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EverLift® Submucosal Lifting Agent results in no foreign body artifacts post endoscopic mucosal resection and endoscopic submucosal dissection:

Making informed decisions when selecting a submucosal lifting agent to support the needs of physicians, patients, and administrators

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Executive Summary

BACKGROUND AND AIMS

The purpose of this whitepaper is to highlight several current best practices regarding the safe and effective treatment of gastrointestinal lesions, with a particular emphasis on the utility of submucosal lifting agents. GI Supply, Inc. ('Laborie'), the manufacturer of the submucosal lifting agent EverLift mentioned in this whitepaper, has produced this informational material as a service to the gastroenterological community.

This paper highlights data from a clinical study with EverLift and peer-reviewed guidance on optimal submucosal lifting agents and potential risks (see "Defining the Clinical Need" starting on page 4), including artifacts that can mimic clinically significant conditions, such as mucin pools, lymphangiomas, and more.

Our aim is to share evidence-based data and expert perspectives on why a Pathology department's needs are important considerations, and thus why pathologists should be made aware of the decision or be a part of the conversation when choosing a submucosal lifting agent within the facility. This whitepaper can help enable gastroenterologists, pathologists, and healthcare system administrators to make informed decisions regarding polypectomies, endoscopic mucosal resections (EMR) and endoscopic submucosal dissections (ESD).

STUDY METHODS & RESULTS

In 2021, with the objectives of confirming that EverLift Submucosal Lifting Agent does not produce artifacts and that its 5 mL pre-filled syringes offer waste-reduction and cost-savings opportunities, Laborie conducted a post-market clinical follow-up study of its 5 mL and 10 mL syringes. Data was analyzed from 71 patients, with no reports of intraprocedural patient reactions caused or contributed by the device, no reports of intraprocedural complications at or adjacent to the injection site, and no report of post-procedure (24-hour)-related complications.[1]

The study generated significant data regarding the cost-effectiveness of offering a 5 mL option in addition to conventional 10 mL syringes.[2] (Please find additional data from this and other studies on page 7).

EXPERT COMMENTARY

"EverLift provides a pliable yet reliable cushion for resection and darker blue hues. The single-serve dosing helps reduce waste for everyday polypectomies. The 5 mL has become our go-to syringe." (Additional context on page 7).

Gary "Taavi" Reiss, MD, Director of Therapeutic Endoscopy at Metropolitan Gastroenterology Associates.

"After completely reviewing the 71 patient cases, I see nothing either in the diagnostic lines, or in the histologic descriptions, that would suggest any artifacts with EverLift. Of note, there appeared to be several cancers included among the samples in a variety of gastrointestinal tract organs, which were confidently diagnosed and described by the pathologists of record without mention of artifact."

Robert M. Najarian, MD, Gastrointestinal Pathologist and Medical Director at University Gastroenterology's Pathology Center.

CONCLUSION

Laborie's 2021 post-market clinical follow-Up study of its 5 mL and 10 mL syringes validated that, unlike other submucosal lifting agents on the market, EverLift Submucosal Lifting Agent does not produce artifacts. The study also confirmed that 5 mL pre-filled syringes offer waste-reduction and cost-savings opportunities. There were no reports of intraprocedural patient reactions caused or contributed by the device, no reports of intraprocedural complications at/or adjacent to the injection site, and no report of post-procedure (24-hour) related complications.[3]

Introduction

Purpose

The purpose of this whitepaper is to highlight several current best practices regarding the safe and effective treatment of gastrointestinal lesions, with a particular emphasis on the utility of submucosal lifting agents. GI Supply, Inc. ('Laborie'), the manufacturer of the EverLift Submucosal Lifting Agent mentioned in this whitepaper, has produced this informational material as a service to the gastroenterological community.

Extensive clinical research followed by years of real-world evidence validate colonoscopy with polypectomy's ability to prevent colorectal cancer.[4] Correspondingly, the important role played by submucosal lifting agents during polypectomies, endoscopic mucosal resections (EMR) and endoscopic submucosal dissections (ESD) is well established.

We presume that the readers of this document understand the benefits of en bloc resection, are well educated on the protocols and techniques (e.g., snares, forceps, knives) to achieve optimal results, and are experienced with the utilization of these procedures. These topics are not covered in this whitepaper.

