rate of delayed post polypectomy bleeding was 1.27% with prophylactic clips placement vs. 0.97% without placement of clips (OR = 0.94; 95% CI: 0.4-2.24; p = 0.9; I^2 71%). With inclusion of high quality studies (Newcastle-Ottawa scale score >6), there was a significant difference in delayed post polypectomy bleeding with clip placement (1.24% vs 3.26%; OR, 0.46, 95% CI: 0.21-1.00, p= 0.05; I^2= 35%). The rate of perforation was 0.16% with prophylactic clip placement vs. 0.017% without placement of

clips (OR = 1.45; 95% CI: 0.26-8.09; p = 0.7; I^2 0%). Subgroup analysis showed that clip placement decreased risk of bleeding in polyps larger than 2 cm (2.2% vs. 7.98%, OR 0.25; 95% CI 0.12-0.51, p <0.001), use of pure coagulation (2.52% vs. 8.89%, OR; 0.24, 95% CI: 0.1-0.57, p = 0.001) and in situations where endoscopic mucosal resection was performed (1.7% vs. 5.7%, OR, 0.28; 95% CI 0.14-0.59, p= 0.0008).

Conclusions: The results of this systematic review and meta-analysis show that prophylactic clip placement reduced the incidence of delayed GI bleeding after snare polypectomy when high quality studies were pooled. Prophylactic clip placement may be protective against delayed GI bleeding if the polyps were > 2 cm and if they were removed with endoscopic mucosal resection and pure coagulation current.

ACKNOWLDGEMENTS

Firstly, I would like to express my sincere gratitude to my committee chair, Dr. Edward Ellerbeck, MD, MPH for the continuous support of my Master of Science study and related research, for his patience, motivation, and immense knowledge. I appreciate his vast knowledge and skill in many areas (e.g., vision, ethics). His guidance helped me throughout during writing of this thesis.

Besides my advisor, I would like to thank the rest of my thesis committee: Dr. Prateek Sharma, MD and Dr. Ajay Bansal, MD for their insightful comments and encouragement, but also for the hard question which incented me to widen my research from various perspectives.

My sincere thanks also goes to Ms. Tanya Honderick for her suggestions throughout the graduate program and revising the thesis draft. I must also acknowledge Ms. Farah Marhusin and all the office staff for all the instances in which their technical assistance helped me along the way. I would also like to thank my friends in different courses for exchanges of knowledge, skills, and venting of frustration during my graduate program, which helped enrich the experience.

Finally, I thank my wife and best friend, Arpeta for love, editing assistance and support throughout all my studies.

TABLE OF CONTENTS

Introduction

Colonoscopy with detection and removal of polyps is the most effective tool for colon cancer screening. Approximately 14 million colonoscopies are performed each year.[1] Bleeding is the most common complication after removal of polyps including polypectomy and endoscopic mucosal resection (EMR).[2,3] Incidence varies from 0.3 to 6.1 percent of polypectomies performed.[4-7] Post-polypectomy bleeding [PPB] can be early or delayed. Early bleeding is identified during the procedure itself whereas delayed bleeding can present up to 30 days after the procedure[4,5] and the incidence is approximately 2%.[6] Delayed PPB risk depends on polyp characteristics, polypectomy techniques and patient related factors. Large polyps (≥ 1cm), right sided location, sessile morphology, prior use of anticoagulants/antiplatelet agents, cardiovascular morbidity, chronic rental insufficiency and use of pure coagulation current during polypectomy increases the risk of delayed PPB.[4,8-11] Delayed PPB rate of up to 7.2% has been reported after EMR of large polyps using pure coagulation current.[12]

In 1998, Hachisu et al first studied prophylactic clip placement at the time of polypectomy to minimize PPB.[13] Three prospective randomized controlled trials (RCT) since then have failed to show any benefit of prophylactic clipping on incidence of delayed PPB.[14-16] On the other hand, Liaquat et el. in a retrospective study, reported a significant risk for delayed bleeding if prophylactic clipping was not performed.[11] A prior meta-analysis studied the role of any prophylactic endoscopic treatment (limited not just to clipping) on PPB, and reported a decrease in incidence of early PPB but no effect on delayed PPB; this was published in 2001.[17] Due to conflicting results, the true efficacy of prophylactic clipping in preventing delayed PPB is still unclear.

Our aim was to conduct a systematic review and meta-analysis to investigate the role of prophylactic clip placement in preventing delayed PPB in patients undergoing removal of colonic polyps.

Methods

Literature Search and Identification of Primary Studies

Articles were searched on prophylactic clip placement for the prevention of delayed post polypectomy bleeding. All articles were searched irrespective of language, publication status (articles or abstracts), or results. A 3-stage search strategy was adopted and implemented. First was a search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials with search terms "colonoscopy," "polypectomy," and "bleeding". Studies between 1990 to December 2015 were searched using PubMed and Ovid search engines and 418 articles were retrieved. The resulting abstracts were then screened for potential suitability, and those that appeared relevant were retrieved and examined in more detail. MeSH terms "colonoscopy," "polypectomy," "bleeding," and "clip" were subsequently used and 19 studies extracted for detailed review. In the second step, a recursive search was performed by using the bibliographies of all obtained articles, reviews, and meta-analyses for additional articles. Third, a manual search of abstracts submitted to Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week (2009-2014) was performed. Where multiple study reports from the same group of individuals appeared to exist, we contacted study authors to seek clarification. The search was restricted to adult patients. There were no language restrictions. Foreign language articles were translated to English using google translator where required. Both full-length publications and abstracts were selected.

