

Cover page

Title: A Pilot Randomized Trial of Polypectomy Techniques for 4-6 mm Colonic Polyps

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Study Protocol

Background:

Colonoscopic polypectomy is one of the most commonly performed procedures in the United States. (1) Despite the frequency with which polypectomy is performed, there is a remarkable absence of data regarding which polypectomy techniques most effectively remove polyps and minimize complications. As a result, polypectomy practice is based on the observational experience of experts and is how it is taught by attending physicians in fellowship training programs. It is not surprising therefore, that polypectomy practice is not consistent across the U.S., particularly for polyps in the 4-6 mm range, with 19% of endoscopists using cold forceps, 21% using hot forceps, 31% using a hot snare, 15% using a cold snare, and the remainder using a combination of these techniques. (2) For polyps 7 mm or larger, in contrast, there is much less variation in polypectomy technique, with 80% of endoscopists using a hot snare. (2)

The effectiveness of colonoscopy in the prevention of colorectal cancer (CRC) depends on polypectomy (3, 4); most polyps removed during colonoscopy are < 1 cm in size. Because of their greater prevalence relative to larger polyps, polyps < 1 cm are responsible for most cases of post-polypectomy bleeding (even though the absolute risk is higher with larger polyps) (5). Perhaps more concerning, several studies of surveillance colonoscopy have reported finding CRC within a few years of a complete colonoscopy. (6, 7) Nearly 30% of these cancers have occurred in colonic segments where prior polypectomy was performed, suggesting that incomplete removal may be responsible for the recurrence of neoplasia; in more than half of these cases, the initial polyp removed was 1 cm or less in size. (7) Unfortunately, these studies are limited because the precise location of the polypectomy site relative to the subsequent cancer is uncertain.

As mentioned previously, there is a remarkable absence of data on polypectomy techniques with which to guide endoscopic practice; indeed, there are no randomized trials of polypectomy techniques published as full manuscripts. There is one abstract comparing hot snare, cold snare, and hot forceps in the removal of 73 diminutive polyps located within the distal 20 cm, in which there was a trend toward more frequent residual tissue with hot biopsy forceps (8). Given the prevalence of the 4-6 mm polyp, the variation in polypectomy technique among endoscopists, and the concern about interval cancers at polypectomy sites, there is a clear and significant need to determine which technique(s) are most appropriate for clinical practice in terms of having the lowest risk for recurrent neoplasia and for major adverse effects (major bleeding, perforation).

The **goal of this line of research** is to determine the superior method for polypectomy (cold biopsy forceps, cold snare, or hot snare) in the removal of adenomatous colonic polyps that are 4-6 mm in maximal diameter for the subsequent risk of recurrent neoplasia at the polypectomy site. A randomized trial comparing these three polypectomy techniques for the outcome of recurrent neoplasia at the polypectomy site requires at least 700 persons per group (at least 2100 persons total). (A trial powered to compare complication rates would require a sample size that is an order of magnitude greater than this and is beyond the feasibility and scope of both pilot and definitive trials.) Further, patients would need to undergo 3- or 5-year surveillance colonoscopy, which requires a research infrastructure to ensure complete and accurate data collection. Before embarking on this large-scale trial to examine effectiveness of polypectomy techniques, we must first demonstrate feasibility of conducting such a trial and determine the time frame, sampling frame, and resources required.

The **specific aim of this proposal** is to conduct a pilot randomized trial to establish:

1. the feasibility of conducting a definitive, single-institution, multi-site clinical trial comparing the three modalities for removing adenomatous colonic polyps 4-6 mm. The processes that will be assessed are patient enrollment, recruitment, exclusion, and determination of final eligibility for the trial.
2. the numbers of patients at each site (IU Hospital, Wishard Memorial Hospital) who would be candidates for the larger, definitive study (This information will help estimate the time line and resources required for the definitive study).

3. the proportions of recruited patients that fall into the 3- and 5-year surveillance groups (or other surveillance interval, along with the reason(s) for the interval).