And although GI Supply Inc. ('Laborie') is the manufacturer of the popular Spot® Ex Endoscopic Tattoo discussing its features and benefits is outside the realm of this whitepaper.

> "Effective lifting agents are also important because they help enable endoscopists to more completely remove lesional tissue from their patients and consequently, helps us as pathologists to make more definitive diagnoses."
>
> Robert M. Najarian, MD,
> Gastrointestinal Pathologist and
> Medical Director at University
> Gastroenterology's Pathology Center

Clinicians must consider several factors when selecting a submucosal lifting agent for use during EMR/ESD procedures. Site administrators must evaluate the cost-effectiveness of every purchase at their institutions. If this whitepaper enhances the ability to make an informed decision on the purchase and use of submucosal lifting agents, with the goal of optimizing patient care and clinical outcomes, the objective was met.

Defining the Clinical Need

Extensive research has validated that colonoscopy with polypectomy reduces the incidence of, and mortality from, colorectal cancer (CRC). Data from National Polyp Study demonstrated a reduction in CRC mortality by up to 50% when adenomas were removed during colonoscopies. Minimizing the risk of incomplete resections is the essence of why cost-effective submucosal lifting agents are important to patients, clinicians, and administrators.[5]

One key objective of polypectomies is to eliminate all neoplasia from the colon. Yet in a pooled multicohort analysis of more than nine thousand patients who had a baseline colonoscopy (with intent to remove all visualized lesions), and with a median follow-up of 47.2 months, invasive cancer was diagnosed in 58 patients (0.6%). The researchers classified 11 of the malignancies (19%) as possibly related to incomplete resection of an earlier, non-invasive lesion.[6]

"When a gastroenterologist successfully captures a lesion completely, it gives pathologists a better look at the adequacy of removal." said Robert M. Najarian, MD, Gastrointestinal Pathologist and Medical Director at University Gastroenterology's Pathology Center.

Trends in procedures and submucosal lifting agents

In their highly regarded paper "Advances in CRC Prevention: Screening and Surveillance" published in *Gastroenterology*, Dr. Evelien Dekker (University of Amsterdam Academic Medical Center) and Dr. Douglas Rex (Indiana University School of Medicine) emphasized devoted significant space to important trends in polyp resection during colonoscopy, several of which are relevant to this whitepaper:

- EMR is emerging as the treatment of choice for nearly all flat and sessile lesions ≤20 mm
- The target set of lesions for EMR over standard polypectomy techniques continues to expand
- All sessile and flat lesions ≥20 mm should be generally treated by EMR rather than use of standard techniques
- EMR is particularly important for serrated lesions because submucosal injection of a contrast agent clearly delineates the lesion perimeter during piecemeal removal
- For serrated lesions, the threshold for performance of EMR should be 10–15 mm
- Inclusion of a contrast agent stains the submucosa so that any muscle injury is readily seen (as the target sign), leading to easy repair and prevention of delayed perforation
- Submucosal injection fluids that are more viscous than saline create superior submucosal cushions and improve the efficiency of resection[7]

Features that deliver important clinical benefits

In their 2020 paper published in *Case Reports in Pathology*, Dr. Patricia N. Ibarra-Arzamendia (Hospital Central de IPS, Asuncion, Paraguay) and Dr. Mark Hanly (Baptist MD Anderson Cancer Center, Jacksonville, FL) highlighted the use of various injection solutions during EMR procedures, including normal saline, hyaluronic acid, glycerol, dextrose water, fibrinogen mixture, hydroxypropyl methylcellulose, and "even autologous blood."[8] More important, in their experience and based on their research, they believe "ideal submucosal injection solutions" contain six specific characteristics. In their expert opinions, the best solutions are:

1. Long-lasting and provide a high submucosal cushion
2. Safe and nontoxic
3. Inexpensive
4. Readily available
5. Easy to inject
6. Preserve specimen tissue for accurate histopathological lesion assessment[9]

Issues Associated with Some Submucosal Lifting Agents

Several published, peer-reviewed papers have addressed the complexities and costs associated with the enduring presence of some submucosal lifting agents. The issue is the potential for pathologists to misinterpret the residue as being clinically significant.

