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A Comparative Study of Early Mucosal Healing Following Hot Polypectomy and Cold Polypectomy

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Background: Cold polypectomy (CP) and hot polypectomy (HP) are both accepted methods for polypectomy. In recent years, the use of CP has increased for reasons of safety. However, there have been few investigations of conditions at follow-up early after resection. This prospective study from a single center aimed to compare colonic mucosal healing at 1 week following HP vs CP of benign colonic polyps <10 mm in diameter.

Material/Methods: Six patients with a total of 52 lesions under 10 mm in size were randomized to either the HP group (n=25) or CP group (n=27) using information in opaque envelopes. One week after endoscopic treatment, the site of treatment was evaluated using colonoscopy. We assessed the mean tumor size, ulcer diameter, exposed blood vessels, residual lesion, and complications.

Results: Mean tumor size did not differ between the 2 groups (CP vs HP: 5.41 mm vs 5.68 mm). The CP group had a smaller ulcer base diameter (2.70 mm vs 4.84 mm; $P<0.05$) and fewer exposed blood vessels than the HP group (3.7% vs 36.0%; $P<0.05$). One residual lesion was found in the CP group. No patients experienced delayed perforation or post-polypectomy bleeding.

Conclusions: Our study findings showed that at 1-week follow-up, cold polypectomy resulted in improved colonic mucosal healing, with a smaller ulcer diameter and fewer blood vessels, when compared with hot polypectomy.

Keywords: **Colorectal Neoplasms • Endoscopes, Gastrointestinal • Wound Healing • Colonic Polyps**

Abbreviations: **DCPs** – diminutive colorectal polyps; **HP** – hot polypectomy; **CP** – cold polypectomy; **PPB** – post-polypectomy bleeding; **CFP** – cold forceps polypectomy; **JFP** – jumbo forceps polypectomy; **ESGE** – European Society for Gastrointestinal Endoscopy; **SSP** – sessile-serrated polyps; **NBI** – narrow band imaging; **JNET** – Japan NBI Expert Team; **PEG** – polyethylene glycol; **WLE** – white-light endoscopy; **CSP** – cold snare polypectomy; **HFP** – hot forceps polypectomy; **HSP** – hot snare polypectomy

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Background

Colonoscopic resection of polyps is useful to prevent colorectal cancer and has been shown to reduce the colorectal cancer mortality rate [1,2]. Both snare polypectomy and forceps polypectomy were shown to be effective for removing diminutive colorectal polyps (DCPs) and are further classified into hot polypectomy (HP) and cold polypectomy (CP). The basic difference is the use of electrocautery by a high-frequency generator in HP, which can minimize immediate procedural bleeding by coagulation [3,4]. HP can damage deeper vessels, with increased risk of delayed post-polypectomy bleeding (PPB) or perforation [3,5-8].

Over recent years, there has been a tendency to transition from electrocautery to non-electrocautery for the complete removal of DCPs. As CP presents a low risk of PPB, it can be performed safely even in patients taking antithrombotic drugs [9-12]. CP is considered safer than HP, and its use has greatly increased in recent years due to the development of specific CP snares and forceps [13-17]. Cold forceps polypectomy (CFP) uses jumbo forceps, which are larger than conventional forceps. It was reported that jumbo forceps are more effective for the complete resection of DCPs than conventional forceps [13,18]. Jumbo forceps polypectomy (JFP) is especially effective for DCPs 4 to 5 mm in size [12]. Recent European Society for Gastrointestinal Endoscopy (ESGE) Clinical Guidelines recommend CFP as the preferred technique to remove polyps ≤ 5 mm [19]. However, local recurrence is a major problem after polypectomy [12,20]. To address that issue, indications for CP are limited to benign lesions < 10 mm, such as adenomas and sessile-serrated polyps (SSP), because of the risk of cancerous and malignant lesions [9,10,21].