Hypotheses:

1. A single-institution, three-site clinical trial is feasible: patients can be recruited and enrolled as potential subjects; final eligibility based on endoscopic and histological findings can be established within a week of enrollment.
2. We can identify the number of patients at each site who would be eligible for participation in a larger, more definitive study, from all patients undergoing colonoscopy. We can establish refusal and exclusion rates. (Knowing both rates is necessary for planning the larger study.)
3. The proportion of recruited patients in the 5-year surveillance group is approximately 80% of all persons with neoplasia; the remaining 20% comprise the 3-year surveillance group.

Study design: Randomized trial

Study setting: Indiana University Medical Center - specifically, the endoscopy units at Indiana University Hospital, Wishard Memorial Hospital and Beltway Surgery Center – Springmill.

Eligibility criteria: Persons undergoing screening, surveillance, or diagnostic colonoscopy who are found to have 1 or more adenomatous colon polyps 4-6 mm in size with Paris morphology of types I or IIa in well-defined segments of the colon.

Pre-randomization exclusion criteria: Patients with any of the following will be excluded:

1. Inability to provide informed consent
2. Requirement for long-term anticoagulation or clopidogrel (plavix)
3. Known INR ≥ 1.5
4. Less than satisfactory colon preparation quality
5. Inability to intubate the cecum or reach the surgical anastomosis in case of cecectomy
6. Age greater than 75
7. Inpatient status (acute lower GI bleeding, etc.)
8. Comorbidity that precludes the need for surveillance
9. Pregnancy
10. Already included in the protocol
11. Pre- solid organ transplantation

Operational steps to the study:

1. Prior to beginning patient recruitment, all participating endoscopists, study investigators, and research assistant (RA) will meet to review the protocol and to establish familiarity with the Paris morphology.
2. Potentially eligible patients will be told initially about the study by the clinical nurse in the pre-procedure area during the process of pre-colonoscopy preparation. Patients will learn about the purpose and design of the study and will be told that the physician endoscopist will discuss the study in more detail after obtaining informed consent for the colonoscopy, and will then ask patients if they would like to participate.
3. After obtaining informed consent for the colonoscopy itself, the physician endoscopist will explain the study and ask if patients are willing to participate. The informed consent form for the study will be signed by each consenting patient.
4. Colonoscopy will be performed in standard fashion. The endoscopist must describe at least three criteria for having reached the cecum and must photograph the cecum (such behavior is / ought to be the standard of care). (3) During withdrawal of the colonoscope, the endoscopist will describe the following parameters for each polyp identified: a) polyp location (segment of the colon the endoscopist believes the polyp to be located; distance in centimeters from the anal verge); b) polyp

size (as measured with open biopsy forceps or the end of a closed snare); c) polyp morphology (flat, sessile, or pedunculated). As soon as the endoscopic criteria for study inclusion are met (one colonic sessile polyp 4-6 mm in maximal diameter with Paris morphology type I or IIa), patients will be randomized to one of the three polypectomy techniques using a system of consecutively numbered, opaque envelopes from a box located centrally within each endoscopy unit.

