Polidocanol injection decreases the bleeding rate after colon polypectomy: a propensity score analysis

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Background: EMR is the standard of care for the resection of large polyps.

Objective: To compare the efficacy and safety profile of submucosal polidocanol injection with epinephrine–saline solution injection for colon polypectomy with a diathermic snare.

Design: After 1-to-1 propensity score caliper matching, comparison of submucosal epinephrine injection was performed with polidocanol injection.

Setting: Endoscopic suite at the University of Foggia between 2005 and 2014.

Patients: Of 711 patients who underwent endoscopic resection of colon sessile polyps 20 mm or larger, 612 were analyzed after matching.

Interventions: Submucosal epinephrine injection in 306 patients and polidocanol injection in 306 patients.

Main Outcome Measurements: Univariate and multivariate logistic regression models aimed at identifying independent predictors of postpolypectomy bleeding (PPB).

Results: The 2 groups presented similar baseline clinical parameters and lesion characteristics. All patients had a single polyp 20 mm or larger; the median size was 32 mm (interquartile range [IQR], 25-38) in the polidocanol group and 32 (IQR, 24-38) in the epinephrine group ($P = .7$). Polidocanol was more effective in preventing both immediate and delayed PPB ($P < .001$ and $P = .003$, respectively), and its efficacy was confirmed in almost all of the subgroups, regardless of polyp size and histology. Postprocedure perforation was observed in 2 patients (0.3%), both in the epinephrine group ($P = .49$). The 2 groups did not differ in the number of snare resections of lesions or the procedure duration ($P = .24$ and .6, respectively).

Limitations: Absence of randomization.

Conclusion: The submucosal injection of polidocanol for colon EMR is effective and significantly lowers the PPB rate. (Gastrointest Endosc 2015;82:350-8.)

A number of studies have shown that removal of adenomatous polyps is associated with a reduction in the incidence of colorectal cancer.[1,2] In this setting, endoscopic polypectomy is now an established procedure for the resection of large pedunculated or sessile colorectal polyps.

EMR is frequently used for polyps larger than 20 mm in diameter.[3,4] The technique involves the injection of fluid into the submucosal space to expand it, rendering polypectomy easier and safer ("inject-and-cut" technique).[4]

The major drawbacks of EMR are postpolypectomy adverse events, such as hemorrhaging (0.3%-6.1%, but this can be as high as 24% in large polyps) and perforation (0.08%-0.69%) as well as inadequate polypectomy (defined as nonradical removal of the polyp, 6.9%).[5-7] Of these,

Abbreviations: IQR, interquartile range; PPB, postpolypectomy bleeding.

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postpolypectomy bleeding (PPB) is the most frequent, and its prevention is a challenge for the endoscopist.

The submucosal epinephrine–saline solution injection is commonly used to reduce postpolypectomy adverse events, minimize mucosal bleeding caused by its hemostatic effect, and enhance complete resection, although the real efficacy of such a procedure is still a matter of debate.[8]

Other substances (such as hyaluronic acid, succinylated gelatin, and other viscoelastic substances) have been introduced in conventional polypectomies and extended EMRs, but evidence of their superiority compared with saline solution injection in terms of safety and efficacy is still unclear.[9-12]

To date, there are no published data on the comparison of sclerosing agents and epinephrine–saline solution injection in colon polypectomy. The aim of this study is to compare the efficacy and safety profile of submucosal polidocanol injection with epinephrine–saline solution injection for endoscopic resection of large (ie, $\geq$20 mm) sessile colon polyps.

The primary endpoint was the prevention of PPB. Secondary objectives were the prevention of postprocedural perforation, en bloc resection rate, procedural time, successful single-session complete removal of the lesion, and recurrent/residual adenoma rate at 3 months. The number of snare resections per lesion, the number of injections, and the volume of injected solution needed were also assessed.

METHODS

Patients

From a prospectively collected database, data regarding 711 consecutive patients who underwent endoscopic resection of laterally spreading tumors or sessile lesions 20 mm or larger at our institution between January 2005 and July 2014 were reviewed. Institutional review board approval for this retrospective report was obtained.

The following exclusion criteria were used: lesion diameter less than 20 mm, patients on antiaggregant or anticoagulant therapy, the presence of diseases impairing normal blood clotting, and age younger than 18 years.

All colonoscopies were performed by 2 board-certified gastroenterologists (each with 20 years of experience: M.d.M., N.M.) at the University of Foggia.

The study population included 2 groups of patients: 331 who underwent polypectomy with submucosal epinephrine injection before November 2008 and 380 with polidocanol injection from December 2008 onward. Such a comparison was favored by the monocentricity of the experience comparing 2 different techniques for the endoscopic removal of colorectal polyps and is a homogeneous approach to the management of such patients. In fact, the sole difference among groups was determined by the endoscopic technique used, with the treatment strategy and the surveillance protocol equally applied throughout the study period.

Written informed consent was obtained from all patients before the procedure.

