A novel submucosal injection solution for endoscopic resection of large colorectal lesions: a randomized, double-blind trial CME

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Background and Aims: SIC-8000 (Eleview) is a new U.S. Food and Drug Administration (FDA)-approved solution for submucosal injection developed to provide a long-lasting cushion to facilitate endoscopic resection maneuvers. Our aim was to compare the efficacy and safety of SIC-8000 with those of saline solution, when performing EMR of large colorectal lesions.

Methods: In a randomized double-blind trial, patients undergoing EMR for colorectal non-pedunculated lesions ≥20 mm were randomized in a 1:1 ratio between SIC-8000 and saline solution as control solution in 5 tertiary centers. Endoscopists and patients were blinded to the type of submucosal solution used. Total volume to complete EMR and per lesion size and time of resection were primary endpoints; the Sydney Resection Quotient (SRQ), as well as other EMR outcomes, and the rate of adverse events were secondary endpoints. A 30-day telephone follow-up was performed. An alpha level <0.05 was considered as statistically significant.

Results: Of the 327 patients screened, 226 (mean age, 66 ± 10 years; males, 56%) were enrolled in the study and randomized between the 2 submucosal agents. Of these, 211 patients (mean size of the lesions 33 ± 13 mm; Paris class Is, 36%; proximal colon, 74%) were entered in the final analysis (SIC-8000, 102; saline solution, 109). EMR was complete in all cases. The total volume needed for EMR was significantly less in the SIC-8000 arm compared with saline group (16.1 ± 9.8 mL vs 31.6 ± 32.0 mL; $P < .001$). This corresponded to an average volume per lesion size of 0.5 ± 0.3 mL/mm and 0.9 ± 0.6 mL/mm with SIC-8000 and saline solution, respectively ($P < .001$). The mean time to completely resect the lesion tended to be lower with SIC-8000 than with saline solution (19.1 ± 16.8 minutes vs 29.7 ± 68.9 minutes; $P = .1$). The SRQ was significantly higher with SIC-8000 compared with saline solution (10.3 ± 8.1 vs 8.0 ± 5.7; $P = .04$) with a trend for a lower number of resected pieces (5.7 ± 6.0 vs 6.5 ± 5.04; $P = .052$) and a higher rate of en bloc resections (19/102, 18.6% vs 12/111, 11.0%; $P = .1$). The rate of adverse events was similar between the 2 arms (SIC-8000, 18.6%; saline solution, 17%), and none of the serious adverse events (SIC-8000, 8.8%; saline solution, 10.7%) were related to the study treatment.

Conclusions: In a double-blind, randomized clinical trial, a new FDA-approved agent for sub-mucosal injection appeared to be a more effective and equally safe submucosal agent for EMR injection than saline solution. (Clinical trial registration number: NCT02654418.) (Gastrointest Endosc 2018;88:527-35.)

(footnotes appear on last page of article)

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INTRODUCTION

Large (≥2 cm) colorectal polyps are clinically relevant due to the intimate relationship between polyp size and risk of advanced neoplasia and malignancy. The same applies to large non-polypoid lesions, especially when non-granular or depressed.[1] Thus, the expected benefit of endoscopic resection in terms of colorectal cancer

prevention is substantial, whereas incomplete resection has been directly associated with an increased risk of interval cancer.[2,3]

Large non-pedunculated lesions represent the most technically challenging to be removed endoscopically. In order to maximize its efficacy and safety,[4-7] EMR is usually assisted by submucosal injection, generating a safe fluid cushion between the luminal and the muscular layers. This cushion is expected to reduce thermal injury and the risk of perforation and bleeding, while facilitating en bloc resection or resection in fewer pieces.

The most commonly used fluid remains 0.9% sodium chloride (NaCl) solution.[8] Its main drawback is its rapid reabsorption, resulting in a short cushion duration and the need for multiple injections, increasing the time of resection. This drawback has been shown to affect the outcome of EMR with a lower rate of en bloc resections and higher number of piecemeal fragments compared with more viscous solutions.[9-13] In addition, saline solution is usually mixed with methylene blue or indigo carmine before EMR, and the time required for such preparation further penalizes the efficiency of the endoscopy unit.

Until recently, there has not been a U.S. Food and Drug Administration (FDA)-approved agent available for submucosal injection. SIC-8000 (Eleview, Aries Pharmaceutical, San Diego, Calif) (Fig. 1) is a new FDA-approved low-viscosity, ready-to-use solution for upper and lower GI endoscopy. It mainly consists of a synthetic co-polymer (poloxamer 188) and methylene blue. Due to transient binding between the co-polymer and the physiological biopolymers present in the submucosal layer of the GI tract, it creates a molecular net that prevents water and fluid migration from the injected area.

To investigate its efficacy and safety in a clinical setting, we compared SIC-8000 with saline solution for submucosal injection when performing endoscopic resection of large non-pedunculated colorectal lesions.

Figure 1. Eleview ampules ready to be used.

MATERIALS AND METHODS

Study design

In a double-blind randomized trial, patients referred for endoscopic removal of non-pedunculated colorectal lesions ≥20 mm to 5 tertiary centers were considered for enrollment in the period between February 2016 and April 2017 (NCT02654418). The study was approved by the institutional review boards of the participating centers, and informed consent was obtained from participating patients. The study was fully supported with a research grant provided by Cosmo Pharmaceutical NV, Dublin, Ireland.

Study population

Patients referred for endoscopic resection of treatment-naive, non-polypoid, or polypoid superficial colorectal lesions ≥20 mm (in at least 1 dimension) were considered for enrollment. The size of the lesions was estimated/measured in situ by comparison of the longest lesion dimension with a stiff open 20 mm resection snare (Boston Scientific Captivator). Patients were excluded when presenting with severe comorbidities (American Society of Anesthesiologists 3-4), coagulation disorders, inflammatory bowel disease, or when the study lesions appeared to be deeply invasive as a result of endoscopic (ulcerated, depressed, Paris type III excavated lesions) or histologic assessment (biopsy-proven invasive carcinoma), as well as on any other staging modalities such as endoscopic ultrasonography. Individuals with other malignant diseases were also excluded. As only treatment-naive lesions were included, those with previous attempts of resection or who had undergone previous radio-chemotherapy were excluded, the only exception being cold biopsy of the lesion.

Randomization process. Before randomization, all the lesions were measured in situ by visual comparison with an open 20-mm snare (with photo-documentation), and classified according to morphology.[14] After size confirmation, individuals were randomly assigned to 1 of the 2 submucosal injection groups (SIC-8000 or control solution) in a 1:1 ratio. The randomization list was computer-generated by CROSS Metrics, using the PLAN procedure of SAS version 9.3 (TS1M1) (SAS/STAT). Each individual was given an envelope specifying the treatment assignment. This was opened by the nurse or assistant designated to prepare the injectate. The specified injectate was then prepared out of sight of the investigator performing the EMR in order to maintain assignment blinding.

EMR. The EMR procedure was performed under sedation according to the standard of care of each site, using high-definition colonoscopy equipment and ancillary techniques. EMR was performed according to the sequential "injection and resection" technique as described previously.[11] Before resection, syringes were pre-filled with either SIC-8000 (ready-to-use) or the control solution