As described in the 2021 paper "Histologic changes caused by injection of a novel submucosal lifting agent for endoscopic resection in GI lesions," published in *Gastrointestinal Endoscopy*, Andrea Olivas, MD, and her University of Chicago colleagues wrote, "Histologically evident gel deposits in resected specimens may pose a potential diagnostic pitfall."[10]

In a 2020 paper published in *Modern Pathology*, "Features of endoscopic procedure site reaction associated with a recently approved submucosal lifting agent," Dr. Carlos Castrodad-Rodriguez, his colleagues at the Montefiore Medical Center/ Albert Einstein College of Medicine in New York City and a co-author from the University of Florida in Gainesville, reported results of patients where ORISE™ Gel Submucosal Lifting Agent was used during procedures. Their key observations and attendant recommendations are summarized below:

- The submucosal lifting agent may persist at injection sites long after EMR or ESD
- Deposits may distribute laterally and deeply beyond the histologic extent of residual tumor and produce the gross impression of a more advanced lesion
- Histologically, deposits may simulate amyloid or pulse granulomata
- Ancillary stains, including Congo Red and PAS-D, may help in the differential diagnosis
- Pathologists should be aware of the histologic features of deposits and the associated reaction so that they may obtain clinical history to properly classify this finding[11]

The previously referenced Case Reports in Pathology addressed similar concerns, observing that some artifacts that remain in the tissue "may mimic a number of other conditions such as mucin pools, lymphangiomas, granulomatous inflammation, and amyloid deposition… unresorbed ORISE submucosal injectable gel may present a unique amyloid or mucin-like appearance on routine hematoxylin and eosin-stained sections, but once recognized, this artifact can be easily recognized, thus preventing the use of unnecessary additional studies."[12]

> "It is critically important for the gastroenterologist to collaborate with the pathologist by mentioning whether a lifting agent was used during lesion removal, and if so, which specific agent was used. If the pathologist is unaware of the artifacts that can be induced by certain lifting agents, additional costly stains may be required to arrive at a correct diagnosis. Thus, the collaboration between endoscopist and pathologist enables better diagnoses and overall patient care."
>
> - Robert M. Najarian, MD, Gastrointestinal Pathologist and Medical Director at University Gastroenterology's Pathology Center

According to Dr. Najarian, reducing or eliminating unnecessary follow-up testing can be achieved through effective communication. Dr. Najarian added that not all practicing pathologists have had access to specialized gastrointestinal tract pathology training nor the exposure to relevant cases that adequately prepares them to account for artifacts caused by some submucosal lifting agents. For this reason, he sees the opportunity for submucosal lifting agents that do not produce artifacts playing an important role during polypectomies, endoscopic mucosal resections (EMR), and endoscopic submucosal dissections (ESD).

Real-World Evidence with EverLift®

In 2021, with the objectives of confirming that its EverLift Submucosal Lifting Agent does not produce artifacts and that its 5 mL pre-filled syringes offer waste-reduction and cost-savings opportunities, Laborie conducted a post-market clinical follow-up study of its 5 mL and 10 mL syringes. Data was analyzed from 71 patients (age 37 - 88, median age 63.5), including names and locations of clinical sites, procedure dates, lesion size and description, syringe size, and total volume injected. There were no reports of intraprocedural patient reactions caused or contributed by the device, no reports of intraprocedural complications at or adjacent to the injection site, and no report of post-procedure (24-hour) related complications.[13]

KEY HIGHLIGHTS FROM THE STUDY

- Two largest lesions were 35 mm polyps (semi pedunculated sigmoid polyp; flat and draped over fold)
- 64/71 (90%) patients resected with 5 mL syringe
- Seven polyps that used >5 mL ranged from 15 mm flat to 40 mm sessile[14]

Following his independent analysis of the biopsy reports and imaging, Dr. Najarian provided this analysis:

"After completely reviewing the reports of 71 patient cases, I see nothing within the histologic diagnoses or diagnostic workups that would suggest any artifacts with EverLift. Of note, there appeared to be several cancers included among the samples in a variety of gastrointestinal tract organs, which were confidently diagnosed and described by the pathologists of record without any mention of artifact from the use of the lifting agent."

