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# Role of prophylactic hemoclip placement in prevention of delayed post-polypectomy bleeding for large colon polyps: a meta-analysis of randomized controlled trials

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**Abstract**

**Background** Polypectomy is a widely used and effective procedure to treat precancerous polyps. Delayed post-polypectomy bleeding (DPPB), a common complication of polypectomy, may diminish the utility of this procedure. Previous data on the efficacy of hemoclips has been conflicting, therefore we aimed to collectively evaluate and analyze the data to reach a definitive conclusion on the efficacy of using hemoclips to prevent incidences of DPPB in patients with large polyps (≥10 mm).

**Methods** We identified a total of 261 studies based on our previously defined search strategy. After screening, we included 6 randomized controlled trials. A meta-analysis was performed comparing the use of prophylactic application of hemoclips to a standard group without prophylactic clip placement for large polyps.

**Results** We found a statistically significant reduction in the incidence of DPPB when using hemoclips for large polyps. The overall incidence of DPPB was lower in the hemoclip group compared to the standard group for all large polyps ≥10 mm (relative risk 0.51, 95% confidence interval 0.35-0.75; P=0.01; $I^2$=0%).

**Conclusions** The use of hemoclips in achieving hemostasis for large polyps has a beneficial effect and appears to prevent DPPB. This reinforces the routine clinical practice of using hemoclips in polypectomy procedures.

**Keywords** Delayed post-polypectomy bleeding, large polyps, colonoscopy

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## Introduction

Colorectal cancer accounts for 9.2% of deaths amongst cancer patients globally and a strong emphasis is placed on screening to prevent the disease [1,2]. Removal of precancerous polyps by colonoscopy and polypectomy are widely accepted as methods of prevention and have been highly effective in reducing colorectal cancer incidence and mortality [2,3]. However, these procedures carry certain risks. Delayed post-polypectomy bleeding (DPPB), defined as bleeding occurring after removal of the colonoscope, has an incidence rate ranging between 0.2 and 2%, with numbers reported to be higher for larger polyps [4,5].

Several risk factors for DPPB have been identified and can be classified into: polyp-related (e.g., size, type); procedure related (e.g., use of electrocautery); and patient-related (e.g., age, anticoagulant use) [5]. Amongst these, polyp size is a key risk factor since removal of polyps <10 mm carry a lower incidence of DPPB while removal of larger polyps (≥10 mm) results in an increased risk [3,6]. Additionally, with every 1 mm increase in the diameter of a polyp, the chances of hemorrhage increase by 9% [2].

Prophylactic clipping, a routinely performed endoscopic procedure, can help reduce the incidence of DPBB by

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achieving hemostasis through mechanical means [7]. While there is abundant data on the efficacy of hemoclips, there is no definitive answer on the success of prophylactic clipping for large polyps (LP) due to conflicting results [4]. Our study aimed to analyze the currently available data and evaluate the efficacy of hemoclip placement as a prophylactic measure to prevent DPPB for large colon polyps ≥10 mm.

## Materials and methods

### Search strategy / article screening / selection

A comprehensive search of the following databases was conducted from inception through March 17, 2020: PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, and Web of Science Core Collection. Search strategy was created using one database by an experienced librarian (W.L.S.) and translated into syntax/vocabulary of other databases. A hand search was not performed. The search strategy was cross checked by another reviewer (M.A.). The screening of articles and selection was performed by 2 independent reviewers (M.G. and M.A.) and any discrepancy in study selection was solved through mutual discussion. The screening was initially conducted using the title and abstracts and full text of relevant articles were further scrutinized. The bibliography of finalized articles was also screened to broaden the literature review. A detailed search strategy using EMBASE is highlighted in Supplementary Table 1.

### Inclusion and exclusion criteria

We used the following inclusion criteria for selecting studies: 1) patients undergoing polypectomy for LPs ≥10 mm; 2) intervention: application of prophylactic hemoclip to close the defect after polypectomy – hemoclip group (HG); 3) comparison of standard polypectomy without prophylactic application of hemoclip to a standard group (SG); and 4) outcomes of DPPB, defined as a significant bleeding event noted within the specified follow-up period. Only randomized controlled trials (RCTs) published as full-length manuscripts were included. No restriction to language or publication date was applied. Abstracts and other study designs (cohort, editorials, case reports, review articles, single arm studies) were excluded. Studies with polypectomy of <10 mm polyps or mixed results without subgroup analysis for ≥10 mm polyps were also excluded.

