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## Submucosal Epinephrine Injection Before Endoscopic Papillectomy: Less is More?

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See “Efficacy of Hypertonic Saline-Epinephrine Local Injection Around the Anal Side before Endoscopic Papillectomy for Ampullary Tumors” by Naoki Okano, Yoshinori Igarashi, Ken Ito, et al., on page 706-712.

Since the first endoscopic papillectomy in 1983, the technique has developed further and has become the first-line treatment for papillary lesions considered endoscopically resectable.<sup>1,2</sup> A recent meta-analysis of endoscopic papillectomy reported a technical success rate of 94.2% and an oncologically curative resection rate of 87.1%.<sup>3</sup> Adverse events are common and reported in almost one in four patients, with intra-procedural bleeding and post-procedural pancreatitis occurring in 11% of the cases.<sup>3</sup>

Submucosal epinephrine injection is commonly used for endoscopic resections in the gastrointestinal tract and is known to prevent intraprocedural bleeding during endoscopic papillectomy. However, one randomized controlled trial (RCT) compared submucosal epinephrine injection followed by endoscopic papillectomy to direct snare papillectomy and found similar rates of intra-procedural bleeding (42% vs. 46%) in both groups.<sup>4</sup> Complete resection rates were clearly lower (50% vs. 81%) in the group that received epinephrine injection, which is in line with the results of another retrospective study.<sup>4,5</sup> The explanation for the lower complete resection rates is that the papillary complex itself is fixed to the rigid sphincter of Oddi complex, while the surrounding tissue becomes

adherent after submucosal injection and buries the papilla, which complicates endoscopic resection. The recent guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends against submucosal injection based on these studies, unless it involves a laterally spreading papillary adenoma.<sup>2</sup>

In this issue of *Clinical Endoscopy*, Okano et al. modified the submucosal injection technique so that it does not hinder endoscopic resection.<sup>6</sup> Instead of injecting into the entire papillary area, the authors only injected epinephrine around the distal part of the papilla where most of the blood vessels are located and bleeding is common. Outcomes of patients treated with this technique since 2010 were compared to those treated before 2010 using the direct snare technique. Intraprocedural bleeding was significantly less in the epinephrine injection group (4.8% vs. 20.5%). In addition, the rate of post-procedural pancreatitis was significantly lower in the epinephrine injection group (11.1% vs. 31.8%). The authors hypothesized that a longer duration of the procedure and additional manipulation associated with the treatment of the bleeding might have increased the risk of pancreatitis in the direct snare group. The rates of complete resection were not negatively affected by the submucosal injection, possibly because of the modified technique. Thus, the authors concluded that local treatment with epinephrine injection prevented both intra-procedural bleeding and post-procedural pancreatitis.

Delayed (>24 h) bleeding is also not uncommon after endoscopic papillectomy due to the thermal effect that lags behind and exposes the blood vessels to the risk of delayed bleeding. Although the vasoconstrictive effect of epinephrine injection wears off within 10-30 minutes and could therefore potentially underestimate the bleeding risk, no significant in-

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crease in delayed bleeding was observed in the study by Okano et al.<sup>6</sup> Several technical interventions to prevent late bleeding have been studied. Prophylactic clip placement on the frenulum, similar to that in the injection site in the study by Okano et al.,<sup>6</sup> compresses the local blood vessels and thus prevents bleeding without the risk of accidentally blocking the bile or pancreatic duct. A retrospective, monocentric study showed a lower incidence (5%) of delayed bleeding in 40 patients with a prophylactic clip compared to 23% in a historical cohort of 40 patients without clip placement.<sup>7</sup> Another strategy is to use argon plasma coagulation (APC); however, treating only the edges of the resection margin with APC did not reduce the incidence of delayed bleeding in an RCT involving 54 patients.<sup>8</sup> Perhaps the key to success in preventing delayed bleeding is to treat the well-vascularized distal part of the papilla. Nevertheless, the risk of delayed bleeding is associated with the size of the resection, which implicates that bleeding in larger lesions will increasingly occur from somewhere other than the frenulum area and cannot be prevented.<sup>9</sup> Treating delayed bleeding includes the discontinuation of anticoagulants and blood transfusion, if applicable, and applying local endoscopic therapy using a coagrasper. In hemodynamically unstable patients in whom the endoscopic therapy failed, an emergency arterial embolization was performed.

The hypothesis put forth by the authors that the treatment of intra-procedural bleeding might increase the risk of pancreatitis seems prudent; however, there is a lack of compelling evidence since the duration of the procedure was not presented in their paper, and evidence from the current literature is lacking. To prevent post-procedural pancreatitis, ESGE recommends the administration of a rectal nonsteroidal anti-inflammatory drug (NSAID) in all patients without an NSAID allergy and placement of a prophylactic pancreatic stent in patients without a pancreas divisum.<sup>2</sup>

Should we change our clinical practice? The retrospective nature of this monocentric study, which compares the outcomes at two different time periods, does not justify such a modification of the current treatment strategy; however, it does validate a new prospective, comparative study on this subject. Papillary neoplasia is rare; therefore, data on this subject are scarce, and conducting large RCTs is challenging. However, the rates of adverse events associated with endoscopic papillectomy are high, and other issues such as the significantly high recurrence rates need to be addressed in future studies that require a multicentric, and preferably, an international approach.<sup>10</sup> Retrospective studies encompassing relatively large groups of patients, which are analyzed using propensity score matching, could also aid in creating a more robust, evidence-based foundation.

In conclusion, submucosal injection of epinephrine only on

the distal side of the papilla might prevent intra-procedural bleeding without affecting the rates of complete resection, and therefore “less is more” seems to apply here. The question now is how more evidence can be gathered so that this modified injection method could imply a change in the future update of the recently published ESGE guidelines.

#### Conflicts of Interest

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#### Author Contributions

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