Inclusion and Exclusion Criteria

Articles and abstracts comparing prophylactic clip placement with no clip placement were selected. The inclusion criteria were: (i) studies reporting delayed PPB as a study end point after colonoscopy (ii) any minor or major bleeding after completion of colonoscopy and within 30 days post procedure (iii) randomized controlled trials (RCTs), cohort or case-control studies and (iv) polypectomy using cold or hot forceps, snare or EMR. The exclusion criteria were: (i) procedures other than colonoscopy (ii) studies not involving delayed GI bleeding as a study endpoint (iii) comparing clip placement to other modalities to control GI bleeding and (iv) endoscopic submucosal dissection (ESD) or circumferential EMR (CEMR) for polypectomy

Data Extraction

Data extraction was independently performed by 2 investigators (A.C., T.R.) and reviewed by a third (P.S.) for agreement. Eligibility assessment was performed independently by 2 investigators by using predesigned eligibility forms. Any disagreements were resolved by consensus. Details of study design (randomization/blinding/concealment), number of subjects, polyp size, morphology, location and number, number of clip placed per patient, total number of clips placed in the study, type of cautery used, anticoagulation status; incidence of delayed post polypectomy bleeding, perforation and total complications were evaluated. Since both randomized, controlled trials (RCTs) and case-control studies were included in the analysis, a quality score based Newcastle-Ottawa scale (NOS)[18] (maximum of 9) was assigned with 7-9 representing high quality and 1-6 poor quality.

Data Analysis

Statistical pooling of the data by using meta-analytical techniques was done for both RCTs and nonrandomized studies. The primary outcome was the incidence of delayed post

polypectomy bleeding. Secondary outcomes included: incidence of perforation and the overall incidence of complications (delayed PPB, perforation and post polypectomy syndrome). Sub-group analysis for delayed post-polypectomy bleeding was performed for type of current, polyp characteristics (size, location and morphology) and polypectomy technique. The effects of prophylactic clip placement were analyzed by calculating pooled estimates of delayed post polypectomy bleeding, perforation, and overall complications. Separate analyses were performed for each outcome by using odds ratio (OR). Random or fixed-effects models were used as appropriate.

Sensitivity analysis were performed separately with RCTs, case-control studies and RCTs with more than 50% sessile polyps and high quality studies with NOS score more than 6. Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for statistical analysis of the data. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency. Generally, an I^2 of 0% to 40% excludes heterogeneity, I^2 of 30% to 60% may represent moderate heterogeneity, I^2 of 50% to 90% may represent substantial heterogeneity, and I^2 of 75% to 100% represents considerable heterogeneity.

Results

Study Selection

The initial search identified 418 articles. Of these, 349 articles were initially excluded as the titles and abstracts were not appropriate. After a second search with the MESH terms, 19 full text publications were assessed for evaluation. Seven more articles were retrieved from bibliography of full text publications to assess eligibility. Finally a total of 11 articles met the

inclusion criteria and were selected for final review and analysis (Fig. 1). Both RCTs and retrospective cohort studies were analyzed.

Study Characteristics

The 4 RCTs included 782 subjects (2 from Japan, 1 from Spain and 1 from China) and the 7 case-control studies (4 from Japan, 2 from USA and 1 from Spain) included 12,526 subjects. Study characteristics are presented in Table 1**.** The total number of polypectomies wherein clips were applied ranged from 42 to 4,735 per study. Except for 1 RCT and 2 case-control study, in all other studies the clips were applied after polypectomy. Of the 11 studies, 9 reported the type of current use: blended current in 7 and pure coagulation and cut in 1 study each.

The mean size of polyps ranged from 7.8 mm to 31 mm. In terms of polyp morphology, 6 studies reported 14.5%-100% of sessile polyps whereas 6 studies had 15 -100% pedunculated polyps. Four studies used predominantly EMR technique for polyp removal in 81-100% of cases.[11,16,19,20] In other studies, methods of polypectomy included cold or hot forceps biopsy, cold or hot snare polypectomy and EMR. Four studies reported anticoagulation status in the patients.[11,16,21,22] with 2.7 to 11% of patients on anticoagulation at the time of colonoscopy.