### Data collection

Data was extracted and tabulated using Microsoft Excel (Microsoft, Redmond, Washington, United States) by 2 independent reviewers (M.G. and M.A.). Any conflict/discrepancy was resolved through mutual discussion. Data for the following was obtained: study characteristics (publication year, country); demographics (age, male sex); mean/median polyp size; type of polypectomy; polyp pathology (adenoma including high-grade lesions, carcinoma, serrated lesions [sessile serrated adenomas, traditional serrated adenoma, and/or proximal hyperplastic polyps], benign/other); proximal polyp (from cecum to transverse colon); and outcomes.

### Statistical analysis

Primary outcome was DPPB within the follow-up period. Secondary outcomes included pain, post-polypectomy syndrome (PPS), and perforation. The outcomes were generated as event over total population in the respective group i.e., HG and SG. Intention-to-treat protocol was used where outcomes were generated based on original randomization/allocation of patients to study groups regardless of study completion. Pooled rates of outcomes were compared using DerSimonian-Laird/Random effects model and relative risk (RR) with 95% confidence interval (CI) were calculated. Forrest plot for each outcome and statistical analysis was conducted using Comprehensive Meta-Analysis (Biostat, Englewood, USA) and SPSS v26 (IBM, Armonk, New York, United States). The $I^2$ statistic was used as test for heterogeneity and value of >50% was considered as substantial heterogeneity [8,9]. A subgroup analysis was also performed for studies that provided polypectomy data for ≥20 mm polyps. A P-value of <0.05 was considered statistically significant for all outcomes. Adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were observed for the purpose of the study. Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence (HIGH, MODERATE, LOW, VERY LOW) for each outcome was utilized [10]. The anticipated absolute effect was defined as the risk in the intervention group (and its 95% confidence interval) based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). Definitions of variables are provided in Supplementary Table 2.

### Bias assessment

The risk of bias in each individual study was assessed using the Cochrane Risk of bias tools for RCTs [11]. Publication bias was assessed based on visual inspection of the funnel plot (qualitative) and Egger's regression analysis (quantitative). Risk of bias assessment is provided in Supplementary Table 3.

## Results

A total of 261 studies were identified in our analysis based on our previously defined search strategy, after excluding all duplicates (Fig. 1). After screening, a total of 6 studies met our

