Title: Safety of Cold Polypectomy for Colorectal Polyps in Patients on Antithrombotic Medication

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Citation: Digestion, 97(1), 76-81

Issue Date: 2018-02

Doc URL: http://hdl.handle.net/2115/72458

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Type: article (author version)

File Information: Digestion97_76.pdf
Safety of cold polypectomy for colorectal polyps in patients on antithrombotic medication

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Short Title: Cold polypectomy in patients on antithrombotic medication

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**Abstract**

**[Background]**
Cold polypectomy (CP) has been increasingly used in recent years. However, there have been few studies about post-polypectomy bleeding (PPB) in patients who underwent CP and who were taking antithrombotic drugs. The objective of this study was to determine the safety of CP in patients on antithrombotic medication.

**[Methods]**
The subjects were patients who underwent CP in our hospital between April 2014 and March 2016. PPB rates were examined in relation to the use of antithrombotic medication.

**[Results]**
CP was performed to remove 2466 polyps in 1003 patients. There were 549 polyps (22.3%) in 186 patients in the antithrombotic group, and 1917 polyps (77.7%) in 817 patients in the non-antithrombotic group.

PPB occurred in 0.55% (3/549) of patients in the antithrombotic group and in 0.10% (2/1917) of patients in the non-antithrombotic group, showing no significant difference (p=0.07). Patients in the antithrombotic group in whom PPB occurred included 1 aspirin user with 1 polyp and 1 aspirin plus clopidogrel user with 2 polyps. No PPB occurred in patients on other antithrombotic agents or receiving heparin bridging. There was no significant difference between PPB rates in patients with small polyps (6-9mm) in the antithrombotic and non-antithrombotic groups, but there was a significant difference between PPB rates in the two groups for patients with diminutive group (1-5mm).

**[Conclusion]**
CP is a safe procedure even in patients on antithrombotic medication.

Key words: cold polypectomy, antithrombotic medication, post-polypectomy bleeding
Cold polypectomy (CP) is a technique for removing polyps by biopsy forceps (cold forceps polypectomy; CFP) or a snare (cold snare polypectomy; CSP) without electrocautery. CP has been increasingly used in recent years because of its convenience and usefulness. Fujiya et al. showed by a meta-analysis that the average procedural time for CP was significantly shorter than that for hot polypectomy (HP) group according to a meta-analysis\(^1\). Several studies have shown that post-polypectomy bleeding (PPB) is less common with CP than with conventional polypectomy\(^2\(3\)(4)\); however, there have been few studies about PPB in patients who underwent CP and who were taking antithrombotic drugs. According to the 2012 update of the Japanese guidelines for periprocedural management of patients taking antithrombotic medications issued by the Japan Gastroenterological Endoscopy Society\(^5\), procedures with a low risk of hemorrhage may be performed with a short interruption or continuation of antithrombotic medication. However, the guidelines do not refer to periprocedural antithrombotic management for CP.

**[Objective]**
The objective of this study was to determine the safety of CSP in patients on antithrombotic medication.

**[Materials and Methods]**

**Study design**
This was a single-center, retrospective study. The study was performed in accordance with the Declaration of Helsinki and was approved in the Ethics Committee of Sapporo Medical Center NTT EC. Information of this study is shown in the website of our hospital (opt-out).

**Subjects**
The subjects were patients who underwent CP at Sapporo Medical Center NTT EC between April 2014 and March 2016. CP was indicated for non-pedunculated polyps smaller than 10 mm, excluding lesions with submucosal invasion and suspected of being cancerous and excluding polyps that found to be hyperplasic at the preprocedural diagnostic
Narrow-band imaging (NBI) or chromoendoscopy was used for diagnosis. The devices used were Profile (Boston Scientific, Marlborough, MA) and Exacto cold snare (US Endoscopy, Mentor, OH) for cold snare polypectomy (CSP) and Radial Jaw4 (Boston Scientific) for cold forceps polypectomy (CFP). When immediate bleeding continued for more than 30 seconds after polypectomy, prophylactic clipping was performed if the endoscopist judged it was necessary.