5. Once the patient has been assigned to a specific polypectomy technique, the endoscopist will proceed to perform polypectomy using the assigned technique. All size- and morphologically-eligible polyps removed as part of the trial in an individual patient will be removed using the same assigned technique. For cold biopsy polypectomy, we will use standard-sized radial jaw 4 cold biopsy forceps, and will record the number of bites taken and amount of time required for resection, measured from first forceps passage to completion of polypectomy or to determination that the polyp is not retrievable (i.e., was lost). For cold and hot snare polypectomy, we will use small snares, and will record the number of times the snare is used to remove polyp tissue. The time to perform cold or hot snare polypectomy will be recorded as the time from initial passage of the snare to polyp retrieval in the scope or determination that the polyp is not retrievable. For hot snare polypectomy, the type and intensity of current will be recorded as well. The time required for polyp removal will be measured by the RA with a stopwatch.
6. Upon completion of the biopsies from the polypectomy site, the endoscopist will inject up to 5 ml of SPOT stain immediately 1-2 cm proximal to the polypectomy site.
7. For any single patient, up to five structurally qualifying polyps may be removed under protocol, per physician judgment. For each eligible polyp, the same technique for polyp removal will be used, along with injection of SPOT just left of the polypectomy site. For polyps of different sizes and /or Paris morphologies, the endoscopist will remove these using whichever method he or she prefers. Polypectomy sites for these other size and morphology polyps will not be marked with SPOT.
8. Patients will be discharged in the usual fashion. They will eventually receive their pathology results as well as endoscopist recommendations for surveillance.
9. For polyps removed as part of the trial, polyp histology will be determined by a single, dedicated pathologist. (For the other, non-trial polyps, the scheduled pathologist will interpret these specimens.) Patients whose study polyp(s) biopsy(ies) shows a non-neoplastic polyp(s) will be excluded post-hoc from the protocol; however, the numbers and clinical characteristics of these patients will be tracked. Based on the endoscopic and histological findings, all patients with at least one neoplastic polyp will be generally recommended to have a surveillance colonoscopy as follows:
 - a. For 1-2 tubular adenomas (TA), 5-10 years
 - b. For 3 or more TAs, 3 years
 - c. For a TA \geq 1 cm, a polyp with villous histology, or one with high-grade dysplasia, 3 years
 - d. For a large sessile polyp removed piecemeal, 3-6 months
10. The dedicated RA will maintain a database of all information, which is to include:
 - a. Patient demographics – per ProVation report
 - b. Procedure indication – per ProVation report
 - c. Prep quality – per ProVation report
 - d. Procedure findings, per ProVation report. For all polyps, the following variables will be included:
 - i. Location, size, morphology, and type of polyp(s)
 - ii. Method used for polyp removal
 - iii. Path results for each polyp (from the electronic medical record [EMR])
 - e. For the study polyp(s), the following variables will be recorded:
 - i. Location, size, morphology, and type of polyp
 - ii. Method used for polyp removal – cold forceps, hot/cold snare
 - iii. Amount of time required for polyp removal and retrieval
 - iv. For hot-snared polyps, the type and intensity of current used

- v. Amount of SPOT injected
 - f. Path results – both overall and for the study polyp(s)
 - g. Recommendation for surveillance exam interval
- 11. Participating patients' charts will be labeled to indicate that they are participating in a surveillance study to alert endoscopy personnel who encounter them in endoscopic follow-up.
- 12. On a weekly basis, the RA will review all colonoscopy reports from all three hospitals to identify all patients who: a) are included in the trial (with final determination to be made after polyp histology is established), and; b) were eligible for the trial based on endoscopic and histological findings, but who either refused to participate, were not approached, or met at least one pre-randomization exclusion criterion. Post-randomization exclusions, which will be tracked by the RA, will be based on endoscopic findings as described in the procedure report and polyp histology as described in the pathology report or EMR.
- 13. On a weekly basis, the RA also will review the endoscopists' recommendations for surveillance for those patients who are enrolled into the trial cohort, and will record the suggested / recommended surveillance interval, along with reason(s) for deviation from the Multi-Society Task Force guidelines for surveillance (9).

Projected numbers:

A total of 5,400 colonoscopies were performed at IU and WMH in 2006. Based on the exclusion criteria and considering the fact that not all procedures are on unique patients, we estimated that about one-third of these procedures would be ineligible for the study. Of the remaining 3,600, about 20% (720) would qualify for initial study inclusion (based on polyp size and morphology). Considering histological findings to determine final study inclusion, about 75% (540) would qualify. Our goal was to recruit 6 patients per week to the study over a roughly 35 week period, for a total sample size of 210, or 70 persons in each group. We discovered that it has taken much longer to recruit the initial 210 study participants. In addition, given our high number of patients who fail to show for their scheduled appointments, we decided to increase the number of study participants to 270, or 90 in each group, to increase the likelihood of meeting the desired number of follow up patients.