A recent retrospective case-control study also provided support that CP could effectively reduce the risk of PPB [5,6,20]. For this reason, CP has increasingly been used over HP. However, the early condition at follow-up after resection has been little investigated [22]. Therefore, this prospective study from a single center aimed to compare colonic mucosal healing following hot polypectomy and cold polypectomy in benign colonic polyps of less than 10 mm in diameter.

Material and Methods

Statement of Ethics

Prior to the initial diagnostic colonoscopy, each patient provided written informed consent about the possibility of subsequent enrollment in a research study. The study protocol was approved by the Institutional Review Board of the Ethics Committee of the Juntendo University School of Medicine before initiating this study (IRB number: 14-050). The ethics standards of the Helsinki Declaration of 2013 were followed.

Patients and Methods

We prospectively examined data on patients who underwent endoscopic polyp resection in our institution from October 2014 to December 2015. Lesions that were followed up by colonoscopy 1 week after treatment were examined. This analysis included men and women 20 to 80 years of age who provided informed consent for participation in the study. The target number of registered patients was set at 15 cases, with a recruitment period of about 1 year. Colonoscopy was indicated based on positive fecal immunohistochemical test results, surveillance, or resection of polyps. Exclusion criteria were: use of an anticoagulant or antiplatelet therapy according to Japanese guidelines or by patients with an existing hemorrhagic diathesis, pregnancy, history of previous abdominal surgical operation, and overweight (body weight over 100 kg). We tried to minimize the possibility of response bias much as possible. Indications for resection included suspected benign tumors such as adenoma and SSP of < 10 mm diagnosed according to surface patterns by narrow band imaging (NBI) magnification [23-26]. Exclusion criteria of colorectal lesion were: (1) pedunculated polyps; (2) polyps > 10 mm; (3) history of inflammatory bowel disease; (4) history of familial adenomatous polyposis; or (5) apparent colorectal cancer diagnosed by colonoscopic observation. Adenomas were diagnosed using magnifying endoscopy findings and vessel and surface patterns (JNET [Japan NBI Expert Team] classification Type 2A), and either an enlarged crypt opening or thick and branched vessels were used to identify SSP [23,24]. Within 1 week after polypectomy, all patients visited our hospital to be informed of the histology results and to undergo colonoscopy using NBI magnification to observe the site of the resection. Judgments of the diameter of the ulcer base, exposed blood vessels, and presence of a residual lesion were made by both an operator and an assistant doctor. A residual lesion was defined as a lesion on the scar after polypectomy and was diagnosed using NBI magnification in as much detail as possible. Thereafter, to confirm the accuracy of the data in the registry, we arranged for another endoscopist to verify the captured image.

Study Endpoints

The primary endpoint of interest in this study was the resection width achieved by HP or CP. The diameter of the ulcer base was evaluated by a measuring device (M1-1C, Olympus Optical Co, Tokyo, Japan).

Procedures

This was a prospective randomized comparison of HP and CP for treatment of colorectal polyps. Patients were randomized according to treatment by HP or CP when a polyp that met the inclusion criteria was found during colonoscopy. The whole

colon was divided into left side and right side with the splenic flexure as the boundary; in each patient, one side was treated with CP and the other side with HP. For patients who met the inclusion criteria, the treatment procedure, either HP or CP, was randomly selected using the envelope method at the moment of treatment.

One week after treatment, the bilateral post-polypectomy state was confirmed by colonoscopic examination. Polypectomy had been performed using the same technique, either CP or HP, on either the right or left side, respectively, in each patient. The alternative technique was then used on the other side in each patient, with the exception of Case 6, who only had eligible polyps on the right side, which were treated with HP. With the exception of this 1 patient, we could follow up differences in healing according to differences in treatment in the same patient.

