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**Prevention of late complications with coverage agents in endoscopic resection of colorectal lesions: current landscape in gastrointestinal endoscopy**

Lorenzo-Zúñiga V *et al.* Coverage agents

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**Abstract**

Endoscopic removal of large (≥ 20 mm) non-pedunculated colorectal lesions (LNPCLs) may result in major adverse events, such as delayed bleeding (DB) and delayed perforation (DP), despite closure of the mucosal defects with clips. Topical application of a coverage agent refers to the creation of a shield with a biocompatible medical device (tissue or hydrogel) with proven bioactive properties. Coverage of the eschar after endoscopic resection provides shielding protection to prevent delayed complications. The aim of the present review was to systematically collect and review the currently available literature regarding the prevention of DB and DP with coverage agents after endoscopic mucosal resection or endoscopic submucosal dissection of LNPCLs.

**Key Words:** Large colorectal lesions; Delayed bleeding; Topical application; Endoscopic mucosal resection; Endoscopic submucosal dissection

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**Core Tip:** The use of coverage agents is the simplest and quickest technique to protect large mucosal defects. Published data have confirmed their efficacy in the prevention of delayed adverse events in patients with non-pedunculated colorectal lesions, especially in proximal lesions with an increased risk of bleeding of at least 2-fold. There are no comparative studies that address the best treatment. We herein review the current landscape of the available agents in gastrointestinal endoscopy.

**INTRODUCTION**

Endoscopic resection of precancerous colorectal lesions is one the most frequently performed medical interventions, which significantly decreases the risk of colorectal cancer incidence and death. Large (≥ 20 mm) non-pedunculated colorectal lesions (LNPCLs) show the highest cancer risk and their careful, complete, and timely removal is especially critical. Endoscopic removal of these lesions may result in major adverse events, such as delayed bleeding (DB) and delayed perforation (DP), especially in high-risk patients with a Spanish Endoscopy Society Endoscopic Resection Group score ≥ 6 or deep mural injury signs II-V, despite closure of the mucosal defects with clips[1-3]. Complete clip closure is not possible in 40% cases due to large size or poor accessibility[4]. The risk of DB ranges from 1% to 12% (1.5% with complete closure, 9% with partial closure and 12% with failed closure), whereas the risk of DP is around 1%[5,6]. The routine use of prophylactic clipping does not reduce the risk of post-procedural bleeding overall[7]. On the other, prophylactic endoscopic coagulation of visible vessels is not effective in the prevention of clinically significant DB[8].

Topical application of a coverage agent refers to the creation of a shield with a biocompatible medical device (tissue or hydrogel) with proven bioactive properties. Coverage of the eschar after endoscopic resection provides shielding protection to prevent delayed complications[9]. A comprehensive understanding of the pathogenic mechanisms of action involved is mandatory to address these challenges. The aim of the present review was to systematically collect and review the currently available literature regarding the prevention of DB and DP with coverage agents after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of LNPCLs.

**SEARCH STRATEGIES**

A comprehensive search of PubMed was performed to identify articles in English. Search strategies and key words were as follows: (1) (“endoscopy” [All Fields] AND (“topical application” [All Fields]); (2) (“large colorectal lesions” [All Fields] AND “EMR” [All Fields] OR “ESD” [All Fields]); and (3) (“delayed bleeding” [All Fields] OR “delayed perforation” [All Fields]). In addition, manually inspected relevant articles that were missed by the above search strategy were also included.

**CLINICAL DATA**

Following our search, 8 studies were identified with 191 patients included in case series, which are summarized in Table 1. Tested agents were: polyglycocolic acid sheets with fibrin glue (PGA-FG), Surgicel®, platelet-rich plasma (PRP), Purastat® and cyanoacrylate. All these measures present biological safety after experience in clinical practice. The first report was published in 2014 to evaluate the shielding technique after ESD in 10 patients with LNPCLs, placing PGA sheets on the mucosal defect with biopsy forceps and then spraying FG through a special double-lumen tube[10]. PGA is an absorbent and hydrophilic suture reinforcement material, hydrolysed *in vivo*, with a degradation and absorption period within approximately 15 wk[11]. To perform this technique, soft and elastic PGA sheets were cut into small pieces, held with biopsy forceps, and transported to the mucosal defect through the channel of the scope. Fibrinogen first and then thrombin were sprayed with different spray tubes to fix the sheets to the ulcer and to enhance the coating effect[12]. The use of PGA-FG in LNPCLs achieved a success rate of 100%, but required a long-procedure time (a mean of 19 min). During follow-up colonoscopy, 80% of patients showed persistence of PGA sheets at 2 wk.