Demographic and clinical parameters of the 2 groups were similar (Table 1).

Resection technique

All colonoscopies were performed with an Olympus CF-230 or CF-240 video colonoscope (Olympus, Tokyo, Japan) after cleansing the bowel by using a polyethylene glycol–electrolyte solution (Selg-Esse; Promefarm, Bergamo, Italy).

All procedures were performed with patients under deep sedation with propofol (Diprivan; AstraZeneca, London, UK) and monitored by a board-certified anesthesiologist.

The first step of the procedure was the submucosal injection at 1 edge of the lesion with a disposable 25-gauge, 4-mm long injection needle (Innoflex; Innovamedica, Milan, Italy) to create a submucosal cushion for safety purposes and better resection. The injection solution contained 9 mL of saline solution with 1 mL of epinephrine 1:10.000 (Adrenalina; SALF, Bergamo, Italy) and 10 mL of polidocanol 1% (Atossisclerol; Kreusseler Pharma, Wiesbaden, Germany) in the 2 groups, respectively. The volume injected varied according to the size of the lesion. Although the assistant injected the solution, the endoscopist tangentially stabbed the colonic wall.

After the submucosal injection, a disposable electrosurgical snare (Rotatable Snare; Boston Scientific, Natick, Mass) was placed over the elevated tissue and gently pressed against the mucosa, while closing until resistance was felt. The safety of the resection after snare closure was determined by the assessment of the ensnared tissue mobility relative to the colonic wall, the degree of closure of the snare handle, and the speed of transection of the ensnared tissue. The polyp was then cut by using the ERBE electrosurgical unit (VIO 300; ERBE, Tubingen, Germany) set to Endocut Q, Effect 3, delivering a cut duration of 2 ms and a cut interval of 1200 ms. No other ablative techniques in addition to snare resection were used in either of the treatment groups.

En bloc resection was performed when feasible. However, in cases in which the lesion was too large for en bloc removal, piecemeal resection was undertaken. Removal of the lesion was considered complete if no residual adenomatous tissue was noted after completion of the polypectomy.

All resected specimens were fixed and embedded in paraffin and retrieved for histopathological analysis by using a polyp retrieval net (Roth Net; US Endoscopy, Mentor, Ohio) placed after stretching on a cork plate.

Depending on the complexity of the procedure and comorbidity, patients were either hospitalized for observation for 24 hours or underwent the procedure as an

TABLE 1. Baseline patient characteristics of study population after propensity score matching

Variable	All patients (N = 612)	Polidocanol (n = 306)	Epinephrine (n = 306)	*P* value	Effect size
Age, y	56 (53-66)	56 (53-66)	56 (53-66)	.9	0.01
Sex, no. (%)					
Male	364 (59.5)	183 (59.8)	181 (59.2)	.7	0.01
Female	248 (40.5)	123 (40.2)	125 (40.8)		0.01
BMI	25.5 (21-28)	25 (21-28)	25 (21-28)	1.0	0.01
ASA score	2 (1-3)	2 (1-3)	2 (1-3)	.9	0.01
Lesion size, mm	32 (26-35)	32 (25-38)	32 (24-38)	.7	0.003
No. of lesions	1 (1-1)	1 (1-1)	1 (1-1)	1.0	0.00
Morphology				.8	
Sessile (Paris 1s)	280 (45.8)	138 (45.1)	142 (46.3)		0.007
LST (Paris 0-IIa)	332 (54.2)	168 (54.9)	164 (53.7)		0.04
Location				.8	
Ascending-cecum	294 (48)	148 (48.3)	146 (47.8)		0.003
Transverse	110 (17.9)	54 (17.6)	56 (18.1)		0.002
Descending	132 (21.6)	66 (21.6)	66 (21.6)		0.001
Sigmoid-rectum	76 (12.5)	38 (12.5)	38 (12.5)		0.001
Histology				.9	
Tubular	185 (30.2)	94 (30.6)	91 (29.7)		0.004
Tubulovillous	278 (45.5)	136 (44.7)	142 (46.4)		0.02
Villous	78 (12.7)	40 (13)	38 (12.5)		0.003
Serrated	71 (11.6)	36 (11.7)	35 (11.4)		0.005

Continuous variables are reported as median values and interquartile range. Comparisons were performed with the Wilcoxon signed rank test for continuous variables and McNemar test for categorical ones. Effect size <0.1 indicates very small differences.
BMI, Body mass index; *ASA*, American Society of Anesthesiologists; *LST*, laterally spreading tumor.

outpatient. In both cases, the monitoring protocol was the same.

Follow-up

According to protocol, a surveillance colonoscopy was scheduled to be performed after 3 years in cases of en bloc resection and after 3 months in cases of piecemeal resection.[13]

All clinical and safety outcomes were assessed blinded to the injection solution used.

Adverse event rates (such as bleeding and perforation) were evaluated during the procedure and, to detect delayed bleeding, at 24 hours and 7, 10, and 14 days by means of patient visits to the hospital or telephone calls.