Polypectomy Protocol

Patients underwent standard bowel preparation. On the day before colonoscopy, patients took 5 mg of Mosapride citrate hydrate tablets (Gasmotin[®], Sumitomo Dainippon Pharma Co, Ltd. Osaka, Japan) 30 min before each meal and 24 mg of Sennoside (Pursennid[®], Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) at 9: 00 PM. No dietary restrictions were imposed for breakfast and lunch the day before the test, but dinner was to be completed by 8: 00 PM. From 4 to 6 h prior to the colonoscopy, the patient drank polyethylene glycol (PEG: Niflec[®], EA Pharma Co. Ltd, Tokyo, Japan) at a rate of about 1.5-2.0 L/h. Patients were then prohibited from eating or drinking until after the examination. While performing the endoscopy, patients were given an anticholinergic agent (butylscopolammonium bromide) or glucagon. Sedation was administered at the endoscopists' discretion when patients reported feeling pain or discomfort. A high-definition colonoscope (PCF-Q260AZI; Olympus Optical Co, Tokyo, Japan) was used for polypectomy by operators who each had performed >3000 colonoscopies. The endoscope-dedicated equipment had a distal tip 11.7 mm in diameter and insertion tube 11.8 mm in diameter (working length, 1330 cm: accessory channel diameter, 3.2 mm). Cecal intubation was confirmed either by ileal intubation or visualization of the appendiceal orifice and the ileocecal valve. Polypectomy was selected for polyps diagnosed to be neoplastic by high-definition white-light endoscopy and NBI endoscopy. [23-26]. Polyp shape was classified according to the Paris classification as elevated (Is, Isp, Ip) or flat (IIa, IIb) [27]. Polyp size was estimated using the complete width of the opening of conventional biopsy forceps. If the size of the polyp was eligible for the study (≤ 10 mm), polypectomy was performed by 1 of 2 randomized methods. After cecal intubation, the operator searched for polyps while withdrawing the endoscope. The operator performed the polypectomies by the allocated

method (CP or HP). Polyps <5 mm were assigned forceps polypectomy and those ≥ 5 mm were assigned snare polypectomy. The CFP was performed by a radial jaw 4 jumbo forceps (M00513360, jaw volume 12.44 mm, maximum jaw opening 8.8 mm; Boston Scientific, Marlborough, MA, USA). The cold snare polypectomy (CSP) was performed as follows: the polyp was excised to include approximately 1 to 2 mm of normal mucosa around the base of the polyp without using electrocautery and retrieved into the trap. In our study, a traditional oval snare (Captivator II Boston Scientific, Natick, MA, USA) with a 10-mm opening width was used. Regardless of allocation, the same forceps and snare wire were decided upon in advance. Retrieved polyps underwent histopathologic evaluations. An ERBE VIO300 (Amco, Tokyo, Japan) was used in the endo-cut mode with the effect 3 current set at output limit 120 W and forced coagulation current set at an output limit of 35 W for HP. Prophylactic clipping at the site of resection was not performed. We evaluated the colonic mucosa after resection using a high-definition colonoscope. The diameter of the ulcer base was evaluated by a measuring device (M1-1C, Olympus Optical Co.).

Statistical Analyses

Results were analyzed by the Mann-Whitney U test and chi-squared test. Continuous variables such as polyp size and ulcer size were analyzed using the Mann-Whitney U test. An SPSS software program was used for statistical analyses (version 22.0 for Windows; IBM Japan, Ltd., Tokyo, Japan). *P* values of <0.05 were considered to indicate statistical significance.

Results

In our study, 6 patients (mean age 70.1 y (67-75 y; 3 males, 3 females) were registered. At the end of the trial, only 6 patients were enrolled because of difficulties in obtaining consent from a larger number of patients. We reviewed 52 neoplastic lesions resected by polypectomy in 6 patients who underwent follow-up colonoscopy 1 week after treatment (**Figure 1**). Study subjects' demographic and clinical characteristics population are shown in **Table 1**. The mean tumor size did not differ between the 2 groups – CP vs HP: 5.41 (3-8) mm vs 5.68 (3-8) mm. The CP group consisted of 10 lesions in the CFP group and 17 lesions in the CSP group, and the HP group consisted of 7 lesions in the HFP group and 18 lesions in the HSP group. **Figure 2** shows the distribution of lesions and details of treatment in each patient. In 3 cases CP was performed on the right side and in the other 3 cases HP was performed on the left side. The opposite treatment, either CP or HP, was administered to the alternate side except in 1 patient (Case 6 had lesions on only the right side). Regarding localization, in the CP group, 66.6% (17 lesions) were right-sided and 32.4% (10 lesions) were

