

Endoscopic Removal of Polyps in the Gastrointestinal Tract

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Endoscopic Removal of Polyps in the Gastrointestinal Tract



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G&H What is the role of endoscopic mucosal resection in the removal of polyps in the gastrointestinal tract?

MW Endoscopic mucosal resection (EMR) plays an important role in the removal of flat or laterally spreading polyps, including those greater than 1 cm, especially in the right colon. However, the procedure has now expanded to include virtually all noninvasive, large, flat polyps in the colon.

G&H What other endoscopic techniques are available for the removal of polyps?

MW Small polyps, which are encountered in more than half of colonoscopies, can be removed by routine polypectomy methods, including cautery or cold-snare removal. Nearly all large polyps (≥ 2 cm) can be resected endoscopically (via EMR or endoscopic submucosal dissection) and should not be referred for surgical resection. Additionally, endoscopists should avoid performing procedures at the index (usually on a screening colonoscopy), as that could make subsequent endoscopic resections more difficult. That includes injection of tattoos directly underneath or very close to the polyp, as the tattoo material causes scarring of the lesion and prevents safe removal, as well as using any method to partially remove the polyp, particularly hot snare or extensive biopsies. When a lesion is found during screening colonoscopy, the endoscopist should photograph it very well. If necessary, a

tattoo can be placed on the wall opposite the lesion, and the patient can then be referred to a physician or center that has expertise in EMR.

G&H What are the goals of a submucosal lift?

MW There are 2 main goals of a submucosal lift. The first goal is to improve the safety of the procedure. Because the colon wall is thin, there is a risk of perforation when removing a very broad or lateral-spreading polyp using the simple snare technique. Thus, the goal of improving safety is based on increasing the thickness of the colon wall and, in particular, separating the mucosal layer, which is to be removed from the muscle, from deeper layers, which should not be removed. The second goal is to improve efficacy. A flat polyp is difficult to grasp with a snare device, and vertically lifting the polyp creates a mound of tissue that can be grasped with a snare device.

G&H How is a submucosal lift performed?

MW The first step is to carefully inspect the polyp to clarify that it is not a deeply invasive cancer, which would be referred for surgery. Once that has been confirmed, the next step is to define the outer boundaries of the polyp to ensure complete removal (Figure 1). A solution is then injected under the polyp to vertically separate the polyp from the deeper layers (Figures 2 and 3). This is best done with agents that can achieve a durable vertical separation. Endoscopists traditionally use saline, often



Figure 1. A 1-cm flat lesion in the ascending colon with slight central depression (Paris classification IIa/IIc).



Figure 2. The same lesion after lifting using a viscous agent with methylene blue.

with a blue dye; however, the challenge with saline is that it dissipates quickly (typically within 1-2 minutes) and, therefore, does not provide sufficient time to resect many polyps.

G&H What agents are available to create lifts?

MW Simple saline is sufficient for small (1 cm) flat lesions in the right colon. For larger lesions, a viscous agent with a blue dye, such as indigo carmine or methylene blue, is optimal. The viscosity allows the lift to remain vertical for a longer period of time, and the blue dye improves the visualization of the injection site. However, the traditionally used viscous agents (eg, hydroxypropyl methylcellulose, hetastarch) are not approved for submucosal lifts in the United States and are considered off-label. Recently, the US Food and Drug Administration (FDA) cleared a viscous submucosal injection agent (Eleview, Aries Pharmaceuticals Inc) as a class II medical device for the removal of polyps, lesions, and early-stage cancers in the gastrointestinal tract.

G&H What are the benefits of using this more viscous solution compared to saline?

MW Compared to saline, all of the viscous agents improve the durability of the vertical lift. Eleview in particular is the first combination of a viscous agent with methylene blue to receive FDA clearance for the purpose of EMR lifting. It also comes in premixed, ready-to-use ampoules, whereas all the other agents require hospitals to mix or compound multiple agents.



Figure 3. The same lesion after en bloc resection, with clear lateral margins.

G&H What limitations are associated with Eleview?

MW My colleagues and I have not observed any limitations of Eleview in the clinical trial we recently conducted. The solution appears to produce a durable vertical lift and reduce the number of repeated injections and snare resections of a large polyp. The addition of methylene blue serves as a contrast agent to better delineate the polyp. Historically, there was some concern regarding whether methylene blue caused DNA damage, although we, and others, have recently demonstrated that the solution does not produce any clinically relevant DNA damage in which EMR is involved. The FDA reviewed

the data and considered the solution to be safe for its intended purpose.

G&H What challenges or limitations are associated with contrast agents?

MW Both of the blue-dye agents (indigo carmine and methylene blue) are currently in limited supply in the United States, which directly affects the ability to receive the agents necessary for an EMR. Furthermore, the presently available methylene blue cannot be mixed with saline because it causes a precipitation. It is only approved for mixing with water, which produces an additional limitation; an electrosurgical current is often used to heat the wire to cut through polyps, and heating of the wire occurs most effectively with saline as opposed to water, which has no electrolytes.

G&H Could you describe the design and key results of your clinical trial?