Bleeding was defined as early (during the procedure) or delayed (overt hemorrhage per rectum at least 1 hour after the procedure).[14] Bleeding during the procedure was defined as being significant if it required interruption of the operation to perform homeostasis or thermal treatment by using coagulation with snare tip or application of clips (Resolution Clip; Boston Scientific).[12]

Other clinical parameters, such as abdominal pain, were recorded immediately after the procedure and at discharge and were classified according to Common Terminology Criteria for Adverse Events 4.0.[15]

Statistical analysis

Categorical variables were reported as the number of cases, and percentage and differences between groups were compared by using the χ^2 and McNemar tests before and after matching, respectively.

Continuous variables were expressed as the median and IQR (1st-3rd quartiles), and differences between groups were explored by the Mann-Whitney and Wilcoxon signed rank tests before and after matching, respectively. All analyses were 2 tailed, and the threshold of significance was set at $P < .05$.

To overcome biases owing to the different distribution of covariates among patients who underwent polypectomy with polidocanol injection and those who underwent epinephrine injection, a 1-to-1 match was created by using propensity score analysis.

The propensity score is the probability of each individual patient being assigned to a particular condition in a study given a set of known covariates.[16]

A multivariate logistic regression model was built to predict the probability of each patient being assigned to the 2 groups on the basis of covariates that are known to affect postoperative outcomes, namely, age, sex, body mass index, American Society of Anesthesiology score, and lesion morphology, location and histology. The predictive values were then used to obtain a 1-to-1 match by using the nearest neighbor matching within a specified caliper distance, which selects for matching an untreated subject whose propensity score is closest to that of the treated subject (nearest neighbor matching approach) with the further restriction that the absolute difference in the propensity scores of matched subjects must be below some prespecified threshold (the caliper distance).[17] Thus, patients for whom the propensity score could not be matched because of a greater caliper distance were excluded from further analysis. As suggested by Austin,[17] a caliper with a width equal to 0.2 of the standard deviation of the logit of the propensity score was used, as this value has been found to minimize the mean square error of the estimated treatment effect.

Effect size was also calculated for each covariate and expressed as an absolute number after logarithmic transformation of variables. Effect size is a measure that is independent of the sample size and can give a more robust estimation of a difference in means or proportions: a value of <0.1 in propensity score analyses means that the 2 groups are well matched for covariates.[16,18]

Finally, the univariate and multivariate logistic regression models were applied in the matched samples to identify the independent predictors of immediate and delayed bleeding after the procedure. The results were expressed as odds ratio and 95% confidence interval.

The statistical analysis was performed by using R Statistical Software 3.0.2 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

The baseline characteristics of the whole study population of 711 patients who underwent colon polypectomy are reported in Supplementary Table 1, available online at www.giejournal.org.

A total of 380 patients underwent polypectomy by means of polidocanol injection and 331 by epinephrine injection. No significant differences in terms of baseline patient characteristics were reported.

After 1-to-1 propensity score matching, 612 patients were selected for comparison: 306 underwent polidocanol injection (group 1) and an equal number underwent epinephrine injection (group 2). The characteristics of the 612 propensity score–matched patients are reported in Table 1.

The median age was 56 years (IQR, 53-66) in both groups ($P = .9$). Most patients were male (59.5%, with no difference between groups), and the median body mass index and American Society of Anesthesiologists score were 25 (IQR, 21-28) and 2 (IQR, 1-3), respectively, in both study groups.

No patient in the study population had more than 1 lesion larger than 20 mm.

The median lesion size detected was 32 mm (IQR, 25-38) in the polidocanol group and 32 mm (IQR, 24-38) in the epinephrine group ($P = .7$).

Polyps were sessile in 45.8% and laterally spreading tumors in 54.2%, and almost half were located in the ascending colon-cecum (48%), with no differences between study groups.

Details of propensity score matching are shown in Supplementary Figures 1A and 1B, available online at www.giejournal.org.

Efficacy

Table 2 reports the detailed description of efficacy outcomes.

The median number of snare resections per lesion was 2 (IQR, 2-4) in the polidocanol group and 3 (IQR, 2-5) in the epinephrine group ($P = .24$). The number of injections and volume of solution injected were 1.5 (IQR, 1-3) and 16.5 mL (IQR, 10-28 mL) in the polidocanol group and 2 (IQR, 1-3) and 20 mL (IQR, 13-27 mL) in the epinephrine group ($P = .13$ and .36, respectively).

En bloc resection was feasible in 37 of 306 (12%) and 43 of 306 (14%) in the 2 cohorts, respectively ($P = .54$).

The procedural time was similar in the 2 groups, with a median of 17 minutes (IQR, 16-18) in the polidocanol group and 19 (IQR, 16-21) in the epinephrine group ($P = .6$).