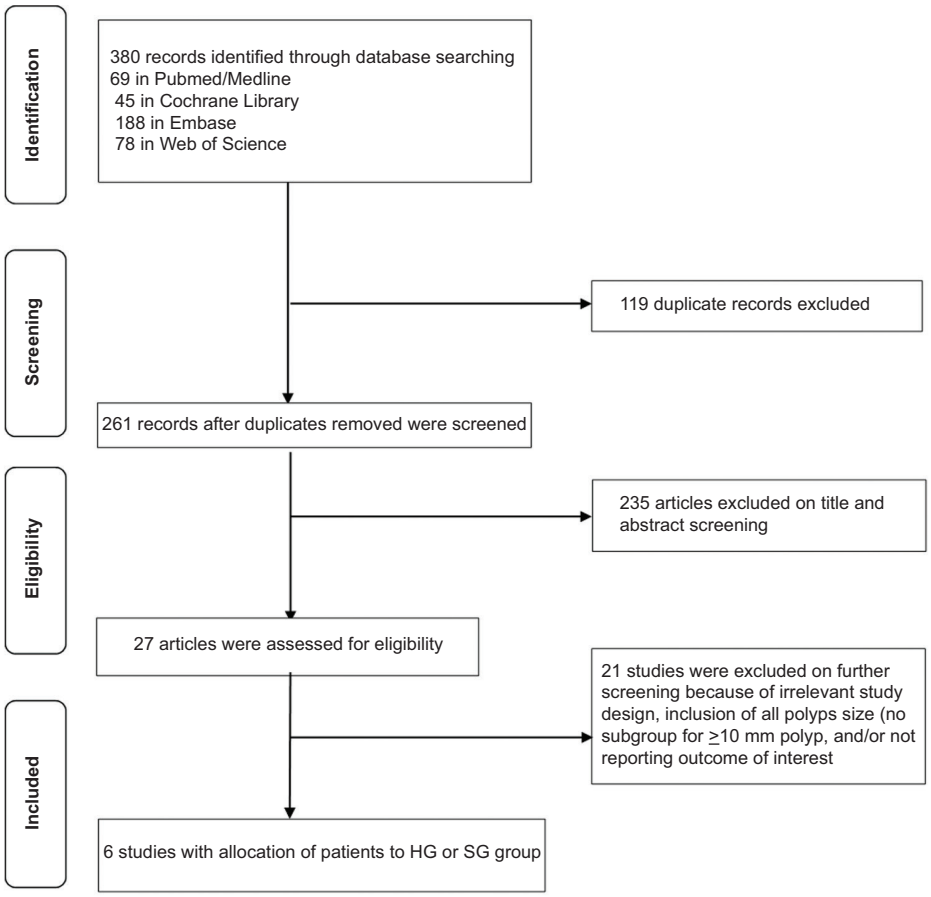


**Figure 1** Flow diagram representing selection of studies
*HG, hemoclip group; SG, standard/control group*

inclusion criteria (Table 1). Publication bias was difficult to assess given the low number of studies with Egger's P value of 0.67 (Fig. 2). Dokoshi *et al* met the inclusion criteria for polyp size, however the outcomes were assessed based on per polyp analysis and not on per patient analysis and therefore their study was excluded. The overall risk of bias across all RCTs was high as highlighted in Table 2.

## Study details and demographics

Study details and demographics are summarized in Tables 1 and 2. The total number of patients in the analysis was 2703 (with 1345 in SG vs. 1358 in HG group respectively). Both groups were similar in terms of age range (58-72 vs. 57-73 years) and male sex (74% vs. 70%) (Table 2).

## Outcomes

Primary and secondary outcomes are displayed in Table 3. The overall incidence of delayed bleeding was lower in HG compared to SG group for all LPs ≥10 mm. (2.8% vs. 5.6%, RR 0.51, 95%CI 0.35-0.76; P=0.01; $I^2$=0%) (Fig. 3A). Similarly, the incidence was also lower in all polyps when the clip was applied in studies with polyp size ≥20 mm (4 studies) (RR 0.48, 95%CI 0.30-0.77; P=0.03; $I^2$=0%) (Fig. 3B). The results of Fig. 3A and 3B are consistent.

The overall perforation was evaluated and compared among the 5 studies for polyps ≥10 mm polyp and did now show any statistical difference when SG was compared to HG (0.644% vs. 1.03%, RR 0.681, 95%CI 0.240-1.932; P=0.722; $I^2$=0%) (Fig. 3C).

**Table 1** Baseline characteristics of included studies

| Study | Year | Type | Total | SG | HG |
|---|---|---|---|---|---|
| Albeniz [20] | 2019 | RCT | 237 | 117 | 120 |
| Feagins [4] | 2019 | RCT | 1098 | 551 | 547 |
| Kouklakis [21] | 2009 | RCT | 64 | 32 | 32 |
| Pohl [7] | 2019 | RCT | 928 | 470 | 458 |
| Zhang [12] | 2015 | RCT | 348 | 174 | 174 |
| Osada [22] | 2016 | RCT | 28 | 14 | 14 |

*RCT, randomized controlled trial; HG, hemoclip group; SG, standard/control group*

Post-polypectomy syndrome was defined as pain, fever, leukocytosis, or other peritoneal signs. The overall incidence of post-polypectomy syndrome was evaluated in 3 studies and it was not significantly different between the 2 groups (0.66% vs. 1.2%, RR 0.792, 95%CI 0.076-8.239; P=0.85; $I^2$=59.7%) (Fig. 3D).

