Safety and efficacy of cold snare polypectomy for small colorectal polyps

A prospective randomized control trial and one-year follow-up study

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Abstract

Trial design: Elimination of small colorectal polyps with cold snare polypectomy (CSP) is reported to be as safe as hot snare polypectomy (HSP). The effectiveness of CSP has not been clearly defined, and the incidence of long-term recurrence has not been determined. We conducted a randomized control study and one-year follow-up study to assess their safety and efficacy.

Methods: Patients with small colorectal polyps were randomized to receive CSP or HSP. Polypectomy was performed to determine the pathological curability, and patients completed a questionnaire about the tolerability of the procedure. Follow-up colonoscopy was performed to determine the local recurrence of adenoma. The major outcome was the non-inferiority of CSP to HSP in the rate of delayed bleeding and minor outcomes, including the incidence of immediate bleeding and perforation, procedural time, and the resection rate.

Results: A total of 119 participants were recruited in this randomized study and underwent polypectomy. Among the 458 polyps, 332 eligible polyps were analyzed. The rate of adverse events was 0.6% (1/175) for CSP and 0% (0/157) for HSP, which showed the non-inferiority of CSP. While the complete resection rate of CSP was very high (100%), the R0 rate was not satisfactory (horizontal margin, 65.5%; vertical margin, 89.1%). Two local recurrences (2.5%) were observed in the follow-up of 80 adenomas treated with CSP. No recurrence was found in 79 lesions in the HSP group, which was not significant (P = .06).

Conclusions: Colorectal polyps were safely resected using CSP, similar to HSP. Most would agree to say that CSP is considered safer than HSP. The main question is then related to efficacy. Our results of the present study demonstrate that recurrence after CSP should be carefully managed for curative treatment.

Abbreviations: CSP = cold snare polypectomy, HSP = hot snare polypectomy, RCT = randomized control trial.

Keywords: colonoscopy, colorectal neoplasms, polypectomy, randomized controlled trials

1. Introduction

Colorectal cancer is the third most commonly diagnosed cancer and the fourth most common cause of cancer-related deaths worldwide. Colorectal cancer is thought to develop from small adenomas, in accordance with the adenoma-carcinoma sequence. Colonoscopy for the early detection of small polyps and simultaneous endoscopic resection to remove adenomatous polyps are recommended to reduce the incidence of colorectal cancer and associated mortality. The guidelines of the American Society for Gastrointestinal Endoscopy recommend that “flat and polypoid lesions found at the time of colonoscopy should be removed.” The guidelines from the European Society of Gastrointestinal Endoscopy recommend that “all polyps be resected except for diminutive rectal and rectosigmoid polyps.” The polyp resection techniques they recommend were selected according to their shape and size. Cold snare polypectomy (CSP) is recommended for small (6–9 mm) sessile or flat polyps because of its safety.

A randomized control trial comparing CSP and hot snare polypectomy (HSP) for resection of polyps in anticoagulated patients demonstrated that CSP was associated with lower rates of intraprocedural and post-procedural bleeding.
clinical evidence of the efficacy of CSP in comparison with HSP is lacking. A meta-analysis reported that the rates of histological eradication and adverse events did not differ to a statistically significantly extent. CSP was not sufficiently defined in these studies. Thus far, the rates of recurrence rate have not been compared between CSP and HSP in randomized control trials (RCTs).

Thus, we performed an RCT to confirm the safety of CSP and to determine patients’ impressions of the procedure using a questionnaire. To evaluate the efficacy, we further conducted a follow-up study to assess local recurrence of resected adenomas.

2. Materials and methods

2.1. Trial design

This prospective study was designed in Asahikawa-Kousei General Hospital from May 2015 to May 2018 and was registered as a clinical trial (University Hospital Medical Information Network Clinical Trial Registry UMIN 00017545). This prospective randomized single-blinded trial was conducted at a single institute. Patients with colorectal polyps were randomly classified into two groups for treatment with CSP or HSP. Data analysis was performed separately at Asahikawa Medical University by HT.

This trial was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Asahikawa Kousei Hospital (approval number: 2703).

2.2. Eligibility criteria

Participants aged ≥20 years of age, who were diagnosed with small colorectal polyps of 6 to 9 mm in size before participation in this study were eligible for enrollment. Written informed consent was obtained from the patients before polypectomy. Patients were excluded if they had serious heart disease, bleeding tendency, serious complications, or pregnancy.

Colorectal polyps, if applicable, were endoscopically removed, regardless of their size. Eligible polyps in this study were 6 to 9 mm in diameter, measured by endoscopic views; smaller or larger polyps and pedunculated lesions were excluded from the analysis.