Surgicel® Fibrillar™, an oxidized regenerated cellulose that swells into a gelatinous mass, was the second substance investigated to reduce late complications in a large case-series of 49 patients with colorectal ESD[13], using one layer of this agent diluted in 10 mL of normal saline through a special spraying catheter. Surgicel® aids in clot formation after blood saturation, serving as a haemostatic adjunct, and has a localized bactericidal effect due to a low pH of 3.4-3.7[14]. To assess the effectiveness of Surgicel® application, a retrospective comparison with another 52 patients with LNPCLs who underwent conventional ESD was performed. All lesions were successfully covered, and the covering procedure was less time-consuming (5 min). During the follow-up period, rebleeding occurred in 0 (0%) patients and 4 (7.7% in the control group) patients. Postpolypectomy syndrome (PPS) was observed in three patients (6.1%) who were treated with Surgicel®, compared with 17 (32.7%) in the non-Surgicel® group. In 20 patients treated with this product, a follow-up colonoscopy was performed the next day, and Surgicel® remained on the defect in all cases. Based on this, the authors speculated that the reduction in the inflammatory reaction was associated with the shielding effect and reduced endotoxemia due to the bactericidal property of this agent, which acidifies the environment.

PRP, also known as autologous platelet gel, has confirmed robust healing properties over the eschar after EMR in preclinical models[15]. Platelets play a fundamental role in haemostasis and are a natural source of growth factors. PRP fluid contains at least a 2-fold peripheral blood platelet count and a large amount of pivotal growth factors for reepithelization, which are released from the alpha granules of activated platelets[16]. The use of PRP is justified in the exponential release of multiple pleiotropic factors, which enhances the physiological and haemostatic healing processes, with a very low risk of fibrotic healing or strictures. In clinical practice, PRP was used as a coverage agent to prevent late complications in a limited number of patients with very large lesions located in the rectum (mean size 54 mm)[17]. PRP was obtained from a sample of patient’s blood (18-36 mL) drawn at the time of endoscopy. DB occurred in 1 of 4 lesions with blood transfusion or endoscopic treatment not required. PRP also showed a very high mucosal healing rate after 4 wk (79%), the time to apply PRP was very quick (2 min), and the force required to pass the composition was appropriate, comparable to saline. Nevertheless, patient number is too small to draw any conclusions on efficacy, and controlled data are lacking.

PuraStat® has also been tested to prevent DB after endoscopic resection of LNPCLs. This agent is a fully synthetic matrix scaffold built from a chain of three types of amino acids than bond together to form a peptide. It forms a transparent gel when it comes into contact with blood or tissue fluids, comprising a network of nanofibers that form an extracellular matrix, providing a physical barrier to stop bleeding by blocking blood vessels. Three case series (single-arm interventional studies) and one randomized clinical trial have been reported in 113 patients with LNPCLs[18-21]. Total lesion surface was completely covered with a dose of 3 mL in a median time of 2 min. Clinically significant DB occurred in 4.4% of patients (range 0%-12%). The concerns with this gel are that it has to be applied through a special catheter, it is affected by gravity, and slowly slides from the ulcer bed after covering. Exsufflation after application seems to be effective in applying the gel to the whole area with less migration.

Recently, cyanoacrylate has been evaluated in a two-arm study[22]. Two groups of fifteen patients with LNPCLs were compared to evaluate early and DB after EMR in association with a modified cyanoacrylate glue (N-butyl-2-cyanoacrylate + methacryloxysulfolane-Glubran 2®) *vs* EMR alone. Cyanoacrylate is a strong and fast-acting synthetic glue with sealing, adhesive and haemostatic properties, which rapidly polymerizes in the presence of water to form long and strong chains. Based on these properties it has been widely used in surgery, and for primary and secondary prophylaxis of bleeding from gastric varices[23]. This substance has been applied using a 7 Fr spray Teflon catheter. No case of early bleeding was reported in both groups. Two cases (13.3%) of DB with readmission to hospital and redo endoscopy with apposition of haemostatic clips were performed in patients with EMR alone, as compared with no cases of DB in the shielded group (*P* = 0.48).

**DISCUSSION**

Endoscopic shielding with coverage agents is a very promising method to prevent late complications in patients with LNPCLs, especially in proximal lesions with an increased risk of bleeding of at least 2-fold. The protective effect of clips is limited to those cases where complete closure was achieved (57% of cases), and the median number of clips to completely close the resection defect was four[4-6]. The absence of efficacy in many cases of the clipping technique, with its cost and technical difficulties, induced the appearance of new endoscopic approaches to solve this unmet need.

The use of coverage agents is the quickest and simplest technique to cover large mucosal defects, and published data seem to confirm their efficacy in the prevention of late complications. However, most of the reports are case series, without a control arm and with a relatively short follow-up. There is a lack of randomized controlled trials and of head-to-head comparative studies of shielding products. Moreover, none of the published series can incorporate blinding, with considerable bias therefore inevitable.

