SIC-8000 versus hetastarch as a submucosal injection fluid for endoscopic mucosal resection: a randomized controlled trial

Douglas K. Rex, MD[1]
Heather M. Broadley, MS [1]
Jonathan R. Garcia, BS[1]
Rachel E. Lahr, BS[1]
Margaret E. MacPhail, MS[1]
Connor D. McWhinney, BS[1]
Meghan P. Searight, BS[1]
Andrew W. Sullivan, BS[1]
Neal Mahajan[1]
George J. Eckert, MAS[2]
Krishna C. Vemulapalli, MBBS, MPH[1]

[1] Division of Gastroenterology/Hepatology, Department of Medicine, Indiana University School of Medicine
[2] Department of Biostatistics, Indiana University School of Medicine

Address correspondence and reprint requests to:
Douglas K. Rex, MD
4100
Indiana University Hospital
550 North University Boulevard
Indianapolis, IN 46202
Email: drex@iu.edu
Phone: (317) 944-5394
Fax: (317) 948-7057

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Abstract

Background and Aims:

Viscous solutions provide a superior submucosal cushion for endoscopic mucosal resection (EMR). SIC-8000 (Eleview, Aries Pharmaceuticals, La Jolla, Calif) is a commercially available FDA approved solution but hetastarch is also advocated. We performed a randomized trial comparing SIC-8000 to hetastarch as submucosal injection agents for colorectal EMR.

Methods:

This was a single-center double-blinded randomized controlled trial performed at a tertiary referral center. Patients were referred to our center with flat or sessile lesions measuring ≥15 mm in size. The primary outcome measures were the Sydney Resection Quotient (SRQ) and the rate of en bloc resections. Secondary outcomes were total volume needed for a sufficient lift, number of resected pieces, and adverse events.

Results:

There were 158 patients with 159 adenomas (84 SIC-8000 and 75 hetastarch) and 57 serrated lesions (30 SIC-8000 and 27 hetastarch). SRQ was significantly better in the SIC-8000 group compared with hetastarch group (9.3 vs 8.1, p=0.001). There was no difference in the proportion of lesions with en bloc resections. The total volume of injectate was significantly lower with SIC-8000 (14.8 mL vs 20.6 mL, p=0.038)

Conclusions:

SIC-8000 is superior to hetastarch for use during EMR in terms of SRQ and total volume needed, although the absolute differences were small.

Introduction

Endoscopic mucosal resection (EMR) as traditionally performed involves submucosal injection of fluid underneath a sessile or flat lesion followed by snare resection. Saline solution has been a commonly used injection fluid for EMR. However, more viscous solutions provide a superior submucosal cushion[1, 2]. For example, in a randomized controlled trial succinylated gelatin was superior to saline solution[3]. Hetastarch has some properties that are similar to succinylated gelatin, is commonly used in the United States for EMR and in one trial produced longer submucosal elevation than saline solution[4]. Recently, 2 commercial submucosal injection fluids have been approved as devices by the U.S. Food and Drug Administration. The first was SIC-8000 (Eleview, Aries Pharmaceuticals, Inc, San Diego, Calif), which was approved on the basis of a randomized controlled trial showing superiority compared with saline solution[5]. SIC-8000 includes methylene blue as a contrast agent. ORIS gel (Boston Scientific, Marlborough, Mass) has been approved as a submucosal injection fluid with reference to SIC-8000 as a predicate device.

At our center, we have generally used hetastarch as our submucosal injection fluid for EMR. Because hetastarch is less expensive than SIC-8000, we performed a randomized controlled clinical trial to compare hetastarch with SIC-8000. Our goal was to determine whether any advantages associated with SIC-8000 would justify its increased cost compared with hetastarch.

Methods

We performed a randomized controlled clinical trial comparing SIC-8000 to hetastarch. Hetastarch was purchased as Voluven (Fresenius Kabi Norge AS, Halden, Norway) and

methylene blue was added in a concentration to match SIC-8000, so as to blind the endoscopist and the technician to the material being injected. Both SIC-8000 and hetastarch were prepared in a separate area so as to keep the endoscopist and the technician blinded to the fluid, and they were delivered to the technician in identical syringes. SIC-8000 was obtained directly from the manufacturer. No epinephrine was added to either the SIC-8000 or the hetastarch. No external support was received for the study.

