Prevention of delayed post-polypectomy bleeding: Should we amend the 2017 ESGE Guideline?

Authors

Alexandra Mack[1], Dileep Mangira[1,2], Alan Moss[1,2]

Institutions

1 Department of Endoscopic Services, Western Health, Melbourne, Victoria, Australia

2 Department of Medicine - Western Health, Melbourne Medical School, The University of Melbourne, Victoria, Australia

Bibliography

DOI https://doi.org/10.1055/a-1196-1602 |

Endoscopy International Open 2020; 08: E1111–E1114

eISSN 2196-9736

Corresponding author

Associate Professor Alan Moss, Director of Endoscopic Services, Western Health, Gordon St, Footscray 3011, Melbourne, Australia

Fax: +61 3 8345 7378

alan.moss@wh.org.au

Colonoscopy and polypectomy of adenomatous polyps decreases risk of colorectal cancer [1, 2]. Bleeding is a known serious complication, with delayed post-polypectomy bleeding (DPPB) occurring at a rate of around 0.23 % to 1.9 % for polyps overall [3–5], and 7 % for large polyps removed by endoscopic mucosal resection (EMR) [6].

Established risk factors for DPPB include polyp size, morphology and proximal colon location, as well as use of antiplatelet or anticoagulant agents [7–9] Older age and presence of comorbidities have also been associated with increased rates of DPPB following EMR of larger polyps [6, 10, 11] Prophylactic endoscopic clip placement following polypectomy or EMR has been proposed to decrease rates of DPPB. Debate has been ongoing for years regarding the role of routine prophylactic clipping to prevent DPPB and studies to date have yielded conflicting results [12–23].

Proponents of prophylactic clipping reference studies showing reduced rates of DPPB [12, 16–18]. Conversely, those against routine clipping point out the lack of proven efficacy [13, 19, 20, 22] and the high cost of clip application. An American study [12] utilized a baseline cost of US$ 150 per clip and calculated the total charge for clips per patient to be on average US$ 555. However, the total charge for clips required to prevent one bleed was US$ 7025. In addition, there are practical challenges to applying clips, including prolonged procedure time, and complete closure of polypectomy and EMR sites is not always achievable, especially for large lesions [16, 17]. Yet those in favor of clips counter that the healthcare costs associated with managing a DPPB may well exceed the total clip cost, particularly if there is a need for readmission to hospital and repeat colonoscopy, or less commonly angiography or surgery.

The 2017 European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline for colorectal polypectomy and EMR [24] recommends routine prophylactic hemostasis only for large pedunculated polyps (head ≥ 20 mm or stalk ≥ 10 mm), using adrenaline injection and/or mechanical haemostasis (e. g. endoloops or clips). The guidelines indicate that mechanical hemostasis prophylaxis may be superior to adrenaline injection, as evidenced by studies that found that use of mechanical devices for pretreatment of the polyp stalk, alone or in combination with adrenaline injection, significantly decreased post-polypectomy bleeding compared to adrenaline alone [24–26]. However, for non-pedunculated (i. e. sessile) polyps, the ESGE guideline did not recommend routine clip closure to prevent delayed bleeding. The guideline suggests that there may be a role in selected high-risk cases, such as large polyps, antiplatelet or anticoagulant use, or major comorbidity, but left this to the discretion of the endoscopist. The guideline noted that more randomized controlled trials (RCTs) were required to guide decision-making in this area. Since the publication of the guideline, there have been three additional RCTs published that addressed this issue [16, 17, 19]. A re-examination of the body of high-quality evidence regarding prophylactic clipping following colorectal polypectomy or EMR is therefore warranted, and has been performed by Kamal et al. in a meta-analysis entitled “Prophylactic hemoclips in prevention of delayed post-polypectomy bleeding for ≥ 1 cm colorectal polyps: Meta-analysis of randomized controlled trials”[27].

Seeking to definitively answer the question “to clip or not to clip,”[28] the primary outcomes of interest were DPPB with polyps ≥ 2 cm and polyps 1 to 1.9 cm. Secondary outcomes included DPPB for all polyps ≥ 1 cm, proximal polyps, distal polyps, anticoagulant/antiplatelet therapy use, perforation

and post-polypectomy syndrome. Inclusion criteria were studies with pedunculated polyps, as well as abstracts, and subgroup analysis was performed based on polyp location and anticoagulant/antiplatelet use. A total of nine RCTs (eight full publications and one abstract) were included in their analysis, comprising 3764 polyps, of which 1917 had prophylactic clip placement and 1847 did not.