Table 1: Clinical Characteristics of 11 Studies Included in Our Meta-Analysis

Study, published year	Study period	Country	Design	Number of subjects	Number of polypectomies	Sex (M/F) in clip group	Sex (M/F) in no clip group	Mean size of polyps in in clip group	Mean size of polyp in no clip group	Morphology (clip group)	% proximal to splenic flexure (Clip group)	Clip application (Beforeafter) polypectomy	% EMR (clip group)	Cautery
Lida et al 1994[26]	NR	Japan	Retrospective cohort	639	42	33/7	NR	23 mm (10±5 mm)	NR	Sessile – 14% Semipeduculated – 24% Peduculated – 57% Uncertain – 2%	NR	Before	NR	Blended
Parra-Blanco et al.[27] 2000	1995-1998	Japan	Retrospective cohort	9,555	4735	NR	NR	NR	NR	NR	NR	After	NR	Pure cut
Sobrina-Faya et al[28] 2002	Jan –Oct 2001	Spain	Retrospective cohort	215	223	NR	NR	>1.5 cm	NR	Pedunculated - 100%	NR	Before (30) After-4	NR	Blended
Masayuki et al[24] 2002	1995-1999	Japan	Retrospective cohort	911	1828	305/132	313/161	NR	NR	NR	NR	After	NR	Blended
Shioji et al.[15] 2003	1998-2001	Japan	RCT	323	413	118/38	130/37	7.8 mm	7.8 mm	Pedunculated (1p)- 7% Semipeduculated (lsp) - 26%) Sessile type (ls)- 29% Superficial elevated type (IIa)- 39%	45.2%	After	100%	Blended
Quintanilla et al.[14] 2012	2007-2010	Spain	RCT	98	105	49/17[a]	24/15[a]	NR	NR	Peduculated – 100%	NR	Before	0%	NR
Matsumoto et al.[21] 2012	2003-2006	Japan	Retrospective cohort	375	403	NR	NR	27.1 mm[b]	-	Sessile – 45.1% Other- 54.9%	NR	After	5.1%	Blended
Liaquat et al. [11] 2013	2000-2012	USA	Retrospective cohort	463	524	NR	NR	31 mm[b]	-	Sessile – 100%	75%[b]	After	100%	Pure coagulation
Feagins et al.[29] 2014	2008-2009	USA	Retrospective cohort	368	1,311	182/2	182/2	12 mm	8 mm	Sessile – 85% Pedunculated- 15%	52%	After	0%	NR
Dokoshi et al.[16] 2015	2001-2014	Japan	RCT	156	288	109/45[a]	99/35[a]	95.1% <2 cm[b]	-	Sessile – 85%[b] Pedunculated- 15%[b]	49.6%[b]	After	81.2%[b]	Blended
Zhang et al.[19] 2015	2012-204	China	RCT	205	205	NR	NR	NR	NR	NR	NR	After	100%	Blended

a- by polyps

b- Overall in the study

Table 2. Delayed post polypectomy bleeding, perforation and total complications in 11 studies included in our meta-analysis

Study, published year	Definition of delayed bleeding	Post polypectomy bleed (by polyps)		Perforation (by polyps)		Total complications[a] (by polyps)	
		Clips	No clip	Clips	No clips	Clips	No clips
Lida et al 1994[26]	NR	0/40	1/599	0/40	3/599	0/40	4/599
Parra-Blanco et al.[27] 2000	Any bleeding per rectum hours or days after discharge	7/565	10/4170	0/565	0/4170	7/565	10/4170
Sobrina-Faya et al[28] 2002	NR	0/34	0/189	0/34	0/189	0/34	0/189
Masayuki et al[24] 2002	Any bleeding per rectum hours or days after discharge	12/846	12/982	NR	NR	12/846	12/982
Shioji et al.[15] 2003	Any bleeding per rectum post procedure	2/205	2/208	0/205	0/208	2/205	2/208
Qunitanilla et al.[14] 2012	Any overt bleeding per rectum, hours after procedure and confirmed with endoscopy	1/66	0/39	1/66	0/39	2/66	0/39
Matsumoto et al.[21] 2012	Clinical evidence of bleeding manifested by melena or hematochezia from 0 to 14 days after the procedure that required endoscopic hemostasis	3/174	14/229	NR	NR	3/174	14/229
Liaquat et al.[11] 2013	Return to any health care facility for evaluation of overt bleeding within 30 days after leaving endoscopy unit and required either hospitalization, transfusion, or repeat colonoscopy or sigmoidoscopy for examination of the polypectomy site or control of bleeding	7/277	24/247	1/277	1/247	10/277	29/247
Feagins et al.[29] 2014	Occurrence of rectal bleeding within 30 days of the procedure that resulted in hospitalization and/or treatment.	3/701	1/610	NR	NR	3/701	1/610
Dokoshi et al.[16] 2015	Rectal bleeding within 1 day and 30 days of procedure	4/154	3/134	NR	NR	4/154	3/134
Zhang et al.[19] 2015	Hematochezia 6 hours to 30 days after procedure	1/99	6/106	0/99	0/106	1/99	11/106

a- Includes post polypectomy bleeding, perforation and post polypectomy syndrome

Delayed Post Polypectomy Bleeding

The timing of reporting of PPB (any bleeding after completion of procedure) varied in the studies, ranging from 14 days till 30 days.[16,21,22] In the prophylactic clip group, 40 delayed post- polypectomy bleeding events occurred of 3,161 polypectomies (1.27%). In the no clip group, 73 post polypectomy bleeding events (0.97%) occurred with 7,513 polypectomies. Pooled analysis showed no significant difference in the incidence of delayed post polypectomy bleeding with prophylactic clip placement ((OR = 0.94; 95% CI: 0.4-2.24; p = 0.9), Fig. 2). There was significant heterogeneity among the studies (I^2 = 71%).