Of the 512 patients who underwent the 3-month follow-up colonoscopy, in 13 of 259 patients (5%) in the polidocanol group and 18 of 253 patients (7.1%) in the epinephrine group, recurrent/residual adenoma was present ($P = .35$).

Successful single-session complete removal of the lesion was achieved in 94.3% (577/612) of patients: 282 of 306 (92.1%) in the polidocanol group and 295 of 306 (96.4%) in the epinephrine group ($P = .15$) (Fig. 1). When complete resection was not feasible in 1 session, another polypectomy was performed in 28 patients; 7 patients underwent surgery.

All available specimens were deemed adequate for histologic evaluation. Histologic evaluation found conventional adenomas in 541 specimens (88.4%), whereas 71 (11.6%) were serrated lesions. There were 110 cases (18%) of high-grade dysplasia and 13 (2.1%) lesions with foci of invasive (submucosal) cancer without significant differences between study groups. Patients in whom invasive cancer was diagnosed underwent surgery.

Adverse events

Bleeding occurred in 11.1% (68/612) of patients, specifically, 5.2% (16/306) in the polidocanol group and 17% (52/306) in the epinephrine group ($P < .001$).

The immediate bleeding rate was 3.9% (12/306) in the polidocanol group and 10.7% (33/306) in the epinephrine group, respectively ($P = .001$), whereas the delayed bleeding rate was 1.3% (4/306) in the polidocanol group and 6.2% (19/306) in the epinephrine group ($P = .002$).

TABLE 2. Main outcomes and adverse events

	Polidocanol group (n = 306)	Epinephrine group (n = 306)	*P* value*
Efficacy outcomes			
No. of snare resections per lesion	2 (2-4)	3 (2-5)	.24
No. of injections	1.5 (1-3)	2 (1-3)	.13
Volume of injection, mL	16.5 (10-28)	20 (13-27)	.36
Procedure duration, min	17 (16-18)	19 (16-21)	.6
En bloc resection rate	37 (12)	43 (14)	.54
Successful single session complete removal	282 (92.1)	295 (96.4)	.15
Recurrent/residual adenoma at 3-month follow-up†	13 (5)	18 (7.1)	.35
Adverse events			
Immediate bleeding	12 (3.9)	33 (10.7)	**.001**
Delayed bleeding	4 (1.3)	19 (6.2)	**.002**
Deep resections containing muscularis propria	4 (1.3)	7 (2.28)	.54
Free perforations	0 (0)	2 (0.5)	.49

Variables are expressed as absolute number (percentage) or median (interquartile range) where appropriate.
*Calculated by means of Wilcoxon signed rank test in case of continuous variables or McNemar test for categorical variables. Bold indicates significant *P* value.
†Rates computed for 512 patients who underwent a 3-month follow-up colonoscopy (259 in the polidocanol group and 253 in the epinephrine group).

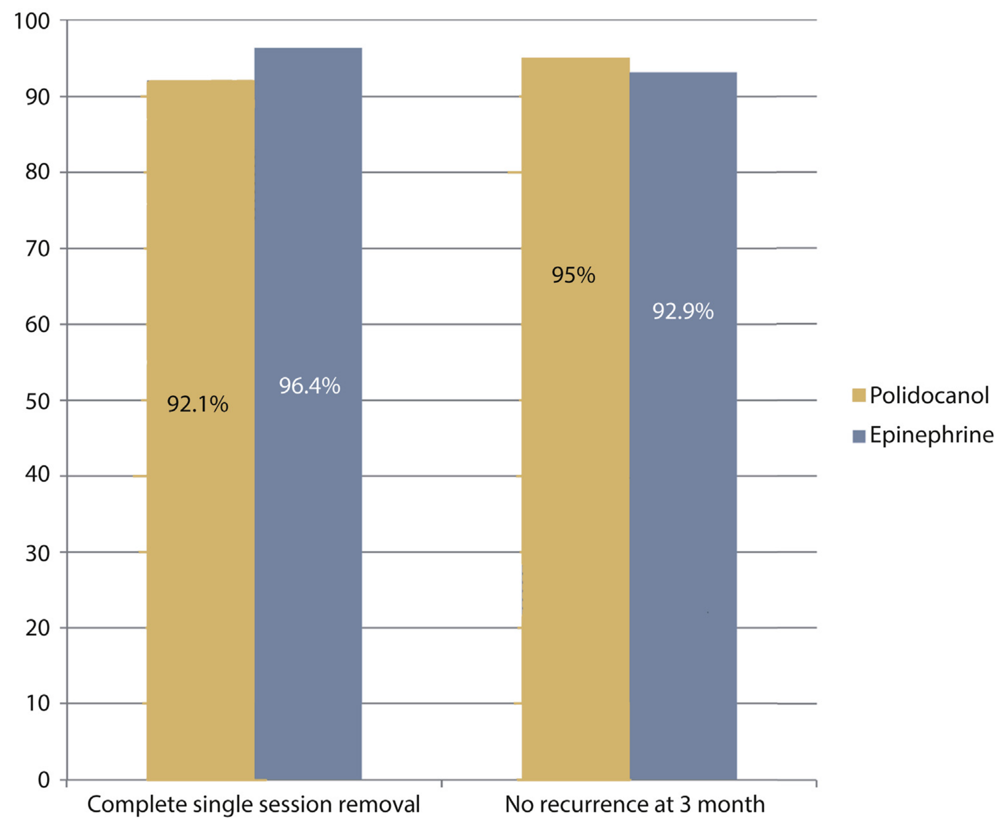

Figure 1. Comparison of complete single-session removal and 3-month recurrence/residual adenoma rates in the 2 study groups.