With regard to the primary outcome of DPPB with polyps ≥ 2 cm, there were five relevant studies with 1492 polypectomies [16, 17, 19, 20, 23], and the rate of DPPB with polyps that were prophylactically clipped was significantly lower at 4 % vs 7 % (pooled RR 0.55; 95 % CI 0.36–0.86). This benefit remained statistically significant for sessile polyps, with a pooled RR of 0.51 (95 % CI 0.32–0.82) when two studies that had included pedunculated polyps were excluded from the analysis. When proximally located polyps ≥ 2 cm were examined specifically, rates of DPPB were again significantly lower with prophylactic clipping at 4 % vs 10 % (pooled RR 0.41; 95 % CI 0.24–0.70). However, there was no statistically significant difference with prophylactic clipping of distally located polyps ≥ 2 cm (pooled RR 1.23; 95 % CI 0.45–3.32). The results for these subgroups were similar after excluding one study that had included pedunculated polyps [19]. In patients taking antiplatelet or anticoagulants, reduced DPPB rates were again demonstrated with prophylactic clipping (pooled RR 0.50; 95 % CI 0.25–0.99). Clipping showed no reduction in rates of perforation or post-polypectomy syndrome.

For polyps 1 to 1.9 cm, four studies were included in the analysis [19, 21, 23, 29]. There was no benefit to clipping in this group (pooled RR 1.07; 95 % CI 0.59–1.97). Although there was a reduction in rates of DPPB for all polyps ≥ 1 cm in size (pooled RR 0.59; 95 % CI 0.42–0.83), this was no longer statistically significant when the authors excluded two studies which included only polyps ≥ 2 cm [16, 17] (pooled RR 0.75; 95 % CI 0.45–1.23).

The findings of this meta-analysis demonstrate a reduction in DPPB with prophylactic clip placement in proximally located colonic polyps ≥ 2 cm. To the best of our knowledge, there has only been one previously published meta-analysis that showed a statistically significant benefit from prophylactic clipping, and this was for large lesions ≥ 2 cm removed by EMR [30]. However, three other meta-analyses showed a trend towards a reduction in DPPB with prophylactic clipping for larger polyps, but did not demonstrate statistical significance [31–33].

There is likely good reason why this most recent meta-analysis was able to draw a statistically stronger conclusion, where earlier analyses could only hint at a trend. This is due to the increasing body of high-quality evidence relating to prophylactic clipping, especially in larger polyps, which has grown substantially with the addition of three RCTs published over the last year [16, 17, 19]. Two of these recently published RCTs examined rates of DPPB in polyps ≥ 2 cm [16, 17], and found a significant benefit, whereas the third examined polyps ≥ 1 cm, and failed to demonstrate a benefit even on subgroup analysis of larger polyps [19].

The conclusions of Kamal et al.'s meta-analysis are supported by another meta-analysis recently accepted for publication by Spadaccini et al [34]. Their review of nine RCTs demonstrated an almost 50 % risk reduction in DPPB with prophylactic clipping in proximal colonic polyps ≥ 2 cm, but no significant benefit from clipping overall. Their findings translated to a number needed to treat with clips of 23 patients to prevent one DPPB in lesions of this large size.

Kamal et al.'s meta-analysis has a number of limitations, including use of one abstract [35], and omission of some potentially relevant studies due to the exclusion criteria [22, 36]. Furthermore, only two studies reported data on anticoagulant or antiplatelet use in patients with polyp ≥ 2 cm, which makes it difficult to draw definitive conclusions regarding best practice in this group. However, considering that they are at an increased risk of DPPB compared to the average patient, it is likely that prophylactic clip placement would have an even greater benefit in these patients. We do not yet know whether there is proven benefit from prophylactic clipping in polyps < 2 cm for patients taking antiplatelet or anticoagulant drugs, and further studies will be required.