MW My colleagues and I recently concluded enrollment for a multicenter, international, double-blind, randomized, controlled trial of injection of Eleview vs saline plus methylene blue. The trial involved patients who had lateral-spreading polyps 2 cm in size or larger, and took place across several expert centers in the United States and Europe. The primary endpoints were the total injected volume to complete the procedure, volume needed per lesion size, and time to resect the lesion completely. Other endpoints included the number of injections, the Sydney Resection Quotient, and the number of snare resections needed to complete the EMR procedure. We screened 327 patients and eventually enrolled 226 patients in the trial; they were well balanced in terms of the size, shape, and location of the colon polyps that were removed. Half of the patients received saline with methylene blue and the other half received Eleview, which comes premixed with methylene blue.

Eleview required significantly less injection volume compared with the saline plus methylene blue comparator (16.1 mL vs 31.6 mL, respectively), which was highly statistically significant. Additionally, significantly less fluid was needed per mm of lesion with Eleview vs saline (0.53 mL/mm of polyp vs 0.92 mL/mm of polyp, respectively). The standard saline plus methylene blue led to a 30-minute procedure, as opposed to 19 minutes with the Eleview agent. Although this is an 11-minute reduction in time to resect the lesion, the result was not statistically significant, as there was a wide range of times in both arms.

The secondary outcome was the Sydney Resection Quotient, which measures the mean size of each snare resection. For example, a 3-cm lesion removed in 3 separate

pieces leads to an average size of 10 mm per resection. The goal is to remove larger pieces per resection so that the procedure is more efficient and fewer snare resections are needed. The Sydney resection quotient for Eleview was 10.3, compared to 8.0 in the saline plus methylene blue arm, which is statistically significant. Lastly, the number of resection pieces was also fewer with Eleview (5.7 vs 6.5; $P=.052$), which was also considered statistically significant.

Other relevant outcomes looked at safety and ease of use. Initially, there was concern that a more viscous Eleview solution might be more difficult to inject through the needle, but it was shown to be no different than saline. The rates of ease of use were similar in both arms; approximately 50% of cases were rated very easy or easy, and 75% of cases were rated neutral or easy.

Adverse events were essentially identical and rare. There was one serious adverse event in the saline arm (perforation), and there were no perforations in the Eleview arm.

G&H How should gastroenterologists incorporate a submucosal injection agent into their clinical practice?

MW A submucosal injection agent such as Eleview is appropriate for lifting most flat or sessile lesions, especially those in the right colon that are 1 cm or greater in size. EMR typically refers to lift-and-cut resections of lesions 2 cm or greater and can be performed by endoscopists with experience in that technique, which may include specialists within larger practice environments and referral centers.

G&H Are there any patients in whom this procedure is contraindicated?

MW Patients who have a deeply invasive cancer (eg, T1SM2 cancer or deeper) that should be referred for surgery would not benefit from an endoscopic approach. In general, any patient who has severe life-threatening comorbid conditions, such as heart failure, other cancers, or severe dementia, would not be expected to benefit from the procedure because they have such a short life expectancy.

G&H What are the priorities of research in this field?

MW One priority is to determine how to further reduce the rate of early recurrence. In expert centers like those that participated in our study, early recurrences happen in approximately 10% to 15% of individuals, although even those early recurrences can usually be managed

with simple polyp-removal techniques. Late recurrences occurred in less than 2% of individuals. The goal is to reduce that recurrence rate further, especially the early recurrence. Several promising methods are now being reported, including prophylactically cauterizing the margin of the resection with snare-tip soft coagulation. Another important area of research is to further reduce the bleeding risk. The postprocedural bleeding in our study was relatively small at 2%, but in other studies it has been as high as 10%. Thus, there is ongoing investigation into how to reduce that rate either by closing the defect site with clipping, using less cautery, or performing the entire procedure with cold-snare resection.

Dr Wallace serves as a consultant to Aries Pharmaceuticals Inc.

Suggested Reading

Bhurwal A, Bartel MJ, Heckman MG, et al. Endoscopic mucosal resection: learning curve for large nonpolypoid colorectal neoplasia. *Gastrointest Endosc.* 2016;84(6):959-968.e7.

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► Eleview™: Ready-to-use submucosal injection agent with methylene blue

Intended Use

Eleview™ submucosal injectable composition is intended for use in gastrointestinal endoscopic procedures for submucosal lift of polyps, adenomas, early-stage cancers, or other gastrointestinal mucosal lesions, prior to excision with a snare or endoscopic device.



Designed for safe and easy resection procedures¹

- Provides an immediate and long-lasting cushion that holds for up to 45 minutes²
- Contains methylene blue to improve visibility of lesion margins¹
- Designed to lower the risk of perforation¹
- Designed for use via a normal, commercially available endoscopic injection needle*
- Sterile and ready to use
- FDA 510(k) cleared as a medical device

*Injection needle not provided as part of Eleview™.

References: 1. Eleview™ Instructions for Use, Aries Pharmaceuticals, Inc. April 2017. 2. Data on File, Aries Pharmaceuticals, Inc.

Important Safety Information

WARNINGS AND PRECAUTIONS

- The safety of Eleview™ has not been established in pregnant or lactating women, or in children under 18 years of age.
- The endoscopist injecting Eleview™ must be experienced in the administration technique.

ADVERSE REACTIONS

- Rarely, local bleeding and/or inflammatory reaction could occur which may or may not be associated with Eleview™.

CONTRAINDICATIONS

- Patients with known sensitivity to any of the components contained in Eleview™.

For more information about Eleview™, including Instructions for Use, visit EleviewUS.com.

Eleview™

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