Future Directions:

During the conduct of this pilot study, we will begin preparing a grant application to the NIH for the definitive trial and expect to submit it for the first submission cycle following completion of the pilot study analysis. We expect the pilot data generated from the current study to serve as strong preliminary data demonstrating feasibility of and serving as the initial sample for the definitive trial. The definitive trial will include at least the three campus hospitals (IU and Wishard), and may include, if necessary, Methodist hospital and satellite sites where endoscopy is available.

Conflict of Interest: Drs. Fatima, Rex, and the IU Gastroenterology Faculty have no conflicts of interest with the proposed research.

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Statistical Analysis Plan:

For the larger, definitive trial, the primary outcome of interest will be the detection of neoplasia at the study polypectomy site. A secondary outcome of interest is detection of neoplasia at any site. However, neither of these outcomes applies to this pilot study. Analysis of the pilot study data will consist primarily of descriptive information, including the number of eligible patients (based on the absence of any pre-randomization exclusion criteria and the presence of at least one adenomatous polyp that satisfies size and morphological criteria); and the number of initially randomized patients who were excluded post-randomization because of non-adenomatous polyps). Knowing these numbers is essential to planning the timeline and personnel needs for the definitive trial. Secondarily, we will compare: 1) the baseline features of patients and polyps in each group (cold biopsy polypectomy, cold snare polypectomy, hot snare polypectomy); 2) time required for polypectomy, and; 3) patients included versus those eligible who were not included in the trial.

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

A PILOT RANDOMIZED TRIAL OF POLYPECTOMY TECHNIQUES FOR 4-6 MM COLONIC POLYPS

Your doctor has scheduled you for a colonoscopy today. You are being asked to participate in a research study, the purpose of which is to compare the different techniques of polyp removal. People coming in for outpatient colonoscopy, who pass our inclusion/exclusion criteria are asked to participate in the study. You were selected as a possible subject because you fulfill the eligibility criteria. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Dr. Hala Fatima, Dr. Douglas Rex, Dr. William Kessler, Dr. Debra Helper and Dr. Michael Chiorean. It is funded by The American Gastroenterological Society.

STUDY PURPOSE

The purpose of this study is to compare three different techniques of polyp removal. A polyp is a warty growth in the lining of the colon that can turn into cancer and therefore has to be removed. The three techniques being compared are cold forceps, cold snare and hot snare. All of these techniques are used universally for polyp removal and are well tested; this study is designed to compare the three to determine which one is the most efficient and effective for removal of polyps 4-6 mm in diameter.

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, you will be one of 270 subjects who will be participating in this research locally. This is a pilot study which will determine the feasibility of conducting a larger study.

PROCEDURES FOR THE STUDY:

If you agree to be in the study, you will do the following things:

You will have a colonoscopy performed in standard fashion. During withdrawal of the colonoscope, the endoscopist will look for polyps just like he would even if you were not taking part in the study. A polyp is a warty growth in the lining of your colon that can turn into cancer and therefore has to be removed when found on colonoscopy. Your final eligibility for the study will be determined by the endoscopist if a polyp is found that fulfills the endoscopic criteria for study inclusion (one medium-sized polyp 4-6 mm in maximal diameter). You will then be randomly selected for one of the three polyp removal techniques using a system of consecutively numbered, opaque envelopes from a box located in the endoscopy unit. The three techniques are cold forceps, cold snare and hot snare polypectomy. Cold forceps polypectomy is performed using cold biopsy forceps that are placed through the biopsy channel of the scope. Cold snare polypectomy is done using a snare that passes down the biopsy channel of the scope. A snare is a wire loop device designed to slip over a polyp and, upon closure, result in transection of the polyp stalk. Hot snare polypectomy is performed using the same device but also utilizes thermal energy to cauterize as it cuts the polyp. For cold and hot snare polypectomy, we will use small snares, and will record the number of times the snare is used to remove polyp tissue. The time to perform cold or hot snare polypectomy will be recorded as the time from initial passage. The endoscopist will proceed to perform polyp removal using the assigned technique. All eligible polyps removed as part of the study will be removed using the same assigned technique. All the techniques of polyp removal resection are standard of care in patients undergoing clinical colonoscopies. Upon completion of polyp resection, the endoscopist will inject a dye to tattoo the polypectomy site. Although this is not standard of care in the removal of small polyps, dye injection is a well-tested technique which is used commonly in clinical practice to mark

large polypectomy sites and colonic tumor location. You will be discharged in the usual fashion after recovery.