**Methods**

The patients were divided into an antithrombotic group and non-antithrombotic group. PPB rates were examined in the two groups. PPB was defined as bleeding that occurred after therapeutic endoscopy and met either of the following criteria: (1) apparent post-procedural bloody stool requiring emergency endoscopic intervention or open surgery and (2) bleeding requiring blood transfusion.

The decision for cessation or continuation of antithrombotic drug medication was made on the basis of the guidelines or by the doctor who prescribed drugs.

**Survey items**

The following information was obtained by retrospectively reviewing medical records: age, sex, specific oral antithrombotic drugs (anticoagulants including warfarin and direct oral anticoagulants (DOAC), antiplatelet drugs including aspirin, clopidogrel, and cilostazole), the cessation of antithrombotic drug medication, polyp size, location, morphology type, pathology, pathologic margin, and use of prophylactic clips.

**Statistical analysis**

Fisher’s exact test was used to compare the two groups. A p-value of <0.05 was considered statistically significant. All statistical calculations were performed using the software JMP® 13 (SAS Institute Inc., Cary, NC).
Results

From April 2014 to March 2016, endoscopic resection was performed in 1852 patients. CP was performed to remove 2466 polyps in 1003 patients. There were 549 polyps (22.3%) in 186 patients who had been taking antithrombotic medication (antithrombotic group) and 1917 polyps (77.7%) in 817 patients who were not taking antithrombotic medication (non-antithrombotic group).

There were significant differences between the numbers of men and women in the antithrombotic group (148 men and 38 women) and the numbers of men and women in the non-antithrombotic group (551 men and 291 women) (p<0.01). There was also a significant difference between the median age of patients in the antithrombotic group (70 years; range, 42-89 years) and that in the non-antithrombotic group (65 years; range, 27-90 years). The reason for the significant difference is that elderly men tended to have diseases that needed antithrombotic treatment.

CFP was performed for 39 polyps (2.7%) and CSP was performed for 2540 polyps (97.3%). Twenty-two polyps (4.0%) in the antithrombotic group were removed by CFP and 17 polyps (0.9%) in the non-antithrombotic group were removed by CFP (p<0.01). This was probably because CFP is more convenient when the size of the polyps is small; endoscopists therefore tended to select CFP for preventing bleeding in the antithrombotic group. There was no significant difference between the two groups in the mean size of polyps. There were significant differences between the two groups in clinical features and baseline characteristics including the distribution and morphology of polyps (Table 1), probably because the antithrombotic group included more elderly people, who have been reported to have more proximal polyps. In both groups, there were some patients with carcinoma; however, all pathological margins were free.

Table 2 shows the types of antithrombotic drugs and Figure 1 shows the way to discontinue antithrombotic drug medication in the antithrombotic group. There were 104 patients with 391 polyps who continued taking antithrombotic medications, including aspirin in 41 patients with 113 polyps, clopidogrel in 13 patients with 17 polyps, dual antiplatelet therapy (DAPT) in 14 patients with 134 polyps, antiplatelet agents other than clopidogrel in 14 patients with 60 polyps, anticoagulant agents in 20 patients with 56 polyps.
polyps, and antiplatelet plus anticoagulant combination therapy in 2 patients with 11 polyps. Heparin bridging was used in 13 patients with 38 polyps.

Post polypectomy bleeding

Bleeding occurred in two patients in each group (1.0% of the patients in the antithrombotic group and 0.24% of the patients in the non-antithrombotic group), and there was no significant difference between the percentages of patients (Table 3a). Endoscopic hemostasis was successful in all cases of bleeding, without requiring blood transfusion. The overall rates of post-polypectomy bleeding (PPB) were 0.55% (3/549) in the antithrombotic group and 0.10% (2/1917) in the non-antithrombotic group, with no significant difference between the two groups.

All of the polyps that bled were cases in which CSP was performed. A comparison of post-polypectomy bleeding rates for CSP cases in the antithrombotic group and non-antithrombotic group showed no significant difference (3/527, 0.57% and 2/1900, 0.1%, p=0.20).