Overall Complications

Overall complications were calculated by including post polypectomy bleeding, perforation and postpolypectomy syndrome rates. Only 4 studies reported post polypectomy syndrome. Pooled analysis showed that there was no difference in incidence of total complications in clip group (1.63%) as compared to no clip group (1.05%) [OR, 1.03; 95% CI: 0.41- 2.62; p= 0.95] (Fig. 3). There was significant heterogeneity among the studies (I^2 = 77%).

Perforation

Seven of 11 studies reported perforation as an adverse event following polyp resection. Two perforations (0.16%) occurred of 1,286 polypectomies in the clip group as compared to 4 perforations (0.07%) of 5,558 polypectomies with no clip group. Pooled analysis showed no significant difference in the incidence of perforation (OR, 1.45; 95% CI: 0.26-8.09; p = 0 .67) (Fig. 4). There was no significant heterogeneity among the studies (I^2 = 0%).

Subgroup Analysis

Subgroup analysis was performed to evaluate the effect of current type, polyp characteristics (polyp size, location and morphology) and polypectomy techniques on incidence of delayed post polypectomy bleeding.

Current Type

Type of current used was reported in 9 studies. Blended current was utilized in 7 studies and pure coagulation and cut in one study each respectively. The incidence of delayed bleeding was significantly higher in no clip group (8.89%) as compared to clip group (2.52%) [OR, 0.24, 95% CI: 0.1-0.57, p = 0.001] in instances when pure coagulation was used for polypectomy. On the other hand, when blended current was used, there was no significant difference in the incidence of post polypectomy bleeding in clip (1.4%) compared to no clip group (1.6%) [OR, 0.73; 95% CI: 0.34-1.58; p= 0.43].

Polyp characteristics

Two studies reported a mean size of polyps greater than 2 cm. The bleeding risk was substantially lower in the clip (2.2%) as compared to no clip group (7.98%) [OR 0.25, 95% CI 0.12-0.51, p <0.001]. On the other hand, studies with reported size of polyps less than 2 cm, there was no significant difference in bleeding risk between the 2 groups (1.51% vs. 0.36%) [OR, 2.34; 95% CI: 0.47-11.76; p = 0.30].

Polypectomy technique

Subgroup analysis of the studies[11,19,20] reporting 100% polyps removed by EMR, the bleeding risk was significantly lower in clip group (1.7%) as compared to no clip group (5.7%) [OR, 0.28, 95% CI: 0.14-0.59, p= 0.0008].

Sensitivity Analysis

We also conducted a sensitivity analysis after restricting the studies to either RCTs or case-control studies. On pooled analysis of 4 RCTs, the bleeding risk in clip group was 1.53% as compared to 2.2% in no clip group [OR, 0.78; 95% CI: 0.29-2.10, p= 0.62; I^2= 0%]. Pooled analysis of only retrospective cohort studies showed no significant difference in PPB between the 2 groups (1.21% vs 0.88%) [OR, 1.09, 95% CI: 0.33-3.62, p= 0.88; I^2= 82%]. Qunitanilla et al. study was the only RCT which evaluated pedunculated polyps and no significant difference in bleeding was noted with clip placement (1.5% vs. 0%). Similarly, the study by Sobrina-Faya et al. was the only cohort study evaluating pedunculated polyps and no difference in rate of delayed bleeding with clip placement (0% in both groups).

Six studies had a Newcastle-Ottawa scale score more than 6 (Supplemental Tab. 1). On pooled analysis of high quality studies only, there was a significant difference in delayed post polypectomy bleeding with clip placement (1.24% vs 3.26%; OR, 0.46, 95% CI: 0.21-1.00, p= 0.05; I^2= 35%).

Discussion

Delayed PPB is a well-recognized complication of colonoscopy-associated polypectomy. Delayed PPB has been suggested to be secondary to sloughing of the eschar covering a sub mucosal blood vessel or excavation of a zone of thermal necrosis caused by the electro-thermal energy used to sever and cauterize the polypectomy site.[23] Various endoscopic measures such as submucosal injection of saline or epinephrine-saline solution, detachable nylon loop application before removal of large pedunculated polyps and argon plasma coagulation have been evaluated to reduce the incidence of delayed PPB.[3] Closure of polypectomy site ulcer with clips with a tamponade effect on exposed submucosal blood vessel

is one of the most promising and attractive measures. With the recent, widespread availability of endoscopic clips, the practice of prophylactic clipping to prevent delayed PPB has become frequent. In the absence of convincing evidence, currently, the use of prophylactic clipping is highly subjective and at the physicians discretion. This may be influenced by patient and polyp related factors.

Our pooled analysis and systematic review demonstrated that there was no difference in the incidence of delayed PPB bleeding, perforation or total complications with prophylactic clip placement compared to no clip placement after polypectomies. Why do clips then not reduce the incidence of PPB? The findings of similar delayed bleeding incidence, despite closing the defect questions not only the mechanism and natural history of healing process of post polypectomy ulcer after clip placement but also total duration a clip is successfully able to close the defect. In Masayuki et al. study[24], on follow up colonoscopy, two types of delayed hemorrhage were noted. In four cases, delayed hemorrhage occurred from well-closed post procedural mucosal defects with clips in place. In contrast, in 6 cases, delayed hemorrhage were noted from mucosal defects in which clips were found to be dislodged on repeat colonoscopy. There was no significant difference in the diameters of transected submucosal vessels in resected polyps which had delayed PPB as compared to no bleed.