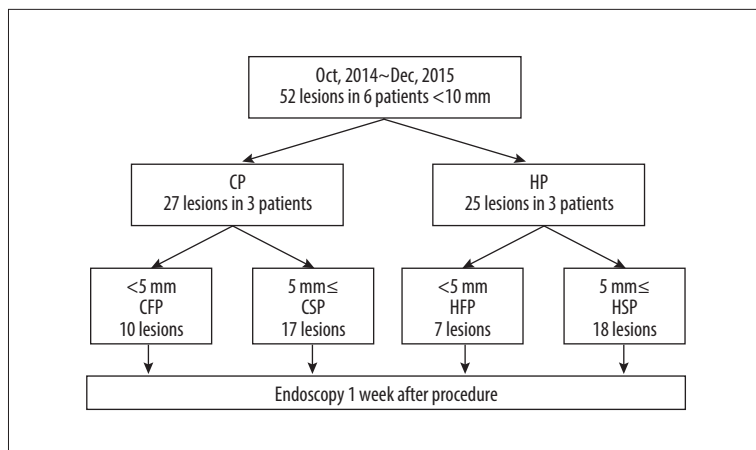


Figure 1. Study flow. HP – hot polypectomy; CP - cold polypectomy; CFP – cold forceps polypectomy; CSP – cold snare polypectomy; HFP – hot forceps polypectomy; HSP – hot snare polypectomy.

Table 1. Comparison of therapeutic results between cold polypectomy and hot polypectomy.

	CP (n=27)	HP (n=25)	p-value
Treatment			
FP	10	7	<i>p</i> =0.24**
SP	17	18	<i>p</i> =0.64**
Location			
Right	17	13	<i>p</i> =0.23**
Left	10	1	<i>p</i> =0.46**
Mean tumor size (range) mm			
FP	5.41 (3-9)	5.68 (3-9)	<i>p</i> =0.27*
SP	3.70 (3-5)	3.86 (3-5)	<i>p</i> =0.58*
Ulcer base diameter one week after treatment (range) mm	6.41 (4-9)	6.38 (4-9)	<i>p</i> =0.47*
FP	2.70 (1-5)	4.84 (2-8)	<i>p</i> <0.05*
SP	2.40 (1-4)	4.66 (2-7)	<i>p</i> <0.05*
Exposed blood vessels	2.88 (1-5)	5.24 (3-8)	<i>p</i> <0.05*
FP	1 (3.7%)	9 (36.0%)	<i>p</i> <0.05**
SP	0	1	<i>p</i> <0.05**
SP	1	8	<i>p</i> <0.05**
Histopathological incomplete resection	8 (29.6%)	5 (16%)	<i>p</i> =0.17**
Residual recurrence	1 (3.7%)	0 (0%)	–
FP	1	0	–
SP	0	0	–
Post polypectomy bleeding	0 (0%)	0 (0%)	–
Perforation	0 (0%)	0 (0%)	–

CP – cold polypectomy; HP – hot polypectomy; FP – forceps polypectomy; SP – snare polypectomy; * Mann-Whitney U test, ** chi-squared test.