The study was approved by the Institutional Review Board at Indiana University on September 18, 2017. Patients were recruited between October 27, 2017 and December 6, 2018. The study was registered as NCT03350217 on October 19, 2017. Eligible patients were referred to the lead author (D.K.R.) for resection of lesions that were reported to be ≥15 mm in size. During colonoscopy, the actual maximum diameter of the lesion was measured using a Captivator II (Boston Scientific, Marlborough, Mass) snare of known diameter (either 15 or 20 mm in size). Lesions were required to be either sessile or flat in shape and ≥15 mm in size to be eligible for the study. Lesions were excluded if they were pedunculated or considered sufficiently scarred from one or more previous attempts at resection that the scarring process appeared likely to restrict lifting and to dominate the resection approach. The decision to include or exclude the lesion based on measurement and extent of scarring was made before the randomization was performed.

We powered the study for all of the study lesions to be adenomas, and to be removed using electrocautery. All colonoscopies were performed using high-definition Olympus (Olympus Corporation, Center Valley, Pa) and in nearly all cases the instruments were adult colonoscopes.

All resections were performed by DKR. Lesions were assessed using the Narrow Band Imaging International Colorectal Endoscopic classification[6] or NICE classification and were accurately recognized as adenomas vs sessile serrated polyps in all cases. Serrated lesions in the study were generally removed by cold EMR[7], other than a few very large serrated lesions early in the study that were removed by EMR using electrocautery. Serrated lesions were also randomized, but were not part of the primary comparison. The rationale for excluding serrated lesions is that the use of the small dedicated cold snares used to perform the cold EMR[7] negated meaningful use of the Sydney Resection Quotient (SRQ) as a primary endpoint. In addition, the lead investigator holds the anecdotal opinion that perhaps because they have minimal to no submucosal fibrosis, serrated lesions have a tendency to lift well regardless of the injection fluid used. Thus, they are inferior to adenomas as a test of injection fluids for EMR. The serrated lesions were randomized as an exploratory exercise.

Lesions with endoscopic changes of deep submucosal invasion (NICE classification 3) were excluded from the study. Adenomas were removed after submucosal injection using snares of 15 or 20 mm diameter and occasionally 10 mm. In general, resections were begun with 15 to 20 mm snares, and 10 mm snares were used as needed to remove small pieces remaining near the end of resection. Polyps were transected using Erbe (Erlangen, Germany) Endocut Q on the 2-1-4 setting. Avulsion was performed if needed using Boston Scientific Radial Jaw 4 hot forceps on the Endocut I 3-1-3 setting.

The primary endpoint for the study was the SRQ, defined as the size of the polyp in millimeters divided by the number of pieces resected. The second primary endpoint was the number of

subjects with en bloc resection of lesions. Secondary endpoints included the total volume of fluid injected, the volume injected for the initial lift, the number of reinjections, the number of resected pieces, the duration of the resection without the performance of clipping, the duration of the resection with clipping, the occurrence of adverse events, and the subjective measures of mound concentration, height, and duration each rated as excellent, satisfactory or poor. In general, if the injected fluid formed a concentrated submucosal mound with minimum lateral spread and lasted the duration of the resection it was considered excellent. At the other end of the spectrum, poor was considered little vertical lift with rapid lateral spread of fluid and dissipation of the fluid mound. In addition, the technician was asked to rate the ease of injection as very easy, easy, difficult or very difficult. All injections were made through a 23-gauge needle. Both the endoscopist and the technician were kept blinded to the fluid being used.

Adenoma resection, which was entirely performed using EMR with electrocautery, was followed by clip closure of the EMR site if the defect size, location and accessibility allowed closure. Serrated lesions, which were largely removed by cold EMR, were not clip closed after resection unless electrocautery was used. For both types of lesions, methylene blue served to stain the submucosa and allow identification of any muscle injury, and highlighted the perimeter of the lesion, which was considered particularly valuable for serrated lesions.

Patients were contacted by telephone 30 days after EMR to ascertain adverse events. Delayed hemorrhage was defined as after release from the endoscopy suite that resulted in a visit to an emergency department, or hospitalization, or transfusions or repeat colonoscopy. Postcoagulation syndrome was defined as abdominal pain necessitating a visit to a provider that was associated with abdominal tenderness with or without fever or elevated white blood cell count.