In our sub-group analysis, there was a significantly reduced risk of delayed PPB after polypectomy of polyps >2 cm, use of EMR and pure coagulation current. The association between polyp size and bleeding have been previously evaluated. Sawhney et al. reported that for every 1 mm increase in polyp diameter, the risk of hemorrhage increased by 9%.[8] In a single center experience by Church et al., 5.6 % risk of delayed bleeding was noted when only more than 2 cm polyps were included.[25] In our meta-analysis, evaluation of studies which included

only large lesions (> 2 cm), showed that prophylactic clipping significantly reduced delayed PPB effectively.[11,21] Similarly, sub-group analysis of studies wherein all polyps were removed using EMR, the bleeding risk was significantly lower in clip group (1.7%) as compared to no clip group (5.7%). These findings suggest that there may be a different mechanism for delayed bleeding in larger ulcer, or EMR induced post polypectomy ulcer in comparison to smaller size ulcer and prophylactic clip placement significantly decreases the risk of delayed PPB in these high risk groups. As has been shown in previous studies, that pure coagulation current (compared to blended current) is associated with a higher incidence of delayed bleeding and lower incidence of immediate bleeding (Gossum et al.[23]), our meta-analysis noted a beneficial effect of clipping when polypectomies were performed using pure coagulation current. Finally, in sensitivity analysis, when only high quality studies (3 RCTs and 3 retrospective cohort studies) were pooled, the preventive effect of clipping was noted. This result could be due to selection of large sized polyps (retrospective cohorts) and rigorous study design (RCTs).

As with any meta-analysis, there are possible limitations in combining results from separate trials including utilizing RCTs and case-control studies as a single group. Significant heterogeneity was noted amongst the studies making the study results less precise. The size of the resected polyps was not identical in all of the trials included in the analysis. We cannot demonstrate the degree to which patients benefit from prophylactic methods because the severity of bleeding was not distinguished in most studies. Mild bleeding generally does not require any special treatment, while moderate or severe blood loss often requires endoscopic intervention and blood transfusions. Additionally, data on the length of the hospitalization stays were not available in the original articles, so role of prophylactic treatment on decreasing the length of the hospital stay is unknown.

In summary, results of our systematic review and meta-analysis show that clipping may decrease delayed post-polypectomy bleeding rates in carefully selected polyps. It may have a role in larger polyps, polyps removed with EMR and if pure coagulation current is used during polypectomy. Future high-quality studies with larger sample size, and analyses of cost-effectiveness are needed in this field.