Meeting the Needs of Administrators and ASC Practices

The post-market clinical follow-up study generated significant data regarding the cost-effectiveness of offering a 5 mL option in addition to conventional 10 mL syringes: Despite a wide range of clinical presentations, gastroenterologists performing polypectomies were able to effectively lift and resect lesions with a 5 mL syringe.[15]

This data point is aligned with the clinical experiences of Gary "Taavi" Reiss, MD, Director of Therapeutic Endoscopy at Metropolitan Gastroenterology Associates. In the study Dr. Reiss and his team used 5 mL or less of EverLift Submucosal Lifting Agent with about 90% of the patients. He added practical advice for gastroenterologists not familiar with this size pre-filled syringe: "Now when you use 5 mL, you probably lose two in the needle and the syringe, so you have to prime it or chase it with a little bit of saline. We've found that in many cases where you think a lesion would require about 8 mL, this approach is effective. You're using 5 mL of EverLift plus 3 mL of saline, which in our experience is adequate if saline is just used as an adjunct. The 5 mL has become our go-to syringe. It really is very useful."

Dr. Reiss acknowledged that all pre-mixed submucosal injections provide an adequate cushion, though he appreciates EverLift's consistency in its operational characteristics.

> "One of the things EverLift is best at, is its deep blue color. It has very good coloration, allowing easy visualization of lesions margins. But the main advantage to us is that it comes in 5 mL aliquot, which is less expensive and easy for us to use. Also, we have not observed any questionable granulomas or anything else that would point to artifacts."
>
> Gary "Taavi" Reiss, MD, Director of Therapeutic Endoscopy at Metropolitan Gastroenterology Associates.

Conclusion and Key Considerations

Laborie's 2021 post-market clinical follow-up study of its 5 mL and 10 mL syringes validated that EverLift Submucosal Lifting Agent does not produce artifacts. The study also confirmed that 5 mL pre-filled syringes offer waste-reduction and cost-saving opportunities. Data was analyzed from 71 patients (age 37 - 88, median age 63.5). There were no reports of intraprocedural patient reactions caused or contributed by the device, no reports of intraprocedural complications at or adjacent to the injection site, and no report of post-procedure (24-hour)- related complications.[16]

Best practice indicates that pathologists should at a minimum be made aware of the use of a submucosal lifting agent during polypectomies, endoscopic mucosal resections (EMR), and endoscopic submucosal dissections (ESD). In some facilities, pathologists engage in collaborative dialogue with gastroenterologists when choosing a submucosal lifting agent.

The US Multi-Society Task Force on Colorectal Cancer published its comprehensive recommendations on the endoscopic removal of colorectal lesions in a 2019 Gastroenterology paper. Dr. Tonya Koltenbach (Veterans Affairs San Francisco, University of California-San Francisco) and her co-authors representing 13 other institutions across the nation, noted, "Reports have shown that residual tissue after polypectomy that is judged to be 'complete' by the endoscopist is common, ranging from 6.5% to 22.7%."

Here are summaries of key task-force recommendations relevant to this whitepaper:

- EMR is the preferred treatment method of large (≥20 mm) non-pedunculated colorectal lesions; EMR can provide complete resection and obviate the higher morbidity, mortality, and cost associated with alternative surgical treatments

- A contrast agent, such as indigo carmine or methylene blue, should be used in the submucosal injection solution to facilitate recognition of the submucosa from the mucosa and muscularis propria layers

- A viscous injection solution should be used to remove ≥20 mm lesions in fewer pieces and with less procedure time compared to normal saline

The Task Force highlighted that submucosal injection is a key step of EMR, adding that the optimal agent is one that is widely available, inexpensive, and that provides a sustained lift to facilitate safe and efficient piecemeal resection when en bloc is not achievable. Its meta-analysis of five prospective, randomized controlled studies of colorectal EMR showed significantly higher rates of en bloc resection (odds ratio [OR], 1.91; 95% CI 1.11–3.29;P¼.02;I2-0%) and lower rates of residual lesions (OR, 0.54; 95% CI, 0.32–0.91;P¼.02;I2-0%) using a colloid solution compared to normal saline for injection of lesions >20 mm.[17]

Indications for Use

EverLift Submucosal Lifting Agent is indicated for use in gastrointestinal endoscopic procedures for submucosal lift of polyps, adenomas, early stage cancers, or other gastrointestinal lesions prior to excision with a snare or other appropriate endoscopic device.

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