Statistical analysis and sample size calculations:

We aimed to enroll at least 150 adenomas in the study. Efficacy and safety of SIC-8000 injectate has only been reviewed in one previous study. Therefore, the planned sample size was not calculated using a statistical power analysis but was regarded as sufficient to repeat the objectives of the COSMO study [5] and satisfy the exploratory purposes of the present study. Patients were randomized using a computer generated sequence (simple randomization, 1:1 ratio), which was sealed until the lesion was deemed eligible for enrollment. Comparison between the 2 groups for differences in patient level data was made using Wilcoxon rank sum tests and chi-squared tests for contiguous and categorical variables, respectively. For polyp level data, to account for correlation among multiple polyps per patient, comparisons were made using generalized estimating equation (GEE) models for continuous, ordinal, and binary outcomes. Serrated lesions were randomized as an exploratory analysis but not included in the primary analysis. A 5% significance level was used for all tests.

If more than one lesion was eligible for inclusion in the study from a patient, all lesions were randomized to the same submucosal injection fluid used for the first lesion found. This was done to facilitate correct assignment of adverse events.

No specific number of serrated lesions was targeted. The number of serrated lesions in the study reflects the number of eligible serrated lesions encountered in subjects who gave consent to participate from the onset of the study until the targeted number of adenomas was enrolled into the study.

Results

Table 1 shows a comparison of demographic features, instruments used, and lesion size and location for the primary study set of adenomas, and separately for the serrated lesions. There were no differences in demographic features, bowel preparation quality scores, type or size of lesions between groups. There were 84 adenomas and 30 serrated lesions (mean size 26 mm and 19 mm, respectively) randomized to injection with SIC-8000. The hetastarch group had 75 adenomas and 27 serrated lesions (mean size 29 mm and 23 mm, respectively).

Tables 2 and 3 show the primary and secondary endpoints for the adenomas, as well as for the serrated lesions. As noted above, because the serrated lesions were almost entirely (86%) removed using cold EMR using a dedicated cold snare, the SRQ was not evaluated for those patients. For adenomas, the SRQ was higher (superior) with SIC-8000 compared with hetastarch, 9.3(6.2) versus 8.1(4.9); $p = 0.001$. The total injection volume with SIC-8000 was lower at 14.8(13.1) mL versus 20.6(20.9) ml with SIC-8000; $p = 0.038$. There was a trend toward the number of reinjections of fluid and the number of resected pieces each being lower with SIC-8000 (Table 2). Total resection time was numerically lower with SIC-8000 compared with hetastarch, but this trend also did not reach significance (Tables 2 and 3). There were no differences in the measures of mound height, quality or duration made subjectively by the endoscopist for SIC-8000 versus hetastarch.

Seventy-eight of 84 adenomas (93%) in the SIC-8000 arm were prophylactically clip closed compared with 64 of 75 adenomas (86%) in the hetastarch arm; p = 0.125. Only the small group of serrated lesions removed by electrocautery were treated by clipping. The cold EMR sites after removal of most serrated lesions were not treated with prophylactic clipping. Intraprocedural bleeding was similar between the 2 study arms (Tables 2 and 3). There were 2 delayed bleeds, one in each arm. Both lesions were removed using electrocautery, and both patients went to the emergency department but neither was hospitalized or underwent colonoscopy or transfusion. There were no perforations in either arm. There was one type 3 deep mural injury in the sigmoid colon in the SIC-8000 arm, treated by clipping. The patient did not require hospitalization or surgery and had an uneventful 30-day follow-up.

Discussion

Submucosal injection fluids that are commercially available for use in the United States, including SIC-8000 and ORISE, are expensive compared with agents such as saline solution and hetastarch. In this double-blinded, randomized controlled trial, we found that SIC-8000, which has previously been shown to be superior to saline solution as a submucosal injection fluid[5] was also superior to hetastarch. There were significant differences between SIC-8000 and hetastarch in the SRQ, and in the total amount of fluid injected. There were non-statistically significant trends toward superiority of SIC-8000 in the number of reinjections required, fewer numbers of resected pieces, and the resection duration. Thus, in this single investigator single-center trial, SIC-8000, administered in a blinded trial, was superior to hetastarch as a submucosal injection fluid for endoscopic mucosal resection.

