

Cold Snare Polypectomy for non-pedunculated colonic polyps sized 10-19mm: A prospective observational study (CSP study)

Version:3

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BACKGROUND:

Removal of polyps via colonoscopy is effective at reducing the incidence of colorectal cancer [1]. Polypectomy techniques among endoscopists can vary, though the choice of method depends principally on the size and morphology of the polyp [2]. Cold snare polypectomy (CSP) is a relatively recent development, but has rapidly gained international acceptance as an effective and safe polypectomy technique. It is now the standard of care internationally for resection of small polyps (i.e. sized <10mm), and has become the standard of care for resection of intermediate sized polyps (sized 10-19mm) at leading academic endoscopy centres all around Australia and New Zealand. It has not yet been adopted at most other non-academic endoscopy centres around Australasia for polyps in this intermediate size range. However, these centres perform a huge volume of colonoscopy cases annually, and are the centres whose patients would most likely benefit from changing to a cold snare based technique, due to significantly increased safety of the cold snare technique, if endoscopists can be convinced of the efficacy of this approach for polyps in this size range.

It was previously thought that electrocautery (applied using a “hot snare”) was required for polyp removal, but it is now known that “cold snares” (that don’t use electrocautery) are also effective for polyp resection. Cold snares use a thin, stiff, monofilament wire to cut out the polyp, without the need for electrocautery. This is a big advance, as it is the electrocautery that is the main cause of post-polypectomy complications such as bowel perforation, serositis, post-polypectomy syndrome, post-procedure pain and post-polypectomy bleeding. Therefore, polypectomy using cold snare has the potential to significantly reduce the risk of complications following colonoscopy. Since there is a significant continuing, year-on-year increase in demand for colonoscopies, particularly as a result of the implementation of the National Bowel Cancer Screening Program, this development has the potential to significantly influence the safety and efficacy of colonoscopy and polypectomy for large numbers of patients at Western Health, and also nationally and internationally.

While the evidence for the efficacy of cold snare polypectomy for resection of small polyps is established, rigorous data for intermediate sized polyps is still limited. Effectively, this technique has become the standard of care at leading centres for polyps in this size range due to the overwhelming safety benefits, however there are no prospective nor multicentre studies proving that this method is effective, in terms of completeness of resection of polyps. In our own practices, and in the setting of small, published retrospective studies, we have observed cold snare polypectomy to be very effective for polyps in this intermediate size range

as well. However, to convince endoscopists that the safety benefits of cold snare polypectomy are also associated with highly effective complete resection of polyps, a well-designed, prospective, multicentre, observational study is required.

LITERATURE REVIEW:

Cold snare resection of diminutive polyps sized ≤ 7 mm was effective when compared to cold forceps polypectomy in a prospective randomized study, where CSP achieved a 97% of complete polyp clearance rate[3]. Another study from Japan randomized 70 patients with ≤ 10 mm polyps on warfarin to cold snare or hot snare polypectomy. Patients in the cold snare polypectomy group had fewer immediate and delayed bleeding rates compared to the hot snare group (0% vs 14% and 6% vs 23% respectively)[4, 5]. Increased risk of delayed bleeding after hot snare polypectomy could be related to sloughing of eschar leading to unroofing of a vessel, resulting in bleeding. HSP is also associated with increased risk of perforation and the risk of post-polypectomy syndrome[6]. However, with cold snare polypectomy the risk of perforation is almost negligible as it can only cut through mucosa and submucosa but not through the muscularis propria layer of the colon.

A concern with any polypectomy is the risk of incomplete resection. In the recent highly referenced prospective study that evaluated the rate of incomplete polyp resection with hot snare polypectomy (the "CARE" study), of the 116 polyps sized 10-20mm, the rate of incomplete resection was 17%[7]. There is limited data regarding the incomplete resection rate with piecemeal cold snare polypectomy for polyps sized 10-20mm. Optimal CSP could result in similar or likely better incomplete resection rates than documented in the CARE study, but potentially with fewer adverse events.

A retrospective observational study evaluated the efficacy and safety related outcomes to piecemeal CSP in 30 sessile polyps sized ≥ 10 mm in 30 patients. Of these, 15 polyps were sized between 10-19mm. All polyps were resected without any

immediate or delayed adverse events [8]. Moreover, of 27 patients who underwent follow-up colonoscopy within 6 months, 80% did not have residual polypoid tissue at the resection site. This suggests that the efficacy of cold snare polypectomy is likely to be similar to hot snare polypectomy (HSP) for polyps of this size range, but with fewer adverse events. In a prospective observational study, the safety of piecemeal CSP was evaluated among 124 patients with 171 sessile polyps (including 43 that were sized between 10-19mm), and no immediate or delayed adverse events such as bleeding or perforation were recorded among study subjects [9].