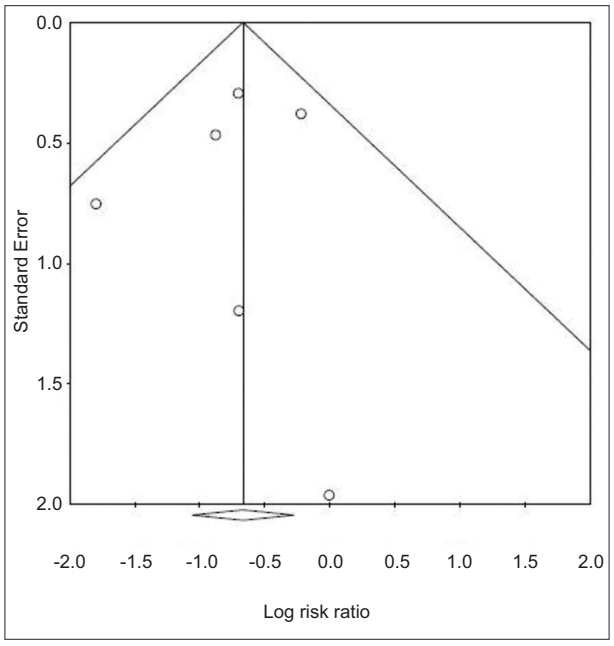


**Figure 2** Funnel plot of publication bias assessment

Pain was defined as subjective. In Albeniz, pain was considered as when a patient required pharmacologic treatment or medical attention. Four studies evaluated subjective pain perception and no significant difference was observed between the 2 groups (0.64% vs. 4.20%, RR 0.605; 95%CI 0.102-3.601; P=0.581; $I^2$=67.8%) (Fig. 3E).

A summary of the findings to assess the certainty of evidence using GRADE assessment is displayed in Supplementary Table 4 and description of certainty is provided in Supplementary Table 5.

## Discussion

Our meta-analysis determined that the use of routine endoscopic clipping as a prophylactic modality reduces the risk of DPPB in LPs of ≥10 mm. There was no significant difference between post-polypectomy syndrome, perforation or pain for SG and HG. These results were consistent on subgroup analysis of studies reporting data for polyps ≥20 mm.

DPPB, a frequent complication of polypectomy, can be a significant health burden for patients. Clipping is an effective modality that may prevent this complication. Several studies have evaluated their efficacy; however, the results have been non-homogenous, with a certain degree of variability. Zhang *et al* reported a reduction in the incidence of DPPB from 6.9% to 1.1%, with the use of clipping in patients with LPs [12]. Similar results were also found by Pohl *et al*, who found

**Table 2** Demographics of included studies

| Characteristics | Albeniz [20] | | Feagins [4] | | Kouklakis [21] | | Pohl [7] | | Zhang [12] | | Osada [22] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SG | HG | SG | HG | SG | HG | SG | HG | SG | HG | SG | HG |
| Mean/Median age, years | 71.1 | 72.7 | 64 | 64.5 | 58.8 | 57.9 | 65.1 | 65.1 | 64.2 | 67.9 | 66.2 | 68.6 |
| Male % | 77 | 81 | 91 | 92 | 44 | 47 | 60 | 58 | 61 | 63 | 36.4% | 64.3% |
| Mean polyp size (mm) | 37.3 | 36.1 | 14 | 13.7 | 27 | 26.1 | 28 | 30 | NA | NA | NA | NA |
| Proximal polyps (n) | 104 | 109 | 275 | 263 | 3 | 4 | 331 | 327 | 51 | 50 | 8 | 10 |
| Adenoma (n) | 104 | 107 | 540 | 541 | NA | NA | 374 | 359 | NA | NA | NA | NA |
| Adenocarcinoma (n) | 5 | 4 | 4 | 3 | NA | NA | 13 | 13 | NA | NA | 3 | 5 |
| Serrated (n) | 7 | 8 | 55 | 47 | NA | NA | 105 | 115 | NA | NA | NA | NA |
| Benign/Hyperplastic | NA | NA | 98 | 78 | NA | NA | 7 | 3 | NA | NA | NA | NA |

*HG, hemoclip group; SG, standard/control group; NA, not available*

**Table 3** Delayed bleeding and other complications

| Complications | Albeniz [20] | | Feagins [4] | | Kouklakis [21] | | Pohl [7] | | Zhang [12] | | Osada [22] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SG | HG | SG | HG | SG | HG | SG | HG | SG | HG | SG | HG |
| Delayed bleeding % (n/N) | 14/117 | 6/120 | 15/551 | 12/557 | 02/32 | 01/32 | 33/470 | 16/458 | 12/174 | 2/174 | 0/14 | 0/14 |
| Polypectomy syndrome | 0/117 | 3/120 | NA | NA | NA | NA | 1/470 | 1/458 | 8/174 | 1/174 | NA | NA |
| Perforation | 1/117 | 1/120 | 0/551 | 0/557 | NA | NA | 6/470 | 3/458 | 1/174 | 1/174 | 0/14 | 0/14 |
| Pain | 2/117 | 6/120 | NA | NA | 0/32 | 0/32 | 2/470 | 1/458 | 29/174 | 5/174 | NA | NA |