Immediate bleeding events were controlled by means of clip application in 9 of 12 patients (75%) in the polidocanol group and 26 of 33 (78.7%) in the epinephrine group ($P = 1.0$).

All patients with immediate bleeding events clinically presented with a small amount of blood, and none of the patients required hospitalization or transfusion; overall, no procedure-related deaths were reported.

TABLE 3. Univariate and multivariate analysis of risk factors for immediate postpolypectomy bleeding

Variables	Univariate analysis, odds ratio (95% CI)	*P* value	Multivariate analysis, odds ratio (95% CI)	*P* value*
Age, reference ≤55 y	1.01 (0.98-1.04)	.34		
Sex, reference female	1.02 (0.57-1.86)	.94		
BMI, reference ≤25	1.01 (0.94-1.08)	.65		
ASA score, reference 1	1.10 (0.75-1.62)	.60		
Size, reference ≤32 mm	2.95 (1.63-5.29)	**<.001**	4.13 (1.97-8.83)	**<.001**
Morphology, reference sessile	0.88 (0.71-1.12)	0.36		
Location, reference ascending cecum		**.02**		.11
Transverse colon	0.82 (0.33-1.11)		0.93 (0.44-1.35)	
Descending colon	0.74 (0.21-0.88)		0.84 (0.75-0.92)	
Sigmoid rectum	0.52 (0.35-0.83)		0.72 (0.43-0.79)	
Histology, reference tubular		.09		
Tubulovillous	1.39 (0.37-5.08)			
Villous	1.63 (0.48-4.21)			
Serrated	1.8 (0.75-5.6)			
Injection, reference epinephrine	0.32 (0.16-0.60)	**<.001**	0.25 (0.11-0.50)	**<.001**

CI, Confidence interval; *BMI*, body mass index; *ASA*, American Society of Anesthesiology.
*Bold indicates significant *P* value.

On univariate logistic regression, the polyp size, location, and solution used for the injection were significantly associated with immediate bleeding (Table 3). Multivariate analysis restricted these parameters to polyp size and the solution injected (Table 3). Subgroup analysis confirmed the significantly better safety profile in terms of immediate bleeding prevention of polidocanol injection in almost all of the cases (in only right colon lesions and tubular histology, statistical significance was not reached, [Fig. 2A]).

With regard to delayed bleeding, only the polyp size and the drug injected were significant parameters and were both confirmed on multivariate analysis (Table 4). Subgroup analysis confirmed the positive impact of polidocanol in preventing delayed bleeding regardless of the polyp size (Fig. 2B). No clip application was needed to control delayed bleeding events.

Mild (grade 1/2) abdominal pain was reported in 13% (40/306) of patients in the polidocanol group and 15% (46/306) in the epinephrine group ($P = .51$).

Free postprocedure perforation was observed in 2 (0.6%) patients in group 2 and none in group 1 ($P = .49$), and both patients underwent surgery. Deep resections containing muscularis propria were reported in 4 patients (1.3%) in group 1 and 7 (2.28%) in group 2 ($P = .54$), and all were treated by application of clips.

DISCUSSION

Bleeding is the most frequent adverse event of endoscopic polypectomy, especially in large pedunculated or flat lesions, with a reported incidence ranging from 0.3% to 6.1%.[4] Bleeding can occur up to 3 weeks after polypectomy, although it most often occurs within the first 24 hours.

Submucosal epinephrine–saline solution injection has been shown to be an effective method for the complete endoscopic polypectomy, especially in flat or sessile lesions[19,20] and is widely used because of its simplicity, low cost, and wide availability. On the other hand, a number of studies have raised concerns about its efficacy in preventing postprocedural hemorrhage.[21,22] In fact, the mucosal elevation created by submucosal injection of epinephrine–saline solution persists only for a short period of time during the procedure.

Consequently, other substances (such as sodium hyaluronate, hydroxypropyl methycellulose, and glycerol) have been tested because they create a longer-lasting submucosal cushion because of their viscous properties, thus enabling lengthier procedures and increasing the rate of en bloc resection even for large lesions.[23,24] However, despite the promising results of the aforementioned reports, their efficacy in preventing PPB is still a matter of debate.