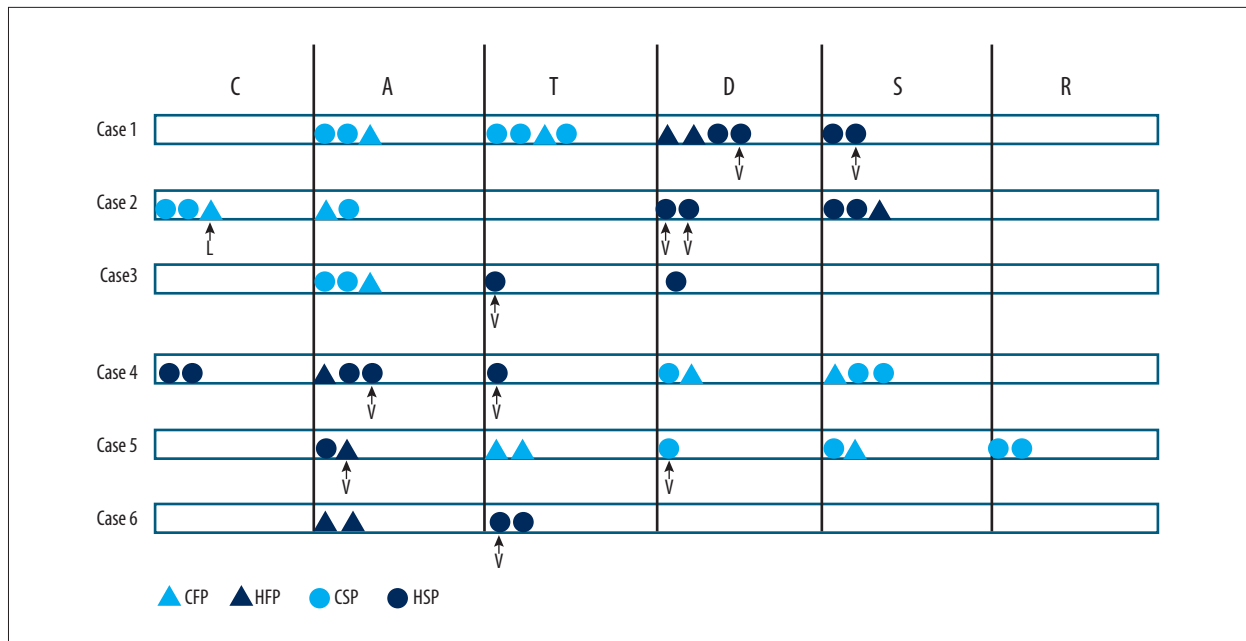


Figure 2. The distribution of lesions and details of treatment in each patient. In 3 cases, CP was performed on the right side and HP was performed on the left side. In the other 3 cases the opposite treatment was administered. There was 1 exception (Case 6), who only had lesions on the left side, for which CP was used. C – Cecum; A – Ascending colon; T – Transverse colon; D – Descending colon; S – Sigmoid colon; R – Rectum; CFP – cold forceps polypectomy; HFP – hot forceps polypectomy; CSP – cold snare polypectomy; HSP – hot snare polypectomy; L – residual lesion; V – exposed blood vessels.

left-sided. In the HP group, 56.0% (13 lesions) were right-sided and 44.0% (12 lesions) were left-sided. Ulcer base diameter 1 week after treatment in the CP group was smaller than in the HP group (2.70 (1-5) mm vs 4.84 (2-8) mm; $P < 0.05$); similarly, lesion size in the CFP group was smaller than in the HFP group – 2.40 (1-4) mm vs 4.66 (2-7) mm; $P < 0.05$. A lower number of exposed blood vessels was found in the CP group vs the HP group (3.7% vs 36.0%; $P < 0.05$) (Figures 2-4). In 8 of 10 cases in the HSP group, ulcers with exposed blood vessels were found. All lesions resected were tubular adenomas with low-grade dysplasia. No malignant lesions were found. Delayed perforation or PPB was not recognized in any patient during the first week after treatment. Histopathological incomplete resections occurred in 8 lesions in the CP group and in 5 lesions in the HP group, with no significant difference. On the other hand, a residual lesion was only found in 1 case in the CFP group (Figure 2); this lesion was removed to confirm complete resection, and histology showed low-grade dysplasia.

Discussion

Both CP and HP are major methods of polypectomy for removing DCPs. In this study, findings showed that 1 week after treatment, the ulcer diameter was smaller and there were fewer exposed blood vessels with CP than with HP. However, 1 residual lesion case was found in the CP group.