2.3. Interventions

Each participant was randomly assigned to either the CSP or HSP group. Concealment of the allocation sequence was generated using the numbered container method. Blinding was not performed after grouping the CSP or HSP. The polypectomy method was opened for endoscopists and medical assistants. The patients were unaware of the study group assignment (single-blind study).

2.4. Procedure

Four endoscopists (TI, KT, MG, and TS) who had sufficient experience with colonoscopy (>400 per year) performed polypectomy in this study. CSP was performed with a small oval flexible or medium flexible Boston Scientific PROFILE Snare (Boston Scientific Japan, Tokyo, Japan), and HSP with MTW Endoskopie Flat bed Snare (ABIS Inc., Hyogo, Japan). An ERBE VIO200D (Erbe Elektromedizin, Tubingen, Germany) was used in the ENDO CUT Q mode (effect 2, cut duration 1, cut interval 3). While polyps were resected, the time from the start of snaring a polyp to recovering the resected polyp was measured as the withdrawal time. The same polypectomy procedure was conducted for patients with multiple polyps, and a larger polyp (≥10 mm in size) was usually treated with HSP. Patients who received treatment were asked to complete a questionnaire (Supplemental Figure S1, http://links.lww.com/MD/G188).

Some procedures were excluded because the procedure was changed or incomplete, for example polypectomy without electrocautery in the HSP group or polypectomy with electrocautery for polyps that were not successfully resected in the CSP group.

Histological examinations were performed by a single pathologist (KS), according to the ninth edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, edited by Japanese Society for Cancer of the Colon and Rectum. The histological diagnoses included low-grade adenoma, high-grade adenoma, adenocarcinoma, hyperplastic polyp, traditional serrated adenoma, or sessile serrated adenoma/polyp. Low- and high-grade adenomas were included in the follow-up study. For pathological assessment, R0 was defined as a resection margin that was negative for tumor cells vertically (VM0) and horizontally (HM0). VMX and HMX were defined when it was difficult to evaluate the margins of the resected tissue in thin sliced sections vertically and horizontally. The recurrence rate was determined using follow-up endoscopy.

2.5. Outcomes

The aim of this study was to evaluate the safety, efficacy, tolerability, and recurrence rate after CSP. The primary endpoint was the incidence of adverse events. The secondary endpoints included the incidence of immediate or delayed bleeding, perforation, procedure time, withdrawal rate, and en bloc resection rate at the first treatment. Immediate bleeding was defined as hemorrhage requiring endoscopic hemostasis using clipping or coagulation. Delayed bleeding was defined as hemorrhage after polypectomy requiring endoscopic hemostasis, blood transfusion, emergency department presentation or hospitalization within 30 days of the procedure. The procedure time was recorded for each polypectomy and total colonoscopy. After polypectomy, the patient was asked to complete a questionnaire to assess their tolerability.

2.6. Follow-up study

Patients who underwent a second-look colonoscopy 1 year later were eligible for the follow-up study. Detailed information from the last polypectomy was presented to the endoscopists (not blinded), and the scar was carefully observed and the lesion where recurrence was suspected was biopsied. Colorectal adenomas were included this analysis: hyperplastic polyps, sessile serrated adenoma and polyp, and traditional serrated adenoma were excluded. The local recurrence rate was defined as the rate of recurrent lesions in cases involving treated adenomas of 6 to 9 mm in size.

2.7. Sample size and statistical analysis

Based on a meta-analysis, the incidence of adverse events after CSP and HSP was 2.5% (95% CI 1.6%–3.5%) and 3.6% (95%
Table 1

Patients characteristics.

| Complication | Cold polypectomy group | Hot polypectomy group | P value |
|--------------|------------------------|-----------------------|---------|
| Gender       | Male: female 38: 21    | 40: 20                | .795    |
| Age          | Mean (SD), year 66.8 (12.4) | 66.9 (9.8) | .869    |
| Past history | Abdominal surgery 19 (32.2) | 25 (41.7) | .285    |
|              | Colectomy 10 (16.9)    | 4 (6.7)               | .062    |
| SD = standard deviation.|

The median number of polyps resected in each patient was 3. The median number of eligible polyps (6–9 mm) per patient was 2. The mean total duration of colonoscopy was 31.2 ± 13.2 minutes in CSP group and 27.1 ± 15.0 minutes in HSP group (P = .06).