Therefore, we have been asked to address the question of whether the ESGE guidelines should be revised in light of the findings of this meta-analysis. Our view is that large pedunculated polyps should continue to be routinely prophylactically clipped as per the existing guidelines, because these typically have a large vessel within the stalk that can result in major bleeding, they usually require only one or two clips to close, and the benefit for this indication has already been established. With respect to sessile polyps, we now have new knowledge that clipping of large (≥ 2 cm), proximal colon sessile polyps is proven to reduce DPPB. However, we believe this does not necessarily translate to recommending it routinely as a standard of care, as multiple other practical factors must be taken into consideration. A major factor to consider is lesion size, as larger defects require more clips to close and may not be amenable to complete closure in many instances. Evidence exists that partial or incomplete clipping of the polypectomy or EMR defect is not effective in reducing DPPB, and that even in expert hands, 43 % of EMR sites sized ≥ 20 mm could not be fully closed with clips [16]. Furthermore, the cost-benefit analysis will vary substantially depending on the number of clips required and the local cost for each clip. Additional factors requiring consideration include local time pressures for endoscopy room access due the excess time required for clip application, and the skill level of endoscopists in safely applying multiple clips to close larger polypectomy or EMR sites, with accidental perforation during clip application a possibility if not performed correctly. Moreover, patient factors, such as comorbidities, ability to tolerate a potential DPPB, anticoagulant or antiplatelet use, and even patients returning to rural areas after their procedure will all influence the decision to clip.

Clips may also complicate surveillance of polypectomy or EMR sites. In some cases, clips remain adherent and may need to be physically removed at surveillance colonoscopy, or alternatively allowed further time to slough off spontaneously, requiring an additional colonoscopy at a later interval to review the polypectomy or EMR site after the clip is no longer present. The ongoing presence of clips often results in growth of granu-

lation tissue, which can be difficult to distinguish from recurrent adenoma [37]. Even once clips have been expelled, the well-described entity of "clip artifact" can impair the assessment of EMR and polypectomy scar sites [37], and in the absence of expertise in interpreting mucosal pit patterns, potentially result in unnecessary further resection at the scar site. Finally, emerging techniques such as cold snare polypectomy and cold snare EMR have demonstrated very low rates of delayed bleeding, even for large polyps including both sessile serrated adenomas/polyps and adenomas [38, 39] and it is unlikely that routine clip placement in this cohort would be worthwhile.

So should we revise the 2017 ESGE guidelines? We believe the answer is yes. The guidelines should have the following additional recommendation: Delayed post polypectomy bleeding following "hot snare" polypectomy or EMR of large (≥ 20 mm sized), sessile, proximal colon polyps is reduced by the application of endoscopic clips. However, this still cannot be recommended as a routine standard of care, due to multiple patient, lesion, and procedural factors that affect risks and benefits of clip application. Therefore, careful consideration by the endoscopist of the role for prophylactic clip application in each case remains the appropriate standard of care.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Winawer S, Zauber A, Ho M et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977–1981

[2] Nishihara R, Wu K, Lochhead P et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013; 369: 1095–1105

[3] Rosen L, Bub D, Reed J et al. Hemorrhage following colonoscopic polypectomy. Dis Colon Rectum 1993; 36: 1126–1131

[4] Reumkens A, Rondagh EJ, Bakker CM et al. Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. Am J Gastroenterol 2016; 111: 1092–1101

[5] Waye J, Lewis B, Yessayan S. Colonoscopy: a prospective report of complications. J Clin Gastroenterol 1992; 15: 347–351

[6] Metz A, Bourke M, Moss A et al. Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. Endoscopy 2011; 43: 506–511

[7] Kwon MJ, Kim YS, Bae SI et al. Risk factors for delayed post-polypectomy bleeding. Intest Res 2015; 13: 160–165

[8] Watanabe K, Nagata N, Yanagisawa N et al. Effect of antiplatelet agent number, types, and pre-endoscopic management on post-polypectomy bleeding: validation of endoscopy guidelines. Surg Endosc 2020: doi:10.1007/s00464-020-07402-0

[9] Sawhney M, Salfiti N, Nelson D et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008; 40: 115–119

[10] Albéniz E, Fraile M, Ibanez B et al. A Scoring system to determine risk of delayed bleeding after endoscopic mucosal resection of large colorectal lesions. Clin Gastroenterol Hepatol 2016; 14: 1140–1147

[11] Bahin F, Rasouli K, Byth K et al. Prediction of clinically significant bleeding following wide-field endoscopic resection of large sessile and laterally spreading colorectal lesions: a clinical risk score. Am J Gastroenterol 2016; 111: 1115–1122

[12] 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

[13] Forbes N, Hilsden RJ, Lethebe BC et al. Prophylactic Endoscopic clipping does not prevent delayed postpolypectomy bleeding in routine clinical practice: a propensity score-matched cohort study. Am J Gastroenterol 2020: doi:10.14309/ajg.0000000000000585

[14] 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

[15] Fukata M, Kijima H, Sanjo A et al. Prophylactic clipping may not eliminate delayed hemorrhage in colonoscopic polypectomies. Jikeikai Med J 2002; 49: 133–142