An ideal submucosal injection solution should be inexpensive, readily available, nontoxic, easy to prepare and to inject, and should provide a long-lasting submucosal cushion.[25]

Succinylated gelatin seems to fulfil these criteria, but a recent randomized, controlled trial, although showing a significant improvement in efficacy outcomes, failed to find decreased PPB and perforation rate after gelatin submucosal injection compared with saline solution.[12]

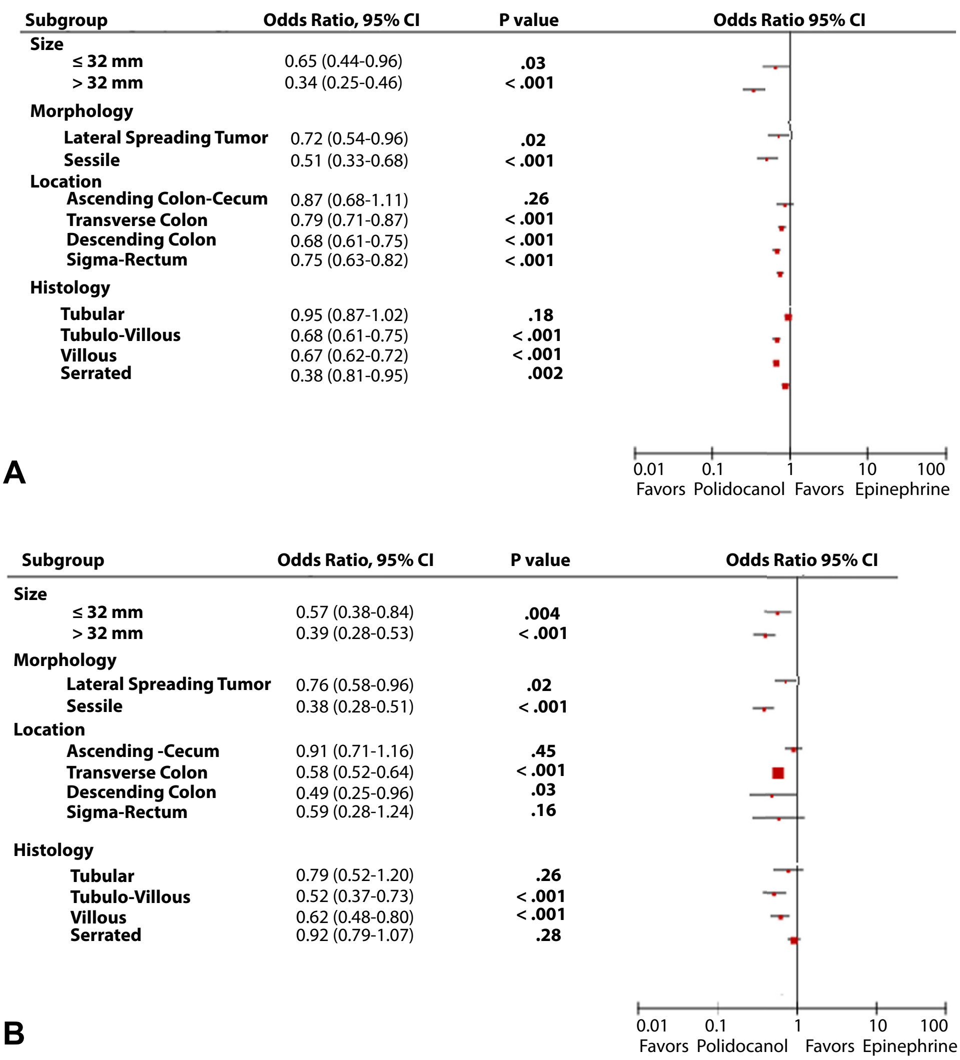

Figure 2. Subgroup analysis of immediate and delayed postpolypectomy bleeding. Polidocanol outperformed epinephrine in almost all subgroups and even when the statistical significance was not reached, a superiority trend emerged. **A**, Subgroup analysis of immediate postpolypectomy bleeding. **B,** Subgroup analysis of delayed postpolypectomy bleeding. *CI*, confidence interval; *OR*, odds ratio.

Polidocanol has been known as a sclerosing agent for several years and is widely used in the treatment of esophageal varices, hemangiomas, and hemorrhoids. At 1% concentration, polidocanol presents a procoagulative effect with no risk of necrosis of deeper mucosa layers.[26] Furthermore, because the polidocanol solution contains ethanol, its electrical conductivity is significantly lower than that of saline solution, and consequently the spread of thermal damage over mucosal layers is more limited.[26]

The theoretical harmful effects in causing inflammation and mucosal necrosis in the injection site have limited its use in polypectomy procedures so far; nevertheless, it has been confirmed that the extent of damage is highly dependent on both the concentration and the volume injected, with only concentrations of more than 2% being responsible for mucosal damage.[26]

Although these properties of polidocanol could theoretically be translated in the field of colon polypectomy, clinical data from large real-life experiences are still lacking.