Sedation was conducted at the patient’s request, and 90 patients underwent polypectomy without sedation: 29 underwent polypectomy with sedation. Participants answered a questionnaire about treatment tolerance (recovery rate 99.2%). Sedation reduced abdominal pain and discomfort during the procedure at 2 weeks later (Supplementary Table S1, http://links.lww.com/MD/G190). A further analysis of the questionnaire responses was carried out separately according to whether the patients underwent polypectomy with or without sedation. There were no significant differences between the CSP and HSP groups with regard to the questionnaire responses. The patients in the CSP group felt that the total colonoscopy time was slightly longer than that in the HSP group. However, the difference was not statistically significant (4.4 ± 2.4 vs 3.4 ± 2.4).

3.3. Study outcomes

The total rate of adverse events, including bleeding and perforation, in the CSP group was 1.7% (3/175), while that in the HSP group was 1.9% (3/157) (Table 3). The major endpoint, delayed bleeding was observed in 1 case (0.6%) in the CSP group (Supplementary Figure S2, http://links.lww.com/MD/G189) and 0 in the HSP group. The difference between these therapies (CSP minus HSP) was 0.6% (95% CI: −0.5%–1.1%), indicating that CSP was similar to HSP and was non-inferior with a margin of 5% (Fig. 2). Immediate bleeding was observed in 2 cases (1.1%) in the CSP group and 3 cases (1.9%) in the HSP group. No other severe adverse events, including perforation, were observed.

The time required for resection of each polyp was equivalent in the CSP group (1.1 ± 1.6 minutes) to in the HSP group (1.3 ± 1.4 minutes). The complete resection and en bloc resection rates of the groups were similar when polyps were removed endoscopically. However, histological evaluation revealed very low R0 rates (HM0, 65.5%; VM0, 89.1%). Evaluation of the margins of the resected tissue in the thin-sliced sections was difficult, especially in the CSP group (HMX, 34.5%; VMX, 10.9%) than in the HSP group (HMX, 8.3%; VMX, 3.8%).
Table 2
Characteristics of the colorectal polyps.

| Numbers | Cold polypectomy group | Hot polypectomy group | P value |
|---------|------------------------|-----------------------|--------|
| Location |                        |                       |        |
| n (%)    |                        |                       |        |
| Cecum    | 5 (2.9)                | 8 (5.1)               |        |
| Ascending| 37 (21.1)              | 32 (20.4)             |        |
| Transverse| 53 (30.3)             | 27 (17.2)             |        |
| Descending| 19 (10.9)            | 28 (17.8)             |        |
| Sigmoid  | 44 (25.1)              | 53 (33.8)             |        |
| Rectum   | 17 (9.7)               | 9 (5.7)               | .018   |
| Size     |                        |                       |        |
| n (%)    |                        |                       |        |
| 6 mm     | 85 (48.6)              | 80 (51.0)             |        |
| 7 mm     | 43 (24.6)              | 31 (19.7)             |        |
| 8 mm     | 33 (18.9)              | 26 (22.9)             |        |
| 9 mm     | 14 (8.0)               | 20 (12.7)             | .445   |
| Type     |                        |                       |        |
| n (%)    |                        |                       |        |
| IIa      | 13 (7.4)               | 12 (7.6)              |        |
| Is       | 66 (37.7)              | 65 (41.4)             |        |
| Isp      | 96 (54.9)              | 80 (51.9)             | .768   |

Figure 1. A flow chart of the randomized control study.
Regarding the histological diagnosis, adenoma was frequently detected (90.3% in CSP and 90.5% in HSP), and low-grade adenoma was the most common histological type (82.3% in CSP and 82.2% in HSP) of small colonic polyps (Table 4). Intra-mucosal carcinomas were observed in 2 polyps from the CSP group and 1 from the HSP group, and these polyps were completely retrieved in the endoscopic and pathological examinations. These high-grade and low-grade adenomas, including intramucosal carcinomas, were subjected to a follow-up study.

3.4. Follow-up study

Of the 119 patients, 160 lesions in the CSP group and 143 in the HSP group were evaluated in the follow-up study. Sixty three patients (52.9%) underwent one-year follow-up colonoscopy. The remaining patients, including 32 patients with 80 lesions in the CSP group and 24 patients with 64 lesions in the HSP group, did not undergo colonoscopy at the one-year follow-up. As a result, 80 lesions (50.0%) in the CSP group and 79 (55.2%) in the HSP group were consequently analyzed to determine the recurrence rate. Local recurrence was found in 2 of 80 lesions (2.5%) in the CSP group after a one-year follow-up colonoscopy. No recurrence was found in 79 lesions in the HSP group; however, the difference between the 2 groups was not statistically significant ($P = .06$). Recurrent lesions were successfully treated using colonoscopy (Fig. 3). A IIa lesion of 8mm in diameter was removed by CSP, and the histological margins were negative during the first polypectomy. A 2-mm lesion, found at the scar on follow-up colonoscopy, was re-eliminated with CSP. The other local recurrence case was a lesion of 6mm in diameter, which had been removed, and which had negative pathological margins in the first polypectomy. The recurrent lesions were also removed by the CSP. Histological examination revealed low-grade adenomas that had been removed with R0 resection.