Prospective studies specifically designed to address the safety and efficacy of CSP for non-malignant polyps sized 10-19mm are required. The primary aim of this prospective observational clinical audit is to rigorously assess the efficacy of the current practice of piecemeal CSP in achieving complete polyp resection for polyps sized 10-19mm. The secondary aims are to measure a range of safety outcomes of CSP and to estimate the overall hospital costs and bed utilisation for patients.

RESEARCH QUESTION:

Is Cold Snare Polypectomy (CSP) an effective and safe method for achieving complete polypectomy for medium sized non-pedunculated polyps measuring 10-19mm?

POTENTIAL CLINICAL SIGNIFICANCE:

This audit aims to determine whether current clinical practice of CSP of medium sized sessile polyps is indeed effective in achieving complete polyp resection with fewer complications. Significant complications related to HSP could be prevented if we can demonstrate the safety and efficacy of CSP.

STUDY DESIGN:

TYPE OF STUDY:

Prospective, observational multicentre study which aims to rigorously audit the current clinical practice of resecting sessile (non-pedunculated) polyps sized 10-19mm with CSP at multiple academic endoscopic units across Australia.

INCLUSION CRITERIA:

Any patient undergoing colonoscopy who is older than 18 years of age with sessile polyp measuring 10-19mm that is suitable for polypectomy

EXCLUSION CRITERIA:

- Polyps that are concerning for malignancy
- Pedunculated polyp
- Active inflammatory bowel disease / colitis
- Pregnant
- Aged younger than 18 years
- Presence of bleeding or coagulation disorders
- All polyps resected using hot snare polypectomy (HSP) technique
- A patient where polyps sized 20mm or greater were resected using cold snare during the same procedure

PRIMARY OUTCOME:

The primary outcome measure is the incomplete resection rate of sessile polyps measuring 10-19mm as determined by the histological examination of polypectomy site biopsies..

SECONDARY OUTCOMES:

- Measure recurrent or residual polyp rate during first routine surveillance colonoscopy
- Intraprocedural bleeding that required haemostatic intervention
- Clinically significant delayed post-polypectomy bleeding
- Perforation
- Post-procedural unplanned admission for pain or serositis
- Complete polypectomy as defined by endoscopist impression of complete polyp resection

ADDITIONAL EXPLORATORY OUTCOMES:

1. Polyp details (anatomic location, polyp histology, en bloc vs piecemeal, ease of polyp resection (easy, moderately difficult or difficult)).
2. Use of submucosal injection (and details of content of the injection)
3. Polypectomy duration
4. Post-procedure pain causing a delay in discharge (compared to the usual intended discharge time)
5. Performance of a CT scan or chest/abdominal x-ray to exclude perforation post procedure
6. Admission post-procedure for a polypectomy related adverse event and length of hospital stay
7. Readmission within 14 days post-procedure for a polypectomy related complication
8. Unplanned presentation to medical attention, without hospital admission within 14 days post-procedure for a polypectomy related complication (e.g presentation to General Practitioner or Emergency Department without warranting a hospital admission)
9. Surgery for a polypectomy related complication
10. Clinically significant delayed post-polypectomy bleeding on antiplatelet or anticoagulant therapy.
11. Assessment of additional hospital costs incurred for the management of polypectomy related adverse events.
12. Death of any cause

METHOD OF SCREENING:

All patients undergoing elective colonoscopy at all participating academic centres will be screened to assess their eligibility into the study based on above exclusion and inclusion criteria.

SEQUENCE OF THE PROCEDURE:

1. During colonoscopy, if a sessile (non-pedunculated) polyp sized 10-19mm is detected that is not suspicious for malignancy, this patient becomes part of the audit.
2. If a polyp in this size range is detected, but appears suspicious for malignancy, this patient will *not* be part of the audit. This patient's management would be left to treating endoscopist's discretion, which may vary from biopsy only to en-bloc resection with EMR or ESD or referral to surgery depending on the practice at that center. If the endoscopist decides to perform hot snare polypectomy, those polyps will be excluded from the analysis.
3. CSP is performed with a dedicated cold snare
4. All suitable polyps are resected with or without submucosal injection. The decision to use submucosal injection is at the endoscopist's discretion. Injection is performed with saline or Gelofusione plus methylene blue or indigo carmine with or without adrenaline (1:100,000 adrenaline concentration)
5. The addition of adrenaline to the injectant is also at endoscopist's discretion.
6. Application of hemostatic clips to the polypectomy defect will be left to the discretion of Endoscopist performing the procedure.
7. After resection and endoscopist's attestation that polyp removal was complete by careful macroscopic inspection of the resection margins with both high definition white light and narrow band imaging, cold biopsies are performed to assess for the possibility of microscopic residual polyp that cannot be identified visually.
8. Eight circumferential polypectomy site margin biopsies are performed if the polyp is resected "en-bloc" (i.e. in a single resection piece). However, if the polyp is resected in more than one piece, an additional cold biopsy is performed within the polypectomy site at the point(s) where snare overlap during resection occurred. These central biopsies are placed in a separately labeled histology