To the best of our knowledge, our study is the first report on the efficacy of polidocanol injection in the endoscopic resection of colon polyps.

The single-center nature of this study favored the comparison, with both consecutive groups undergoing a homogeneous treatment strategy and the same monitoring and surveillance protocols during the study period and the sole difference among groups being determined by the endoscopic technique adopted. This is demonstrated by the balance in baseline clinical parameters and lesion characteristics between the 2 groups, with the absence of any patient selection bias. Moreover, a propensity score matching analysis was performed on the basis of covariates known to have an effect on postoperative outcomes. Thus, 2 perfectly balanced treatment groups were obtained (Table 1).

TABLE 4. Univariate and multivariate analysis of risk factors for delayed postpolypectomy bleeding

Variables	Univariate analysis, odds ratio (95% CI)	*P* value	Multivariate analysis, odds ratio (95% CI)	*P* value*
Age, reference ≤55 y	1.01 (0.97-1.06)	.43		
Sex, reference female	1.57 (0.66-4.14)	.32		
BMI, reference ≤25	1.00 (0.90-1.10)	.92		
ASA score, reference 1	0.67 (0.36-1.18)	.17		
Size, reference ≤32 mm	4.00 (1.72-9.54)	**.001**	4.13 (1.76-9.93)	**.001**
Morphology, reference sessile	0.92 (0.78-1.23)	.25		
Location, reference ascending cecum		.11		
Transverse colon	0.93 (0.42-1.70)			
Descending colon	0.82 (0.33-1.25)			
Sigmoid rectum	0.71 (0.30-1.37)			
Histology, reference tubular		.08		
Tubulovillous	1.28 (0.69-2.15)			
Villous	0.93 (0.57-1.93)			
Serrated	1.74 (0.72-2.32)			
Injection, reference epinephrine	0.20 (0.05-0.54)	**.003**	0.19 (0.05-0.52)	**.003**

CI, Confidence interval; *BMI*, body mass index; *ASA*, American Society of Anesthesiology.
*Bold indicates significant *P* value.

The rate of both immediate and delayed bleeding was significantly lower in the polidocanol group. The type of injection used and the size of the polyp were the only prognostic factors on the multivariate analysis for PPB, both immediate and delayed. Interestingly, the location of polyps in the right side of the colon, known to be at higher risk of bleeding,[14,27] was a significant predictor of immediate PPB on univariate regression but was not confirmed on multivariate analysis (Table 3). This is probably because of the prevailing effect in PPB prevention attributed to polidocanol injection, which in a multivariate setting "masked" the predictive role of lesion location.

To better explore the efficacy of the 2 treatment regimens, a subgroup analysis was performed. This confirmed the superiority of polidocanol in preventing both immediate and delayed bleeding in all of the subsets of patients who underwent polypectomy. As described in Figure 2, odds ratios were always less than 1.0, and even when statistical significance was not reached, a superiority trend in favor of polidocanol was found.

This finding demonstrates the efficacy of polidocanol in every kind of situation, regardless of polyp histology, location, size, or morphology and is probably attributed to its previously cited procoagulative and sclerosing effects.

Other postprocedural adverse events were similar in the 2 groups and in keeping with published literature,[7,25,28] thus confirming the favorable safety profile of polidocanol in this setting.

Efficacy outcomes were similar in both study groups and did not differ in terms of eradication of the lesions or duration of the procedure. These findings show the well-proven effectiveness of EMR with the "inject-and-cut" technique in the removal of large sessile and flat lesions. Despite not reaching statistical significance, polidocanol injection shortened the procedure duration and lowered the number of snare resections per lesion and the solution volume needed to infiltrate the polyps. These promising results indicate the superior efficacy of polidocanol in colonic EMR but require further confirmation.

This study has a number of strengths. First, it is the study of the efficacy and safety profile of polidocanol injection in the endoscopic treatment of large sessile colon polyps. Second, the large number of patients and the completeness of the collected data strengthen the results of our analysis. Third, the monocentricity of the current study is a guarantee against eventual biases due to different treatment procedures or endoscopic training.

Nevertheless, the study has some weaknesses. The main limitation is the retrospective nature of the study, which could have led to selection bias. However, a propensity score matching analysis based on the baseline covariates known to influence postprocedural outcomes was performed to obviate such a problem. Thus, the study groups were perfectly balanced without statistically different baseline parameters. In addition, cost considerations were beyond the scope of this study and could not be addressed.

Despite such limitations, our analysis provides robust evidence in favor of a new endoscopic technique based on the injection of a safe, inexpensive, and broadly available drug.

Submucosal injection of polidocanol appears to be an efficient and safe technique leading to a lower PPB rate and comparable efficacy in terms of eradication of polyps and procedure duration. Prospective randomized trials are needed to confirm the results of our analysis.