4. Discussions

This randomized control study compared the effectiveness and safety of CSP to HSP for small colonic polyps. As the major endpoint, the incidence of delayed bleeding in CSP was similar to that in HSP. The minor endpoint was safety, as reflected by immediate bleeding, perforation, procedure time and resection rates, in both groups. The most distinguishable finding in this study was that a local recurrence rate of 2.5% was observed in the CSP group, while there was no local recurrence in the HSP group. Histological evaluation of the resection margins revealed a low R0 rate in the CSP group.

The safety of CSP in comparison with HSP has been reported in several studies. A meta-analysis revealed that the rates of adverse events, such as bleeding and perforation, were not significantly different. Although there was not enough clinical superiority, the European guidelines suggest that CSP should be used for resection of small colorectal polyps. The biggest advantage of CSP could be the safety in high-risk cases, such as those involving patients receiving anticoagulant medications. Immediate bleeding was inhibited by the use of CSP (23% vs 5.7%). Very recently, CSP has been applied for polypectomy of duodenal polyps or multiple polyposis, such as that observed in familial adenomatous polyposis and Peutz-Jeghers syndrome.
Local recurrence of colorectal polyps was reported in 0.34% of 34,433 patients who underwent polypectomy in a Japanese national survey. No detailed information on the targeted polyps was described, because it was a questionnaire survey. A meta-analysis reported that the rate of colon neoplasm recurrence after endoscopic mucosal resection was 12.2% (106/866). One study reported that a relatively large number of patients presented negligible incomplete resection rates for small colonic polyps (5.8% in 5–7mm, 9.4% in 7–9mm). A multicenter prospective study with jumbo-cold forceps and CSP showed a low recurrence rates of 2.1% and 0.98%, respectively. The authors noted that the recurrence rate was acceptable, in comparison to the reported recurrence rate (cumulative recurrence rate of 17% over 5 years). In our study, the recurrence rate of CSP (2.5%) may be acceptable; however no recurrence was observed in the HSP group. The local recurrence rate was one of the minor outcomes assessed in our study, and the difference between CSP and HSP was not statistically significant. To estimate the sample size to compare local recurrence, a sample size of 912 polyps would be required if the recurrence rates of the CSP and HSP groups were 97.5% and 99.5%, respectively. Assessing the superiority of conventional HSP to the recently developed CSP procedure may not seem informative in a study with such a large number of participants.

Histological examination revealed poor resectability in the CSP group. CSP was associated with low R0 rates in a few studies, reported in Japan.[24–26] The reasons for the low R0 rate in patients undergoing CSP were explained by Yamamoto et al.[27] Electrosurgery may provide extra power in cutting through the mucosa and muscularis mucosa. Polypectomy using electrosurgical generators with automated controlled cutting and coagulation may result in less tissue damage and allow for a better histological interpretation of the specimen. Conversely, a lack of thermal fulguration in CSP may lead to difficulties in confirming the resection margin, leading to a low R0 rate. Our pathologist (KS), agreeing with this explanation, had diagnosed unknown horizontal and vertical margins in many specimens. According to the European guidelines, the advantages of CSP include a lower rate of delayed bleeding, lower frequency of post-polypectomy syndrome and shorter procedural duration.[4] Our study confirmed the noninferiority of CSP regarding the

| Table 4 | The Histological diagnosis of resected polyps. |
|---------|-----------------------------------------------|
|         | Cold polypectomy group | Hot polypectomy group | P value |
| Histological diagnosis | Number | % | Number | % | |
| Intramucosal carcinoma | 2 | (1.1) | 1 | (0.6) |    |
| High-grade adenoma | 13 | (7.4) | 13 | (8.3) |    |
| Low-grade adenoma | 144 | (82.3) | 129 | (82.2) |    |
| Mixed grade adenoma | 1 | (0.6) | 0 | (0) |    |
| SSA/P | 4 | (2.3) | 3 | (1.9) |    |
| TSA | 2 | (1.1) | 3 | (1.9) |    |
| Hyperplastic polyp | 8 | (4.6) | 7 | (4.5) |    |
| Other | 1 | (0.6) | 1 | (0.6) | .974 |
| Tissue margin | Number | % | Number | % | |
| Horizontal margin | 114 | (65.5) | 142 | (91.0) |    |
| Vertical margin | 155 | (89.1) | 150 | (96.2) |    |

SSA/P = sessile serrated adenoma/polyp, TSA = traditional serrated adenoma.