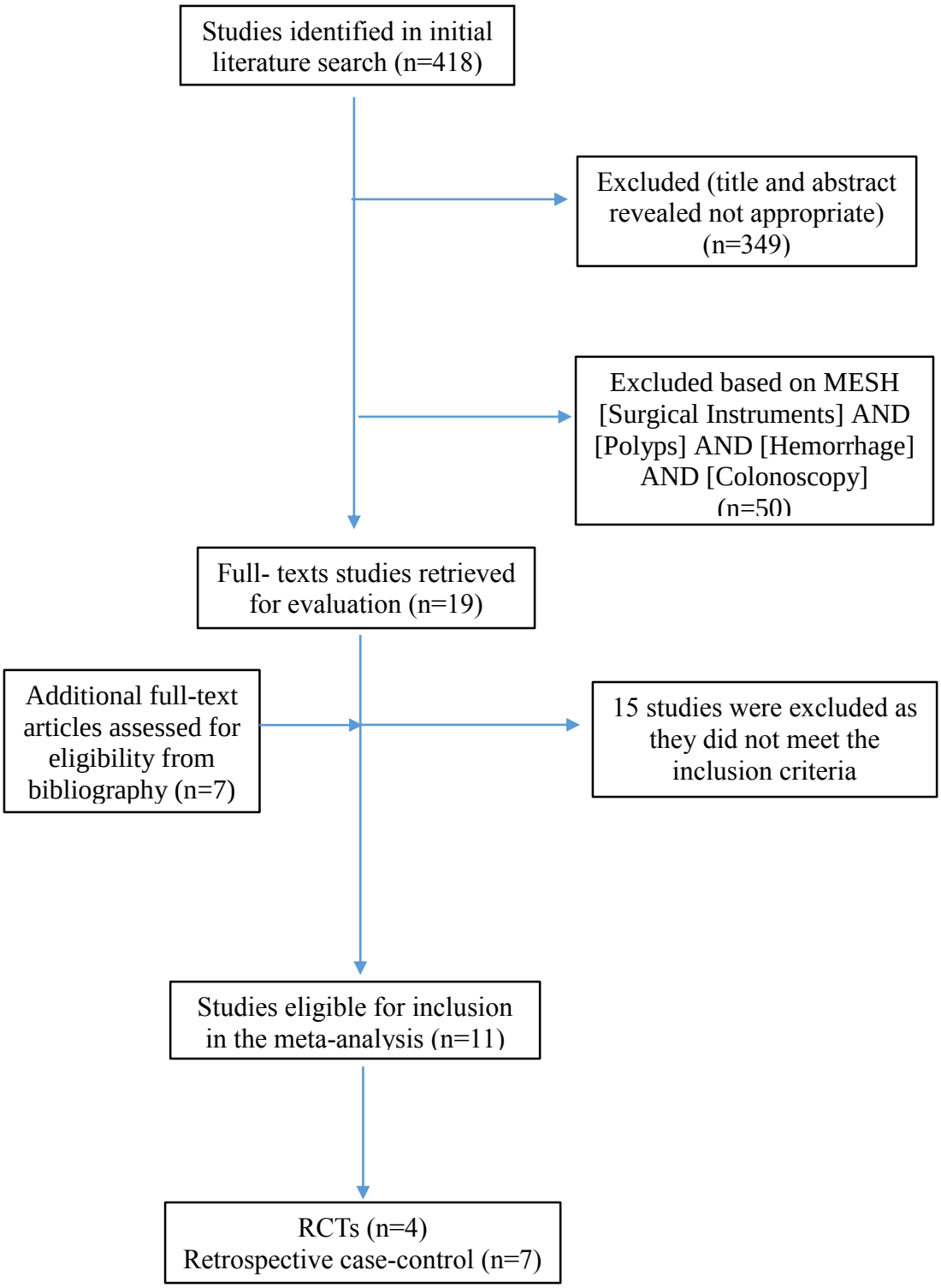


Fig 1. Flow chart of studies included in the meta-analysis

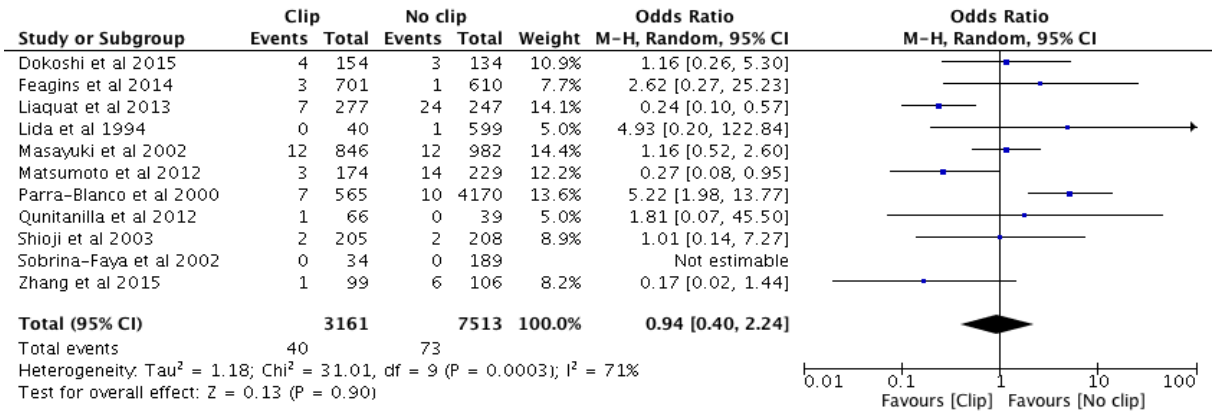


Fig 2. Post-polypectomy bleeding

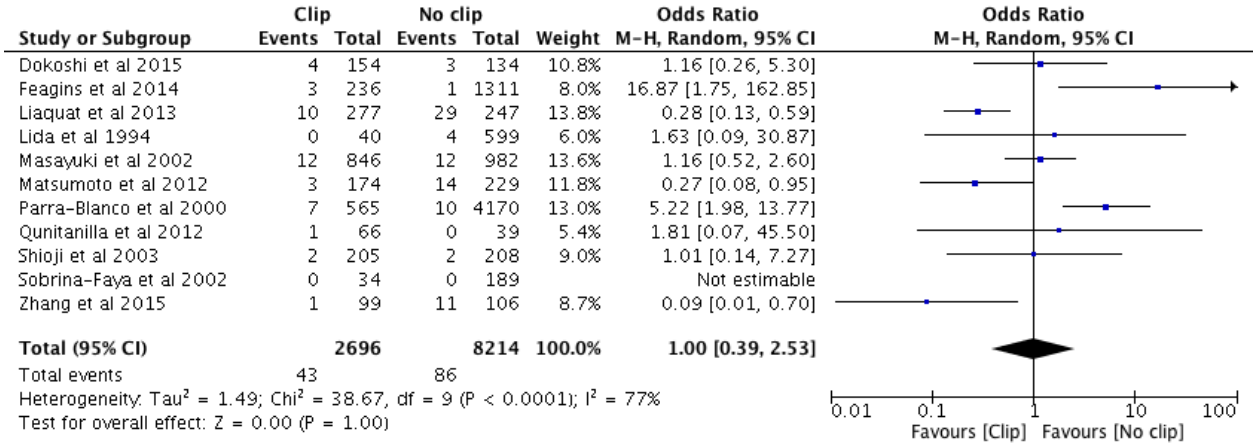


Fig 3. Total complications

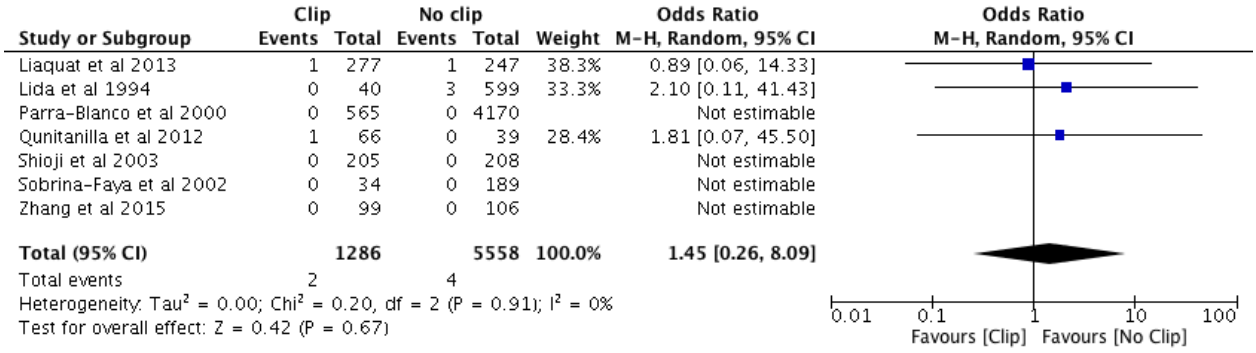
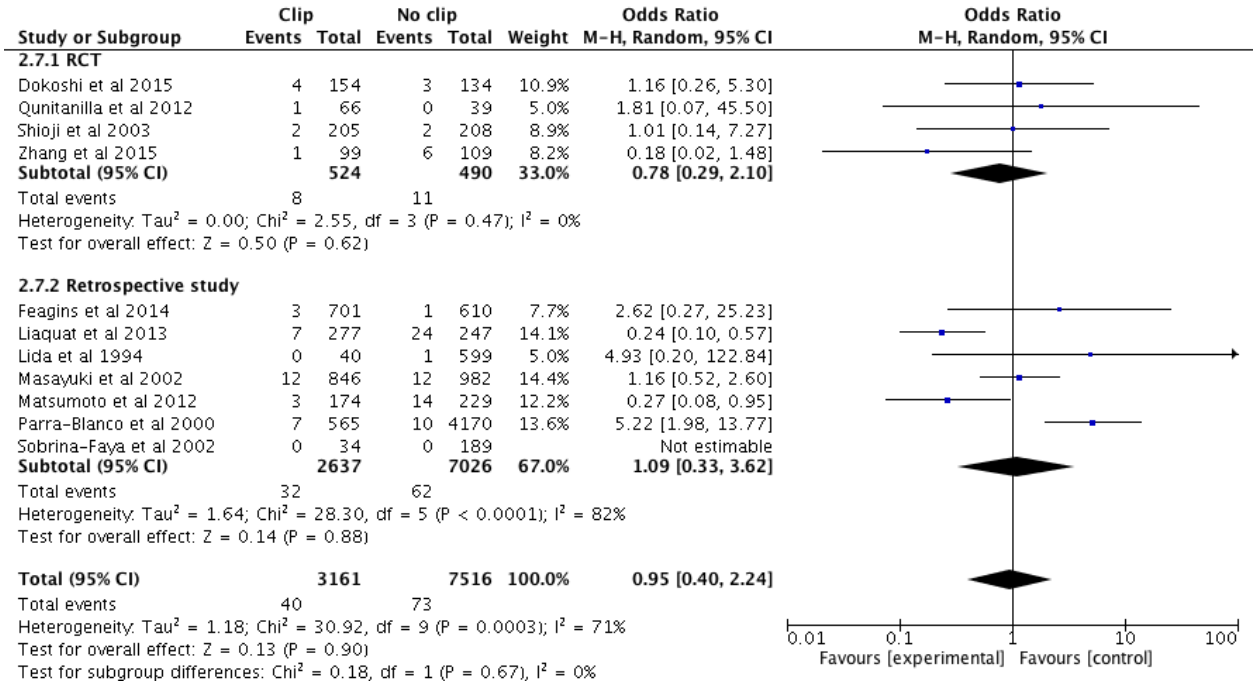


Fig 4. Perforation

Supplemental Table 1. Newcastle-Ottawa scale for assessment of quality of included studies

Study	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Lida et al 1994	x	*	*	*	x	x	x	x	3
Parra-Blanco et al 2000	*	*	*	*	x	*	x	x	5
Sobrina-Faya et al 2002	x	*	*	*	x	x	x	x	3
Masayuki et al 2002	*	*	*	*	*	*	x	x	6
Shioji et al 2003	*	*	*	*	**	*	x	x	7
Qunitanilla et al 2012	*	*	*	*	*	*	x	x	6
Matsumoto et al 2012	*	*	*	*	*	x	*	*	7
Liaquat et al 2013	*	*	*	*	**	*	*	*	9
Feagins et al 2014	*	*	*	*	**	*	*	*	9
Dokoshi et al 2015	*	*	*	*	**	*	*	x	8
Zhang et al 2015	*	*	*	*	**	*	*	*	9



*NOS- Newcastle-Ottawa scale

Supplemental Fig 1. Post polypectomy bleeding for NOS* score >6

References

1. Seeff LC, Richards TB, Shapiro JA, et al. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. Gastroenterology. 2004;127: 1670-1677.