The bleeding cases are shown in Table 3b. In the 3 cases of post-polypectomy bleeding in the antithrombotic group, the antithrombotic medications being used were aspirin in 1 patient with 1 polyp (0.9%, 1/113) and DAPT (aspirin and clopidogrel) in 1 patient with 2 polyps (1.5%, 2/134).

The PPB rates were 1.5% (1/65) for patients taking only aspirin, 0% (0/26) for patients taking thienopyridine, 0% (0.45) for patients taking anticoagulants, and 0% (0/13) for patients receiving heparin bridging therapy.

Polyp sizes

All of the polyps were divided into a small group (polyp sizes of 6-9 mm) and a diminutive group (polyp sizes of 1-5 mm). The number of polyps in the small group was 469 (19.0%) and in the diminutive group was 1997 (81.0%).

The PPB rate in the small group was 0.64% (3/469); the rates were 1.01% in the antithrombotic subgroup (1/99) and 0.54% in the non-antithrombotic subgroup (2/370). There was no significant difference between the PPB rates in these two subgroups (p=0.60).

The PPB rate in the diminutive group was 0.10% (2/1997); the rates were 0.44% in the antithrombotic subgroup (2/450) and 0% in the
non-antithrombotic subgroup (0/1547), the difference between these two subgroups being significant (p<0.01).

**Prophylactic clipping**

Clipping after CP was more likely used in the antithrombotic group [i.e., 13.5% (74/549) vs. 4.6% (88/1917); p<0.01]. No significant difference in post-polypectomy bleeding rate was observed between lesions with and without clipping (0% with clipping vs. 0.34% without clipping; p=0.55). There was no significant difference either within the antithrombotic and non-antithrombotic groups.

**[Discussion]**

In endoscopic treatment, some reports have shown that patients taking antithrombotic drugs are more prone to post-procedural bleeding than those not taking antithrombotic drugs\(^8\)\(^9\). However, in our study on the safety of cold polypectomy, there was no significant difference in post-procedural bleeding between the antithrombotic group and the non-antithrombotic group.

It is known that heparin bridging therapy significantly increases the risk of post-procedural bleeding\(^10\)\(^11\)\(^12\)\(^13\). Horiuchi et al. reported that delayed bleeding requiring hemostasis occurs significantly less commonly after CSP than after HP despite continuation of warfarin\(^14\). In our study, there was no bleeding case with continuation of warfarin or heparin bridging therapy, and CP might therefore be a safe procedure for patients **taking** anticoagulant drugs.

Concerning antiplatelet drugs, some recent studies have shown that continuation of clopidogrel was a low-risk factor in CP\(^15\)\(^16\)\(^17\). In our study, there was only one patient **taking** clopidogrel and no bleeding occurred in that patient.

Mabe et al. reported that the rate of bleeding complications in patients **taking** antithrombotic drugs who underwent to low-risk procedures was 0.2%\(^18\), a rate not so different from that for CP in our data. For patients **taking** antithrombotic drugs, the rate of post-biopsy bleeding in the colon
was reported to be 0.09%. CP therefore seems to be a procedure with a low risk for bleeding, similar to biopsy.

In a previous study, we found that patients on hemodialysis (HD) were at a higher risk for bleeding during endoscopic treatments. Nevertheless, in the present study, there was no bleeding in HD patients (0/78), indicating that CP may be a safe procedure for HD patients.

According to the European Society of Gastrointestinal Endoscopy (ESGE) clinical guidelines say that polyps up to 9mm should be removed by CP. There is no mention in the Japanese Colorectal Polyp guidelines about CP, but it is stated in the guidelines that conventional polypectomy for polyps < 5 mm in size involves more risk than benefit. We think this should be changed in the future. In addition, some studies have shown that CP is useful for removing polyps of more than 10 mm in size; however, some of those reports recommend piecemeal polypectomy. The reported rate of incomplete resection by CP was 3.9% and there is a report of recurrence after CP; thus, careful consideration for the indication of size is necessary.

Some recent studies have shown that a dedicated snare is useful, indicating that the choice of device is also important.