[16] Albéniz E, Alvarez MA, Espinos JC et al. Clip closure after resection of large colorectal lesions with substantial risk of bleeding. Gastroenterology 2019; 157: 1213–21 e4

[17] Pohl H, Grimm IS, Moyer MT et al. Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology 2019; 157: 977–984 e3

[18] 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

[19] Feagins LA, Smith AD, Kim D et al. Efficacy of prophylactic hemoclips in Prevention of Delayed Post-Polypectomy Bleeding in Patients With Large Colonic Polyps. Gastroenterology 2019; 157: 967–976 e1

[20] 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

[21] Matsumoto M, Kato M, Oba K et al. Multicenter randomized controlled study to assess the effect of prophylactic clipping on post-polypectomy delayed bleeding. Dig Endosc 2016; 28: 570–576

[22] 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

[23] 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

[24] Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017; 49: 270–297

[25] Paspatis G, Paraskeva K, Theodoropoulou A et al. A prospective, randomized comparison of adrenaline injection in combination with detachable snare versus adrenaline injection alone in the prevention of postpolypectomy bleeding in large colonic polyps. Am J Gastroenterol 2006; 101: 2850; quiz 2913

[26] Kouklakis G, Mpoumponaris A, Gatopoulou A et al. Endoscopic resection of large pedunculated colonic polyps and risk of postpolypectomy bleeding with adrenaline injection versus endoloop and hemoclip: a prospective, randomized study. Surg Endosc 2009; 23: 2732–2737

[27] Kamal FK, Khan S, Marella H et al. Prophylactic hemoclips in prevention of delayed post-polypectomy bleeding for ≥ 1 cm colorectal polyps: Meta-analysis of randomized controlled trials. Endosc Int Open 2020; 08: E1102–E1110

[28] Jacobs C, Draganov PV, Yang D. To clip or not to clip: still no closure for all. Transl Gastroenterol Hepatol 2019; 4: 80

[29] Mori H, Kobara H, Nishiyama N et al. Simple and reliable treatment for post-EMR artificial ulcer floor with snare cauterization for 10- to 20-mm colorectal polyps: a randomized prospective study (with video). Surg Endosc 2015; 29: 2818–2824

[30] Ayoub F, Westerveld DR, Forde JJ et al. Effect of prophylactic clip placement following endoscopic mucosal resection of large colorectal lesions on delayed polypectomy bleeding: A meta-analysis. World J Gastroenterol 2019; 25: 2251–2263

[31] Mangira D, Ket SN, Majeed A et al. Postpolypectomy prophylactic clip closure for the prevention of delayed postpolypectomy bleeding: A systematic review. JGH Open 2018; 2: 105–110

[32] Forbes N, Frehlich L, James MT et al. Routine prophylactic endoscopic clipping is not efficacious in the prevention of delayed post-polypectomy bleeding: a systematic review and meta-analysis of randomized controlled trials. J Can Assoc Gastroenterol 2019; 2: 105–117

[33] Boumitri C, Mir FA, Ashraf I et al. Prophylactic clipping and post-polypectomy bleeding: a meta-analysis and systematic review. Ann Gastroenterol 2016; 29: 502–508

[34] Spadaccini M, Albeniz E, Pohl H et al. Prophylactic clipping after colorectal endoscopic resection prevents bleeding of large, proximal polyps: meta-analysis of randomized trials. Gastroenterology 2020: doi:10.1053/j.gastro.2020.03.051

[35] Ji J-S, Lee K-M, Lee S-W et al. Effect of prophylactic clip application for the prevention of postpolypectomy bleeding in large pedunculated colonic polyps: a randomized, controlled multicenter trial. United Europ Gastroenterol J 2017; 5: A137

[36] Osada T, Sakamoto N, Ritsuno H et al. Closure with clips to accelerate healing of mucosal defects caused by colorectal endoscopic submucosal dissection. Surg Endosc 2016; 30: 4438–4444

[37] Pellisé M, Desomer L, Burgess N et al. The influence of clips on scars after EMR: clip artifact. Gastrointest Endosc 2016; 83: 608–616

[38] Mangira D, Cameron K, Simons K et al. Cold snare piecemeal EMR of large sessile colonic polyps ≥ 20 mm (with video). Gastrointest Endosc 2020; 910: 1343–1352

[39] Tutticci N, Hewett D. Cold EMR of large sessile serrated polyps at colonoscopy (with video). Gastrointest Endosc 2018; 87: 837–842