2. Rex DK, Lewis BS, Waye JD. Colonoscopy and endoscopic therapy for delayed post-polypectomy hemorrhage. Gastrointest Endosc. 1992;38: 127-129.

3. ASGE Standards of Practice Committee, Fisher DA, Maple JT, et al. Complications of colonoscopy. Gastrointest Endosc. 2011;74: 745-752.

4. Rosen L, Bub DS, Reed JF,3rd, et al. Hemorrhage following colonoscopic polypectomy. Dis Colon Rectum. 1993;36: 1126-1131.

5. Sorbi D, Norton I, Conio M, et al. Postpolypectomy lower GI bleeding: descriptive analysis. Gastrointest Endosc. 2000;51: 690-696.

6. Waye JD, Lewis BS, Yessayan S. Colonoscopy: a prospective report of complications. J Clin Gastroenterol. 1992;15: 347-351.

7. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med. 2006;145: 880-886.

8. Sawhney MS, Salfiti N, Nelson DB, et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy. 2008;40: 115-119.

9. Kim HS, Kim TI, Kim WH, et al. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. Am J Gastroenterol. 2006;101: 1333-1341.

10. Watabe H, Yamaji Y, Okamoto M, et al. Risk assessment for delayed hemorrhagic complication of colonic polypectomy: polyp-related factors and patient-related factors. Gastrointest Endosc. 2006;64: 73-78.

11. Liaquat H, Rohn E, Rex DK. Prophylactic clip closure reduced the risk of delayed postpolypectomy hemorrhage: experience in 277 clipped large sessile or flat colorectal lesions and 247 control lesions. Gastrointest Endosc. 2013;77: 401-407.

12. Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc. 2012;76: 255-263.

13. Hachisu T. Evaluation of endoscopic hemostasis using an improved clipping apparatus. Surg Endosc. 1988;2: 13-17.

14. Quintanilla E, Castro JL, Rabago LR, et al. Is the use of prophylactic hemoclips in the endoscopic resection of large pedunculated polyps useful? A prospective and randomized study. J Interv Gastroenterol. 2012;2: 183-188.

15. Shioji K, Suzuki Y, Kobayashi M, et al. Prophylactic clip application does not decrease delayed bleeding after colonoscopic polypectomy. Gastrointest Endosc. 2003;57: 691-694.

16. Dokoshi T, Fujiya M, Tanaka K, et al. A randomized study on the effectiveness of prophylactic clipping during endoscopic resection of colon polyps for the prevention of delayed bleeding. Biomed Res Int. 2015;2015: 490272.

17. Li LY, Liu QS, Li L, et al. A meta-analysis and systematic review of prophylactic endoscopic treatments for postpolypectomy bleeding. Int J Colorectal Dis. 2011;26: 709-719.

18. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

19. Zhang QS, Han B, Xu JH, et al. Clip closure of defect after endoscopic resection in patients with larger colorectal tumors decreased the adverse events. Gastrointest Endosc. 2015;82: 904-909.

20. Shioji K, Suzuki Y, Kobayashi M, et al. Prophylactic clip application does not decrease delayed bleeding after colonoscopic polypectomy. Gastrointest Endosc. 2003;57: 691-694.

21. Matsumoto M, Fukunaga S, Saito Y, et al. Risk factors for delayed bleeding after endoscopic resection for large colorectal tumors. Jpn J Clin Oncol. 2012;42: 1028-1034.

22. Feagins LA, Nguyen AD, Iqbal R, et al. The prophylactic placement of hemoclips to prevent delayed post-polypectomy bleeding: an unnecessary practice? A case control study. Dig Dis Sci. 2014;59: 823-828.

23. Van Gossum A, Cozzoli A, Adler M, et al. Colonoscopic snare polypectomy: analysis of 1485 resections comparing two types of current. Gastrointest Endosc. 1992;38: 472-475.

24. Masayuki F, Hiroyuki K, Akira S, et al. Prophylactic Clipping May Not Eliminate Delayed Hemorrhage in Colonoscopic Polypectomies. 2002.

25. Church JM. Experience in the endoscopic management of large colonic polyps. ANZ J Surg. 2003;73: 988-995.

26. Iida Y, Miura S, Munemoto Y, et al. Endoscopic resection of large colorectal polyps using a clipping method. Dis Colon Rectum. 1994;37: 179-180.

27. Parra-Blanco A, Kaminaga N, Kojima T, et al. Hemoclipping for postpolypectomy and postbiopsy colonic bleeding. Gastrointest Endosc. 2000;51: 37-41.

28. Sobrino-Faya M, Martinez S, Gomez Balado M, et al. Clips for the prevention and treatment of postpolypectomy bleeding (hemoclips in polypectomy). Rev Esp Enferm Dig. 2002;94: 457-462.

29. Feagins LA, Spechler SJ. Use of hemoclips and other measures to prevent bleeding during colonoscopy by gastroenterologists in Veterans Affairs hospitals. Am J Gastroenterol. 2014;109: 288-290.