After examination of the polyp tissue removed from your colon by the pathologist, you will receive the results. You will also receive recommendations from the endoscopist as to when you will need a repeat colonoscopy for follow-up of polyps. At the time of your surveillance follow-up colonoscopy, the endoscopist will examine the sites of the previous polyp resection and look for any evidence of residual or new polyp tissue.

RISKS OF TAKING PART IN THE STUDY:

The risks of colonoscopy include:

1. Reaction to the sedative medication that is given to you to make you comfortable
2. Bleeding from the lining of the colon if a polyp (a warty growth that can turn into cancer) is removed
3. Perforation, which means making a hole in the colon. A perforation is generally the most serious of complications because it would require surgery to fix it. The chance of a perforation is less than 1 in 1,000.
4. If you are pregnant, you will be excluded because the sedation medications can have adverse effects on the developing baby.

The risks of colonoscopy are the same whether or not you decide to participate in this study. In order to keep the risks low, your procedure will be performed entirely by a doctor who is very experienced at colonoscopy. Continuous cardio-respiratory monitoring of patients will be done. This means that you will be hooked up to a heart monitor and your blood pressure, heart rate, breathing and oxygen level will be monitored continuously. Standard procedure precautions will be taken when using electrocautery. Electrocautery is the process of burning or destroying polyp tissue by use of a small probe with an electric current running through it. The polyp is grasped with a loop or snare and is then cut using current through the snare. This current helps cut the polyp while preventing it from bleeding. Furthermore, instructions will be given to avoid aspirin and non-steroidal anti-inflammatory drugs for e.g. ibuprofen if cautery is used.

There is also a risk of possible loss of confidentiality. This will be minimized by:

1. Storing records in a locked facility.
2. De-identifying data by replacing names with unique code numbers.
3. Not mentioning the subject by name in any data collection sheet, report or publication.
4. Protecting the database with a password and will only allowing access to the study investigators and the research assistant.

All these measures will ensure complete subject confidentiality.

BENEFITS OF TAKING PART IN THE STUDY:

You will not get any benefit yourself from participating in this study. However, the potential benefits derived from this study would be realized by future patients based on the results of this study. The results of this study will pave the way to conduct a definitive randomized clinical trial. This in turn will provide better understanding of the effectiveness of the various polyp resection techniques for polyps in the size range of 4-6 mm. Determining the superior method of polyp removal is key to effective and complete removal of precancerous polyps and hence will play a major role in prevention of colorectal cancer.

ALTERNATIVES TO TAKING PART IN THE STUDY:

The alternative to participating is to just have your colonoscopy and polyp removal in a standard fashion, without participating in the study.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published and in databases in which results may be stored.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, the study sponsor, The American Gastroenterological Society, and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) [for FDA-regulated research and research involving positron-emission scanning], the National Cancer Institute (NCI) [for research funded or supported by NCI], the National Institutes of Health (NIH) [for research funded or supported by NIH], etc., who may need to access your medical and/or research records.

COSTS

There is no cost to you for participating in this study.

PAYMENT

You will not receive payment for taking part in this study.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled. If you are participating in research which is not conducted at a medical facility, you will be responsible for seeking medical care and for the expenses associated with any care received.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher Dr. Hala Fatima at 317-274-3505. If you cannot reach the researcher during regular business hours (i.e. 8:00AM-5:00PM), please call the IU Human Subjects Office at (317) 278-3458 or (800) 696-2949. After business hours, please call 317-944-5000 and ask for the GI on-call physician.

In the event of an emergency, you may contact the on-call GI physician at 317-944-5000.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (317) 278-3458 or (800) 696-2949.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with the hospital or university.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study.

I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject's Printed Name:_____

Subject's Signature:_____ **Date:**_____

the subject)

(must be dated by

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date:**_____