*HG, hemoclip group; SG, standard/control group; NA, not applicable*

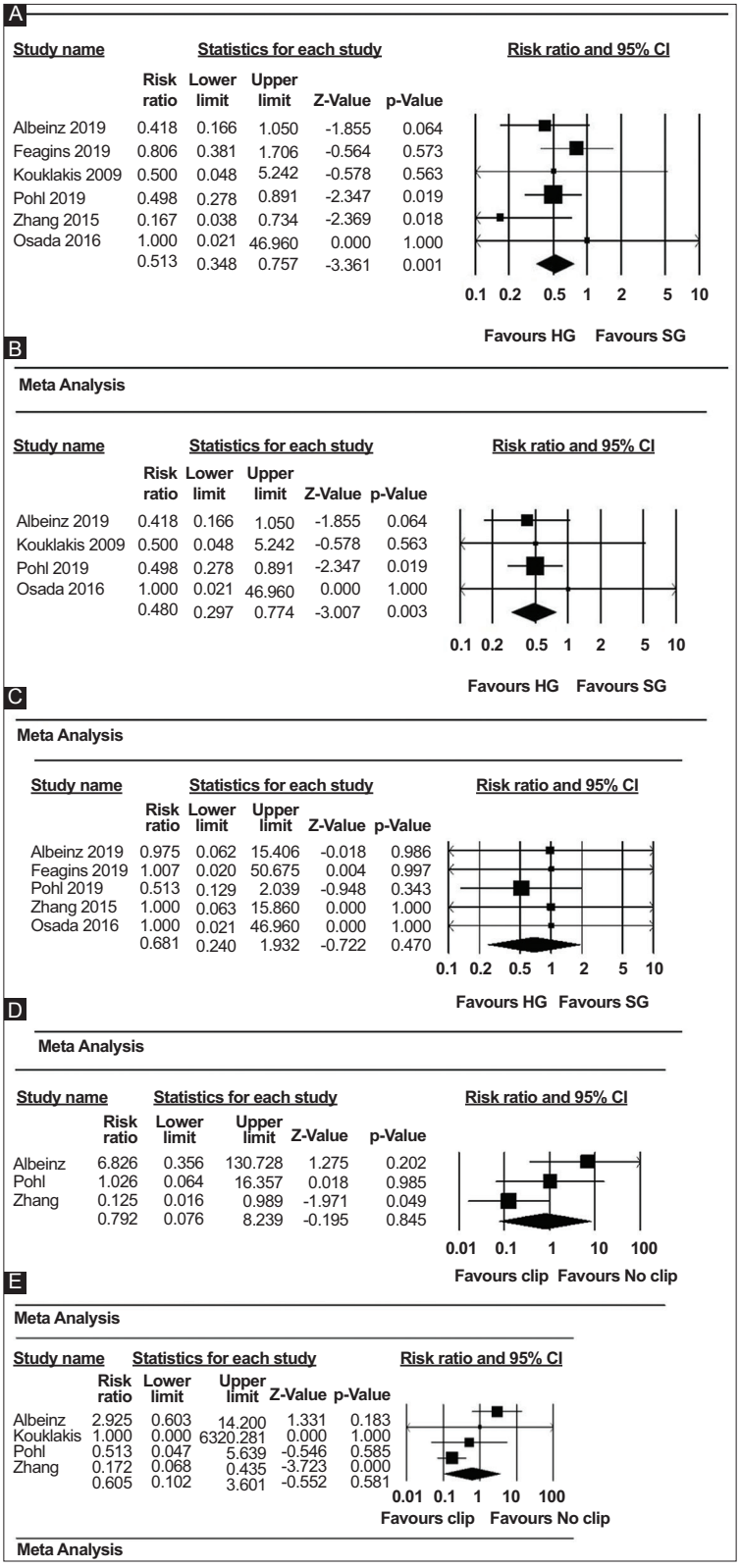


**Figure 3** (A) Forest plot comparing delayed bleeding in hemoclip vs. standard/control group for all large polyps ≥10 mm. (B) Forest plot comparing delayed bleeding in hemoclip vs. standard/control group for all large polyps ≥20 mm. (C) Forest plot comparing perforation rates for polyps ≥10 mm. (D) Forest plot comparing post-polypectomy syndrome for polyps ≥10 mm. (E) Forest plot comparing subjective pain perception for polyps ≥10 mm
*CI, confidence interval*

the incidence rate of DPPB to be twice as high in patients who did not undergo clipping in comparison to patients who underwent clipping (7.1% vs. 3.5%) [7]. A previously conducted randomized trial by Shioji *et al* found no evidence on the reduction in DPPB. However, the majority (76.9%) of the recruited patients had undergone polypectomy of small polyps (<10 mm), which have a lower tendency to bleed [13]. LPs on the other hand pose a complex problem as they have a higher tendency to cause DPPB. Dokoshi *et al*, in a RCT, reported higher bleeding rates and procedural time for polyps ≥20 mm with no other factor affecting the bleeding rate [14]. We excluded this study because the outcomes were determined based on the bleeding per polyp.