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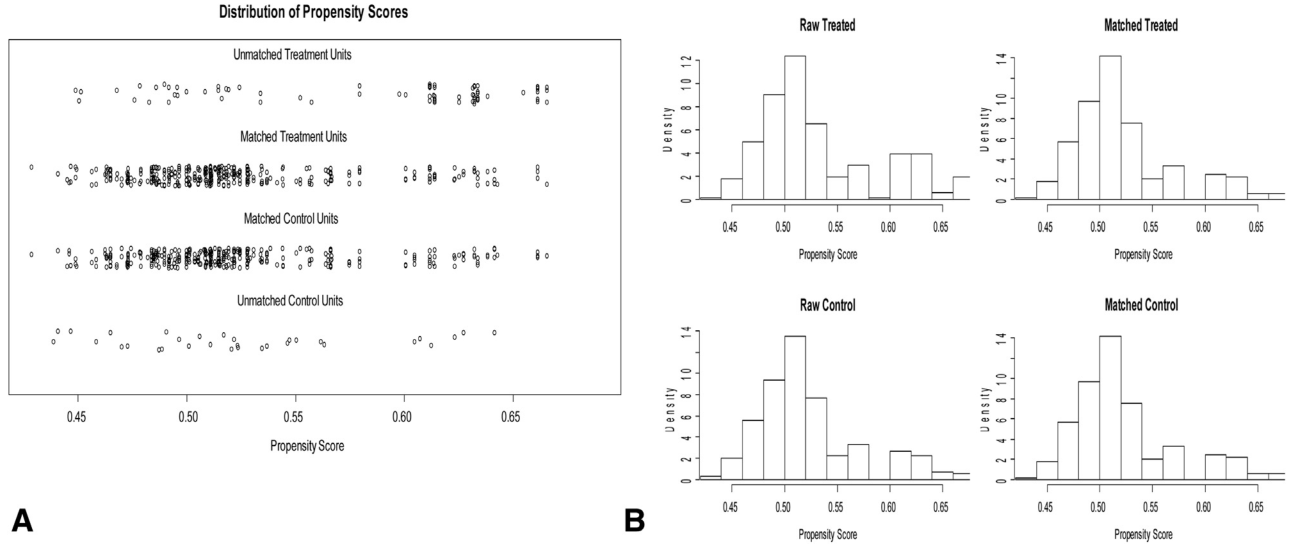

Supplementary Figure 1. Propensity score matching. Of the initial 711 patients, after 1-to-1 propensity score caliper matching, 612 patients were selected for comparison: 306 received an epinephrine injection and 306 received a polidocanol injection. **A**, Propensity score matching jitter plot. **B**, Propensity score matching histogram.

SUPPLEMENTARY TABLE 1. Baseline patients' characteristics of study population before propensity score matching

Variable	All patients (n=711)	Polidocanol (n=380)	Epinephrine (n=331)	*P* value	Effect size
Age (years)	54 (52-66)	54 (51-65)	56 (53-68)	.8	0.09
Gender					
M	422 (59.3%)	223 (58.7%)	199 (60%)	.7	0.02
F	289 (40.7%)	157 (41.3%)	132 (40%)		0.02
BMI	26 (21-28)	26 (20-28)	25 (23-29)	.7	0.01
ASA score	2 (1-3)	2 (1-3)	2 (1-3)	.9	0.05
Lesion size (mm)	31 (25-37)	32 (26-36)	31 (24-38)	.7	0.14
Number of lesions	1 (1-1)	1 (1-1)	1 (1-1)	1.0	0.02
Morphology					
Sessile (Paris 1s)	329 (46.27%)	175 (46%)	154 (46.5%)	.6	0.03
LST (Paris 0-IIa)	382 (53.73%)	205 (54%)	177 (53.5%)		0.04
Location					
Ascending-cecum	324 (45.5%)	170 (44.7%)	154 (46.5%)	.7	0.02
Transverse	132 (18.5%)	82 (21.5%)	70 (21.1%)		0.01
Descending	138 (19.4%)	71 (18.7%)	67 (20.2%)		0.03
Sigma-rectum	117 (16.6%)	57 (15.1%)	40 (12.2%)		0.08
Histology					
Tubular	219 (30.8%)	123 (32.4%)	96 (29.1%)	.7	0.06
Tubulo-villous	310 (43.6%)	161 (42.4%)	149 (45.2%)		0.02
Villous	99 (13.9%)	55 (14.4%)	44 (13.3%)		0.01
Serrated	83 (11.7%)	41 (10.8%)	42 (12.4%)		0.01

Continuous variables are reported as median values and interquartile ranges (25th and 75th percentiles). Comparisons were performed with Mann-Whitney U test for continuous variables and Fisher exact test for categorical ones. For continuous variables, the effect size was measured after log10 transformation.

The following variables, known to be able to affect post-procedural outcomes, were selected for propensity score calculation: age, ASA score, size, morphology, location and histology of polyps.

BMI, Body mass index; *ASA*, American Society of Anesthesiology; *LST*, Lateral spreading tumors.