Although differences between SIC-8000 and hetastarch were statistically significant, readers could reasonably ask whether the differences are clinically significant and justify the cost associated with SIC-8000. Currently the cost differences between SIC-8000 and hetastarch are reduced because both indigo carmine and methylene blue have become more expensive. Because one of these agents is typically added to hetastarch before injection, the cost of those agents is added to the cost of hetastarch. In contrast, SIC-8000 comes from the manufacturer with methylene blue added.

Strengths of this study include the blinded, randomized design. Limitations include the single-center single endoscopist design, which could limit the generalizability. A multicenter comparison of these agents would be appropriate.

In summary, in a prospective double-blind, randomized controlled trial, we demonstrated that SIC-8000 was superior to hetastarch as a submucosal injection agent for colorectal EMR. Additional randomized controlled trials comparing available submucosal injection agents are needed.

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Figure legend:

Figure 1. Patient enrollment in the study.

Table 1. Patient and procedure characteristics in both groups

	SIC-8000	Hetastarch	*P* value
Adenoma subset			
Number of patients (number of lesions)	**66 (84)**	**63 (75)**	**-**
Age, years (SD)	67.6 (8.3)	67.2 (9.4)	0.906
Male gender, n (%)	33 (50)	34 (54)	0.652
Boston Bowel Preparation Score, mean (SD)	8.7 (0.7)	8.5 (1.1)	0.761
No fibrosis, n (%)	52 (62)	48 (64)	0.914
No prior resection, n (%)	57 (68)	49 (65)	0.866
Size of the lesion, mean (SD)	25.6 (11.4)	28.3 (14.5)	0.198
Location of the lesion, n (%) Right colon Transverse colon Left colon	 57 (68) 12 (14) 15 (18)	 54 (72) 5 (7) 16 (21)	0.287
Serrated subset			
Number of patients (number of lesions)	**16 (30)**	**19 (27)**	**-**
Age, years (SD)	64.8 (8.3)	60.8 (11.5)	0.361
Male gender, n (%)	4 (25)	9 (47)	0.172
Boston Bowel Preparation Score	8.4 (1.02)	8.8 (1)	0.057
No fibrosis, n (%)	12 (86)	16 (89)	0.788
No prior resection, n (%)	11 (85)	18 (95)	0.335
Size of the lesion, mean (SD)	18.9 (6.3)	22.5 (15.4)	0.247
Location of the lesion, n (%) Right colon segment Transverse colon Left colon segment	 17 (57) 12 (40) 1 (3)	 15 (56) 5 (19) 7 (26)	0.027†