A recent analysis by Spadaccini *et al* showed a significant correlation between clipping of LPs (≥20 mm) and the reduced risk of DPPB [15]. This is similar to our findings, however there is a distinction in our classification of polyps. We considered all polyps ≥10 mm as large, as this correlates to an elevated risk of DPPB, when stratifying based on polyp size and are a well-established, independent risk factor for DPPB [2,3,6]. Hence, it is important to establish the utility of hemoclips in patients with polyp sizes ≥10 mm. Our analysis provided evidence showing the benefit of clipping all polyps ≥10 mm. Furthermore, our study evaluated all the remaining parameters such as incidences of overall bleeding, perforation, pain and post-polypectomy syndrome based on this population subset. Our findings also help explain the variability in results of previously conducted RCTs and systematic reviews due to the comparison of heterogeneous populations, without stratifying the polyp size.

Polyp location has also been a well-known risk factor for DPPB, although there have been contradictory reports. Amongst studies that found a significant correlation, proximal or right sided polyps were found to have a higher tendency to bleed compared to their distal or left-sided counterparts [16-19]. There has been speculation on whether the histology and morphology of a polyp may play a role in the development of DPPB, however they have not as yet been established as significant risk factors [17-19]. Amongst histological types, adenomas and hyperplastic polyps have been reported to have higher incidences of DPPB, and, in regards to morphology, sessile polyps compared to pedunculated have been reported to have a higher incidence of DPPB [5]. In our analysis, due to lack of data, we could not evaluate the association of the previous factors with DPPB, although we found a higher proportion of proximal polyps and adenomas occurring with DPPB.

As with all systematic reviews, our review has its strengths and its limitations. Our reviews strengths include the incorporation of a wide variety of data, helping to reduce sampling bias and increase generalizability. We conducted an extensive search from all major databases, and enrolled up to 261 studies as part of our initial search strategy, and, after early and final screening, there were 6 RCT studies that met our inclusion and exclusion criteria. Since our research solely comprised data from RCTs, the chances of confounding bias occurring is reduced. We also found a significant correlation between the intervention and the outcome, and a considerably low amount of heterogeneity within the studies, when evaluating our primary outcome, i.e., the incidence of DPPB.

Although our study provides strong evidence pertaining to the use of clipping as an effective method of achieving hemostasis, there are a few limitations. First, while polyp size has a high correlation with the incidence of DPPB, we did not take into account other risk factors which may have contributed to the incidence of DPPB. Several studies have highlighted age, hypertension and the use of anticoagulants influencing the incidence of DPPB. In addition, variables such as polyp type and location also play a crucial role. Further studies need to be conducted to evaluate the impact of hemoclip when these risk factors are used as independent variables. Second, amongst 2 of our examined outcomes, post-polypectomy syndrome and post-procedure pain, there was considerable heterogeneity within the results. This may be attributed to the varying study designs and the diverse population groups, such as the differences in endoscopists' practices (e.g., clip type), distinct clinical settings, and the use of anticoagulants prior to treatment.

In conclusion, the use of hemoclips in achieving hemostasis for LPs has a beneficial effect and appears to prevent DPPB. This reinforces the routine clinical practice of using hemoclips in polypectomy procedures. Further studies are required to establish their effectiveness in patients with additional risk factors such as anticoagulation or hypertension, and to establish their priority compared to different hemostasis procedures.

**Summary Box**

**What is already known:**

- Polypectomy can lead to post-procedure hemorrhage, particularly delayed post-procedure bleeding (DPPB)
- Data on the efficacy of hemoclips to control DPPB vary
- Established risk factors can lead to increased incidences of DPPB

**What the new findings are:**

- When stratified for size, hemoclips were effective in reducing the rates of DPPB
- Hemoclips did not have a statistically different effect on other complications of polypectomy
- Stratifying for different risk factors of bleeding can explain the variety of results produced by previously conducted research

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