Regarding the type of active treatment used, there is no ideal treatment, and all have pros and cons (Table 2). As options developed to prevent DB and DP it is important to consider the cost-effectiveness of each treatment. The overall rate of delayed adverse events is assessed as 10%, and the cost for management of these complications, including admission and additional therapies, is estimated at 5000 $ per patient. The cost for an economical prophylactic measure for each patient without adding to the overall financial cost is around 500 $ per cushion. Commercially available data show the price range per 1 mL to be 10-150 $; thus, it is necessary to consider the economics, the upfront cost for the added prophylactic intervention, and the downstream cost savings for an avoided hospitalization. If the mean used volume is 3 mL, we can estimate the cost-effectiveness of each tested agent, from PRP, the cheapest, to cyanoacrylate, the most expensive.

Apart from efficacy, mucosal healing activity is another important issue to consider. All these prophylactic measures help and accelerate mucosal reepithelialisation, but the healing process has only been measured with PRP. The ideal coverage agent should have a chemical structure and physical properties showing an appropriate adhesion capacity to avoid migration against gravity and adherence failure, some refractoriness to bacterial degradation in order to increase the bioactive period and reduce the incidence of PPS, and healing activity to increase mucosal healing rate. Application should be straight with minimal force to pass the agent, ideally using standard devices accessible to all endoscopy units, inducing a small increase in the time of the resection procedure and with a short learning curve. Ideally, it should also be able to release bioactive drugs to treat specific conditions such as colorectal cancer or inflammatory bowel disease. All these properties are still to be confirmed in proof of concept studies with robust data.

To obtain the ideal agent, larger prospective studies with control groups and a comparison of the different substances are needed.

**CONCLUSION**

The use of coverage agents is the quickest and simplest technique to cover large mucosal defects, and published data seem to confirm their efficacy in the prevention of late complications. However, most of the reports are case series, without a control arm and with a relatively short follow-up. There is a lack of randomized controlled trials and of head-to-head comparative studies of shielding products. Moreover, none of the published series can incorporate blinding, with considerable bias therefore inevitable.

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**Footnotes**

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**Table 1 Outcome of coverage agents to prevent delayed bleeding and perforation after endoscopic resection of colorectal lesions**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Year | Design | *n* | Size (mm) | Agent | Primary endpoint | Follow-up | Outcomes |
| Tsuji *et al*[10] | 2014 | SA | 10 | 39.7 | PGA-FG | Prevent late complications | 2 wk | 0% DB/0% DP |
| Myung *et al*[13] | 2016 | SA | 49 | 38.8 | Surgicel® | Prevent late complications | 1 wk | 0% DB/0% DP/6% PPS |
| Lorenzo-Zúñiga *et al*[17] | 2021 | SA | 4 | 53.7 | PRP | Prevent late complications | 4 wk | 25% DB/0% DP/79% MHR |
| Pioche *et al*[18] | 2016 | SA | 22 | 38.5 | Purastat® | Prevent delayed bleeding | 4 wk | 6.7% DB |
| Subramanian *et al*[19] | 2019 | SA | 31 | 44.2 | Purastat® | Prevent delayed bleeding | 4 wk | 0% DB |
| Soons *et al*[20] | 2020 | SA | 17 | 38.4 | Purastat® | Prevent delayed bleeding | 4 wk | 11.7% DB |
| Subramanian *et al*[21] | 2021 | RCT | 43 | 33.7 | Purastat® | Prevent late complications | 4 wk | 5.5% DB |
| Martines *et al*[22] | 2020 | TA | 15 | 25 | NBCA-MS | Prevent delayed bleeding | - | 0% DB |

SA: Single-arm interventional case series study; TA: Two-arm interventional case series study; RCT: Randomized clinical trial; PGA-FG: Polyglycocolic acid sheet with fibrin glue; PRP: Platelet-rich plasma; NBCA-MS: N-butyl-2-cyanoacrylate with methacrylosulfolane (Glubran 2®); DB: Delayed bleeding; DP: Delayed perforation; MHR: Mucosal healing rate.

**Table 2 Pros and cons of coverage agents based on ideal properties**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Property | PGA-FG | Surgicel® | PRP | Purastat® | Cyanoacrylate |
| Appropriate adhesion capacity | + | + | + | + | + |
| Absence of special device | - | + | + | - | + |
| Not time-consuming | - | + | + | + | + |
| Refractory to bacterial degradation | + | + | - | - | + |
| Healing activity | + | + | + | + | + |
| Price range of 1 mL ($) | 20-25 | 15-20 | 10-12 | 100-150 | 150 |
| Drug-release | - | - | - | - | - |

PGA-FG: Polyglycocolic acid sheet with fibrin glue; PRP: Platelet-rich plasma.