There have been many reports about therapeutic results, usefulness of devices, and adverse events after endoscopic resection [10,12,14,28-30]; however, there have been few studies on early-phase follow-up after resection. In previous reports, Suzuki et al endoscopically confirmed the condition of the wound immediately after the procedure and 1 day later [30]. They found that the mucosal defect immediately after CSP was significantly larger than that after HSP, and that it decreased within 1 day after CSP but increased with HSP. In the present study, we compared HP and CP 1 week after resection.

In the CP group, the ulcer base diameter was smaller and there were fewer exposed blood vessels 1 week after treatment than in the HP group, suggesting that the cold technique did not damage ulcers and their edges because of the lack of a burn artifact. Non-energized devices perform very well in making incisions with a low level of iatrogenic damage compared to energized devices [31]. Electrocautery provides an efficient method of early hemostasis, but involves several drawbacks such as lateral tissue damage from the passage of electrical current. HP can damage deeper vessels and the mucous membrane, with an increased risk of delayed healing [32]. HP appears to delay mucosal regeneration compared to CP. In fact, edema and redness were prominent in the ulcer margins in the HP group.

In many studies, measurements of the depth of injury have shown histologic effects of various lasers (electrocautery) in

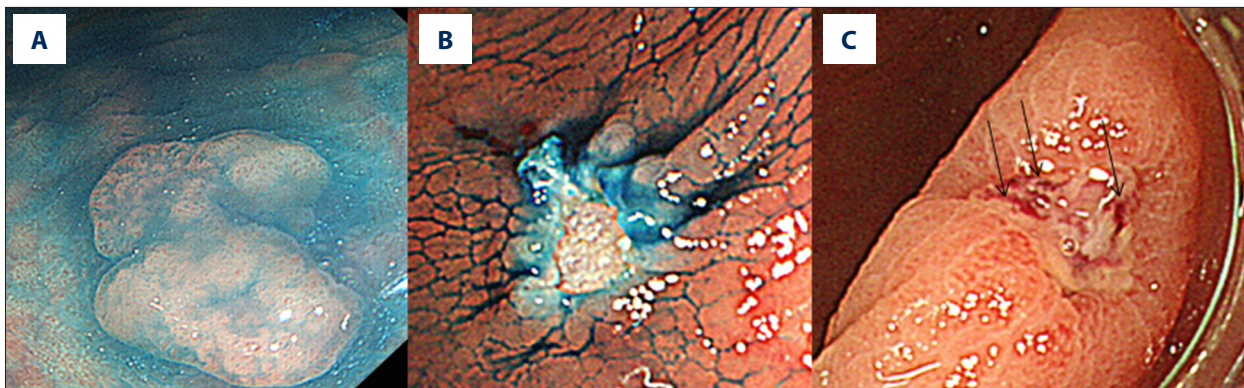


Figure 3. Representative case of HP. (A) A non-polypoid (IIa) lesion (7 mm) located in the descending colon. (B) The lesion was resected en bloc by HSP. (C) One week after HP, the ulcer was 7 mm and had an exposed blood vessel. HP – hot polypectomy; HSP – hot snare polypectomy