n, number of lesions; SD, standard deviation; †, Fisher exact

Table 2. Outcome measures for adenoma subset

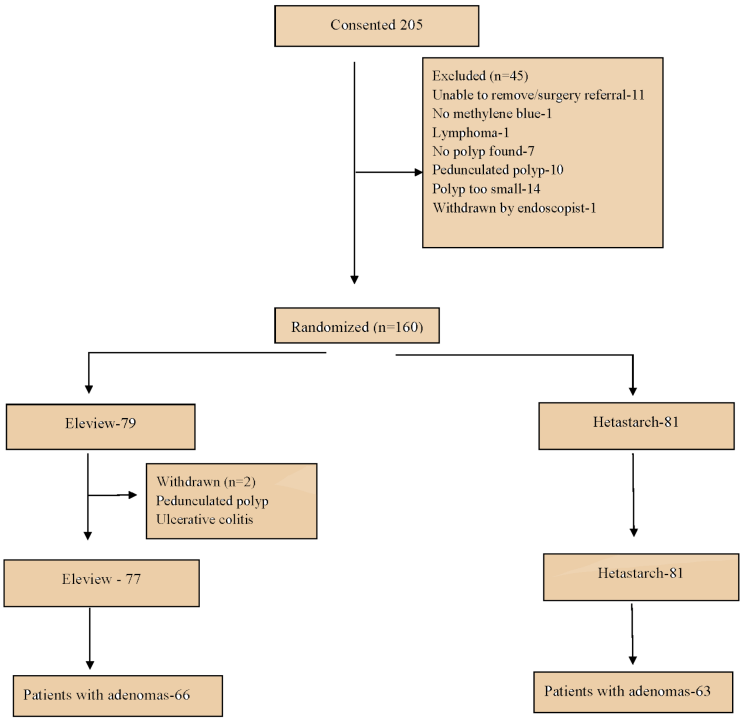
	SIC-8000	Hetastarch	*P* value
Number of patients (number of lesions)	**66 (84)**	**63 (75)**	-
Sydney Resection Quotient, mean (SD)	9.3 (6.2)	8.1 (4.9)	0.001
En bloc resection, n (%)	66 (79)	61 (81)	0.515
Injectate used for initial lift, mean (SD)	10.4 (5.4)	11.6 (7)	0.28
Total injectate used, mean (SD)	14.8 (13.1)	20.6 (20.9)	0.038
Number of reinjections, mean (SD)	0.61 (1.3)	1.01 (1.6)	0.074
Number of resected pieces, mean (SD)	4.5 (5)	5.5 (5.3)	0.12
Resection duration without clipping (minutes), mean (SD)	14.8 (11.4)	16.02(13.9)	0.292
Resection duration with clipping (minutes), mean (SD)	17.3 (12.1)	19.4 (16.2)	0.235
Mound concentration diameter			0.911
Excellent	43 (51)	38 (51)	
Sufficient	34 (40	30 (40)	
Inadequate	7 (8)	7 (9)	
Mound concentration height			0.84
Excellent	45 (54)	41 (55)	
Sufficient	31 (37)	28 (37)	
Inadequate	11 (13)	6 (8)	
Mound duration			0.406
Excellent	41 (49)	40 (53)	
Sufficient	31 (37)	31 (41)	
Inadequate	11 (13)	4 (5)	
Ease of injection			0.686
Very easy	39 (47)	33 (45)	
Easy	43 (52)	38 (51)	
Difficult	1 (1)	3 (4)	
Very difficult	-	-	
Adverse events			
Intraprocedural bleeding, n (%)	18 (22)	12 (16)	0.571
Delayed bleeding, n (%)	1 (1.2)	-	1†
Postprocedure abdominal pain, n (%)	-	1 (1.3)	0.488†

n, number of lesions; SD, standard deviation; †, Fisher exact

Table 3. Outcome measures for serrated lesion subset

	SIC-8000	Hetastarch	*P* value
Number of patients (number of lesions)	**16 (30)**	**19 (27)**	-
Sydney Resection Quotient, mean (SD)	12.3 (4.0)	11.1 (6.5)	0.702
En bloc resection, n (%)	2 (7)	2 (7)	0.915
Injectate used for initial lift, mean (SD)	7.1 (4.9)	8.7 (4.3)	0.123
Total injectate used, mean (SD)	7.8 (5.7)	10.7 (8.8)	0.129
Number of reinjections, mean (SD)	0.1 (0.31)	0.3 (0.9)	0.316
Number of resected pieces, mean (SD)	7 (5.9)	8.2 (7)	0.413
Resection duration without clipping (minutes), mean (SD)	5.9 (4.2)	7.1 (9.1)	0.518
Mound concentration diameter			0.586
Excellent	21 (70)	16 (59)	
Sufficient	7 (23)	11 (41)	
Inadequate	2 (7)	-	
Mound concentration height			0.603
Excellent	22 (73)	17 (63)	
Sufficient	6 (20)	10 (37)	
Inadequate	2 (7)	-	
Mound duration			0.993
Excellent	19 (66)	18 (67)	
Sufficient	10 (34)	8 (30)	
Inadequate	-	1 (4)	
Ease of injection			0.634
Very easy	13 (43)	13 (48)	
Easy	15 (50)	14 (52)	
Difficult	2 (7)	-	
Very difficult	-	-	
Adverse events			
Intraprocedural bleeding, n (%)	-	2 (7)	0.181
Delayed bleeding, n (%)	-	1 (5.3)	1†
Postprocedure abdominal pain, n (%)	-	-	

n, number of lesions; SD, standard deviation; †, Fisher exact



Acronyms and abbreviations

Endoscopic mucosal resection – EMR

Millimeter – mm

Sydney Resection Quotient – SRQ

Douglas K. Rex – DKR

Generalized estimating equation – GEE

Milliliters – ml

Standard deviation – SD