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9. Duration of polypectomy is recorded which begins with commencement of first contact with lesion until retrieval of all histology specimens.
10. A small tattoo is placed 3cm distal (anal side) to the polypectomy site as a mark for future reference. If a tattoo is not placed, the location of the polypectomy site is described in great detail so as to enable future identification for the surveillance colonoscopy. This takes the form of distance from the anus in centimeters with a straight scope on withdrawal, anatomical region, location relative to landmarks such as the ICV or appendix orifice, medial or lateral aspects of the hepatic flexure, proximal or distal to colonic haustral fold etc., so as to maximize the likelihood of finding the scar at follow-up
11. During the procedure, data is recorded by the Gastroenterology registrar or clinical research nurse regarding the technical aspects of the procedure
12. Usual post colonoscopy care is recorded.
13. Any adverse events are recorded including immediate or delayed bleeding, muscularis propria injury or perforation, persistent pain indicative of serositis (inflammation of the outer layer of the bowel wall) or an unscheduled admission or readmission.
14. Patients are contacted by the research nurse or by research fellow by telephone 14 days following their procedure to assess ongoing symptoms and advise of any adverse events including unscheduled presentations to medical care or readmissions.
15. The formal histology results of the resected specimens are recorded on the follow-up data sheet.
16. If there is any histological evidence of residual polyp in the biopsy specimens, patient will be recalled for a repeat colonoscopy at next available appointment to complete resection of the residual polyp.
17. If there is no residual polyp, patients will undergo next surveillance colonoscopy as per current standard of care.
18. During the surveillance procedure the polypectomy site is thoroughly examined with both high definition white light endoscopy (HD-WLE) and narrow band imaging (NBI) of the region described in the original colonoscopy report and biopsies of the scar tissue are performed.

DATA SECURITY:

Patient data will be de-identified and a study code assigned to their information. The study code will however be able to be used to re-identify the patient for the purposes of linking follow up information. An external encrypted, password protected, web-based database will be established with the assistance of Western Health Research grant fund. Database will be always accessible to the all participating centres nationally, for centralised submission of de-identified data. Information from study data sheets will be entered into this database securely at each participating site. This will enable maximal participation from multiple sites, allow for efficient data entry and analysis, will ensure the security of data, and will minimise the possibility of data entry errors. Paper datasheets collected are securely stored in a locked research office. The Western Health Endoscopy Fellow is the custodian of both electronic and paper data storage.

STATISTICS:

The study is a prospective audit of all new cases of CSP for one year with an additional follow up to review endoscopic findings during the first routine surveillance colonoscopy (SC1). At least five leading endoscopy centres around Australia are expected to contribute to the study. 350 polypectomy cases are expected to be recruited during the study during the first year, another three years of follow up is required to obtain results of the surveillance colonoscopies.

The estimates of recurrence rate in medium sized polyps with the use of CSP are lacking in the current literature, therefore sample size estimation is not possible. 350 polypectomy cases has been chosen as this is a volume of polypectomies that is likely to be recruited within 1 year thus eliminating the effect of change in standard of care. Furthermore, this sample will enable fairly small confidence intervals for each of the outcomes and will allow a superiority margin of 5.5% when compared to recurrence rate from the CARE study(17%). If the 350 polyp target is not reached within a year, the study will be extended until this number of polyps is recruited.

Primary analysis will involve detailed descriptives of primary, secondary and exploratory outcomes within CSP cohort. Where possible, outcomes of this study will

be compared to the outcomes of already published CARE study (HSP cohort) using binomial probability test for categorical variables and one-sample t-test for continuous variables (polypectomy duration).

Additional analysis will explore which patient's, polyp's and procedural characteristics are associated with each of the outcomes using univariate analysis (Fisher's exact and Wilcoxon rank sum test) and multivariate logistic regression.

A p value of < 0.05 will be considered significant. Statistical analyses will be performed with SPSS statistical software (IBM Corp. 2012. IBM SPSS Statistics, Version 21.0. Armonk, NY) and/or Stata 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) with the help of an independent statistician.

RESEARCH ETHICS APPROVAL

The audit proposal will be submitted initially to the Western Health Research Ethics office for approval. All other participating centres will be listed on the ethics application as additional study sites. Local governance approval will be required at each participating centre according to local requirements. Exemption for signed informed consent to study participation is requested, as the procedures are being conducted according to current standard clinical practice. Furthermore, it would be impractical to obtain consent from a large group of patients for a relatively low prevalent endoscopic finding of 10-19mm sized polyps. Previous studies have shown that for every hundred adenomatous polyps detected during screening colonoscopies, there is only a 5% chance of finding a polyp that is larger than 10mm[10].

DISSEMINATION OF RESULTS

The final study results will be submitted for peer review for presentation at an internationally regarded scientific meeting, followed by manuscript submission to a quality peer-reviewed scientific journal. Only de-identified pooled results will be presented.

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