In this study, there was a significant difference between PPB rates in patients with diminutive polyps in the antithrombotic group and non-antithrombotic group. However, bleeding occurred in only 1 patient in the antithrombotic group (1 patient with 2 bleeding polyps). There is a possibility that the patient had hemorrhagic diathesis, although it is not possible to conclude that diminutive polyps in patients taking antithrombotic drugs tend to bleed.

Although there was a difference in the number of patients in whom prophylactic clipping was performed between the two groups, there was no significant influence of prophylactic clipping on PPB rate. Therefore, prophylactic clipping might not prevent PPB. As for EMR and hot
polypectomy, it was reported that prophylactic clipping showed no efficacy for prevention of PPB, as was the case for CP; however, a larger number of cases is necessary to prove this hypothesis.

As for the limitations of this study, this was a single-center, retrospective study. The criteria for choosing CSP or CFP, for determining the way to discontinue antithrombotic drug medication and for performing prophylactic clipping were not established in the study protocol. There might therefore be a selection bias. PPB is a very rare phenomenon, and it is therefore difficult to prove statistically significant differences regarding PPB. However, we consider that this study is valuable because of the large number of cases analyzed.

In the future, large-scale prospective studies should be carried out to confirm our findings.

【Conclusion】
Cold polypectomy is a safe procedure for patients on antithrombotic medication.

【Conflicts of Interest】
The authors declare that they have no competing interests.
【References】


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Figure Legend

Figure 1

The way to discontinue antithrombotic drug medication in the antithrombotic group

Tables

Table 1. Background of patients and polyps.

Table 2. Types of antithrombotic drugs.

DAPT: dual antiplatelet therapy

Table 3.  a) Rate of post-polypectomy bleeding.

b) Bleeding cases.
- Heparin bridging therapy, 13, 7%
- Discontinue, 64, 35%
- Continue, 106, 57%
- Cilostazole bridging therapy, 2, 1%
- Antiplatelet drugs, 84, 45%
- Anticoagulant drugs, 20, 11%
- Antiplatelet+anticoagulant, 2, 1%
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Location</th>
<th>Antithrombotic group (549)</th>
<th>Non-Antithrombotic group (1917)</th>
<th>p-Value</th>
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<tbody>
<tr>
<td></td>
<td>Proximal</td>
<td>60.6% (333)</td>
<td>52.1% (997)</td>
<td>&lt;0.01</td>
</tr>
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<td>Distal</td>
<td>39.3% (216)</td>
<td>47.9% (920)</td>
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<td>Morphology type</td>
<td>Protruded 42.2% (232)</td>
<td>50.7% (972)</td>
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<td>Superficial</td>
<td>57.7% (317)</td>
<td>49.3% (945)</td>
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<td></td>
<td>Mean size (㎜)</td>
<td>4.20 ± 0.06</td>
<td>4.25 ± 0.03</td>
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<tr>
<td>Pathology</td>
<td>Low grade adenoma</td>
<td>82.7% (454)</td>
<td>75.8% (1453)</td>
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<tr>
<td></td>
<td>High grade adenoma</td>
<td>1.3% (7)</td>
<td>1.1% (21)</td>
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<tr>
<td></td>
<td>Carcinoma</td>
<td>0.2% (1)</td>
<td>0.3% (5)</td>
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<td>Hyperplastic polyp</td>
<td>5.6% (31)</td>
<td>11.7% (224)</td>
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<td>Serrated adenoma</td>
<td>2.4% (13)</td>
<td>3.8% (72)</td>
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<td>SSA/P</td>
<td>1.5% (8)</td>
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<td>Discard</td>
<td>5.1% (28)</td>
<td>2.8% (54)</td>
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<td>1.3% (7)</td>
<td>2.3% (45)</td>
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<td>Pathological margin</td>
<td>Positive 0.4% (2)</td>
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<td>Negative 52.8% (275)</td>
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<td>Unclear 37.5% (206)</td>
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<td>No judgement 7.1% (37)</td>
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<td>Bleeding case</td>
<td>Patients</td>
<td>2/186 (1.07%)</td>
<td>2/817 (0.24%)</td>
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<td>Polyps</td>
<td>3/549 (0.55%)</td>
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