Figure 3. Colonoscopic images of the recurrent cases. A IIa lesion 8mm in diameter was treated with cold snare polypectomy (A, B). A 2-mm lesion at the scar was observed on follow-up endoscopy (C) and successfully removed again with cold snare polypectomy (D). White arrows indicate the recurrent lesion. An is lesion 6mm in diameter enhanced with narrow-band imaging (E) was removed with cold snare polypectomy (F). The recurrent lesion at the scar observed on follow-up colonoscopy was also removed with cold snare polypectomy (G, H). White arrowheads indicate the recurrent lesion.
incidence of adverse events. However, we found 2 disadvantages of CSP. First, 3 cases of CSP were excluded from the full set analysis because cold polypectomy failed and was changed to HSP. A unit and module should be prepared for polypectomy if electriﬁcation is required. Our study also included 5 cases of immediate bleeding, when an electrocoagulation unit was used as a hemostat. Under these conditions, electriﬁcation should be prepared for CSP, as is the case for HSP. Second, the local recurrence rate was low; however, recurrence was observed in 2 lesions (2.5%). No local recurrence was observed in the HSP group. Very recently, the local recurrence rate after CSP for colorectal polyps has been reported to be 1.9%.28 The recurrence rate in our study may be acceptable for clinical applications. Fortunately, the 2 recurrent regions were histologically diagnosed as low-grade adenomas and were treated with CSP. Thus, follow-up colonoscopy is still needed within a few years. The clinical concern is the frequency of follow-up colonoscopy after polypectomy.

One of the strengths of this study was the recruitment of participants in whom small polyps had been found before study entry. We obtained a high complete resection rate, and en bloc resection rate, and low complication rate (bleeding and perforation), and found that adenoma could be diagnosed with high accuracy in colonoscopy in comparison to the histological diagnosis. The diagnostic accuracy supported the technical prominence of our study. In our study, immediate bleeding was deﬁned as hemorrhage requiring endoscopic hemostasis, and the rate was not high in CSP. The reason is that physicians who have already observed bleeding after CSP will stop making a detailed observation. A major point in this study, delayed bleeding, which has been frequently reported in HSP,29 was not observed in our HSP group. Our expert endoscopists may have empirically noticed that the overuse of electrocautery causes tissue damage, resulting in delayed bleeding. We recently modiﬁed the HSP procedure to perform momentary electriﬁcation. In our previous RCT, the effectiveness of prophylactic clipping was determined and indicated that the delayed bleeding procedure time was associated with the rate of delayed bleeding, regardless of whether prophylactic clipping had been performed.129 Thus, such adverse events may have been reduced by a technical approach.

Our study had some limitations. First, the main purpose of our RCT was not to determine the superiority of CSP. Because CSP is reported to be safer and faster, the study was designed as a non-inferiority test.11,12 Our secondary endpoints indicated that the rates of adverse events were equal in both groups. Based on our results, it would be difﬁcult to create a novel study design to assess the superior in safety of CSP. We currently think that the biggest advantage of CSP is the fact that it is cheap and convenient, because CSP is performed without a special apparatus or grounding pad. A cost efﬁcacy analysis would be meaningful to compare CSP and HSP. It is true that the CSP procedure did not use the apparatus. We would like to call attention to the fact that the electro surgical unit should be prepared for CSP, even in cases involving failed cutting or immediate bleeding. Second, this was a single-blinded RCT. The endoscopists and medical assistants were not be blinded. There must be some bias in these procedures. Third, the study was performed at a single institute. Unfortunately, no clinical superiority was found in the efﬁcacy and safety of CSP in this RCT. In addition, 2 cases with recurrent adenoma were found on follow-up colonoscopy, 1 year later. Follow-up colonoscopy was only completed in only half of the patients. The high dropout rate also needs to be improved. We initially planned this study with a two-years recruitment period and a one-year follow-up period. Since some patients underwent colonoscopy a few years after endoscopic treatment, a longer follow-up period should be designed. A systematic monitoring system should be planned for a large study to assess the superiority of HSP in terms of the local recurrence rate.

In summary, this was a randomized controlled study to assess the safety of CSP for small colorectal polyps. CSP is likely to be safe but may not cure colonic adenoma as completely as HSP (determined histologically). With respect to local recurrence, there was still some anxiety regarding curability. Therefore, this technique should be conducted carefully for an appropriate adenoma.

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