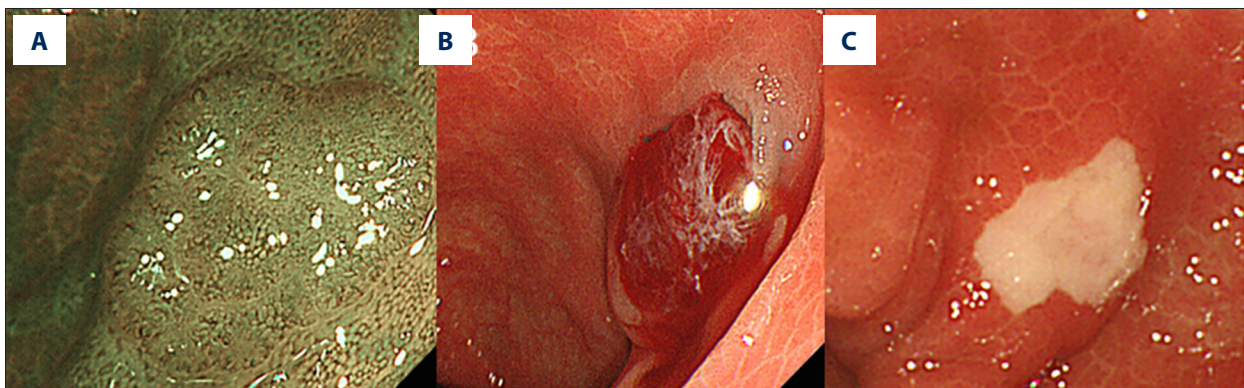


Figure 4. Representative case of CP. (A) A non-polypoid (IIa) lesion (6 mm) located in the descending colon. (B) The lesion was resected en bloc by CSP. (C) One week after CP, the ulcer was 3 mm and no exposed blood vessels were observed. CP – cold polypectomy; CSP – cold snare polypectomy.

the upper aerodigestive tract [33-37]. A greater depth of injury with electrocautery than with non-electrocautery was shown in most of these studies. In a prospective randomized study in a rat model, histologic depth of injury was measured in the upper aerodigestive tract of rats after creating incisions using a scalpel and electrocautery [29]. Wounds created by non-electrocautery resulted in the least tissue destruction, whereas wounds created by electrocautery had a significantly greater postoperative depth of damage [35,37].

Further, another animal study suggested that energized incisions resulted in more substantial effects at both the gene transcription level and the protein level than low-energized incisions [38]. Tissue incised with energized techniques exhibited higher levels of hemostasis remnants, more inflammation, more immune-related genes and proteins, and less wound healing [38].

In our study, non-electrical treatment caused less mucosal damage than energized treatment in removing DCPs. The risk of PPB could be theoretically reduced by avoiding electrocautery

in CP. Also, with CP there were fewer exposed blood vessels compared to HP, which is important when considering PPB complications, although no delayed PPB complications occurred in the present study. There are several reasons for the failure to demonstrate a difference between the 2 groups. In general, the incidence of delayed PPB is 0.6-2.4% [7,39]. Because the number of lesions among study participants was small, this result was not unexpected, and this may also have been because no patients received antithrombotic treatment. This issue should be further evaluated in more patients to detect delayed PPB.

Our study revealed 1 residual lesion in the CP group. Din et al reported that after CFP for polyps ≤ 5 mm, the overall recurrence rate was 17% [29]. Several recent reports showed that CSP was associated with histopathologically incomplete resection rates of 1.8% and 3.9% [8,40], which are thought to be involved in recurrence after resection. As CP does not use an energized unit, specimens resected by CP are fragile and show no effects of burning. It is sometimes difficult to discriminate the resected margin of lesions without a burning effect or lesions that are partially collapsed. Also, polypectomy specimens were

small and fragile and were not pinned, so a real horizontal vertical margin was not evaluated in some of the specimens. For these reasons, it is important to make an accurate endoscopic diagnosis before treatment and to exclude the presence of a residual tumor after treatment.

This study had some limitations. Firstly, the number of samples was small, and the study took place at a single center, making randomization inadequate. It was a heavy burden for the patient to undergo 2 colonoscopies during 1 week. Therefore, the target number of cases was not reached. Secondly, since the study patients participated on a voluntary basis, they may have been healthier than the general population, causing a selection bias. Thirdly, experienced operators are aware that HP is believed to cause more delayed PPB than CP. Thus, operators in this clinical study may have unconsciously performed HP more carefully to reduce damage to the deep submucosal layer in the HP group.

Despite the above limitations, the main strength of this study is that observations were made in the early phase after treatment

by different methods in the same patient; therefore, patient-specific healing factors could be ruled out, lessening the chance for between-patient errors.

Conclusions

Our findings from this prospective study from a single center showed that at 1 week after treatment, CP resulted in superior colonic mucosal healing with a smaller ulcer diameter and fewer blood vessels when compared with HP.

In conclusion, CSP is a safe method for the removal of DCPs. These results support the safety of CP.

Declaration of Figure Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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