Prospective randomized controlled trial describing the recurrence rate of adenomas in sessile or flat colonic lesions 15mm or larger receiving post-resection site treatment with snare tip soft coagulation or argon plasma coagulation

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Prospective randomized controlled trial describing the recurrence rate of adenomas in sessile or flat colonic lesions 15mm or larger receiving post-resection site treatment with snare tip soft coagulation or argon plasma coagulation

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Abbreviations

AE	Adverse Event
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
US	United States

1.0 Background & Rationale

Endoscopic resection of large benign lesions is the preferred treatment over surgical resection. Endoscopic mucosal resection (EMR) is associated with a lower risk and cost compared to surgical treatment. However, it is important that patients undergo endoscopic follow-up after piecemeal EMR in approximately 6 months because there is an approximately 25% risk of recurrence of adenoma polyps [1].

A randomized controlled trial in only 24 patients showed a significant reduction of the recurrence rate by treatment of the normal appearing perimeter of the EMR defect using the argon plasma coagulator [2]. A recent non-randomized trial suggested a substantial reduction by treatment of the perimeter with the snare tip in the soft coagulation mode [3].

In this study we are proposing a randomized controlled trial to test Argon Plasma Coagulation (APC) versus Snare Tip Soft Coagulation (STSC) vs no treatment. In a previous trial of APC, the recurrence rate of the control arm was very high at 67%. With only 24 patients in the study the actual benefits of APC remain uncertain. The previous study using STSC was a non-randomized trial. In this trial we hope to provide definitive evidence regarding the efficacy of APC and STSC vs control.

2.0 Objective(s)

2.1 Primary Objective

To investigate the efficacy of APC or STSC in reducing the recurrence rate at the first follow-up after polypectomy of large colon polyps

Hypothesis:

APC or STSC treatment of the perimeter of the EMR defect will reduce the recurrence rate of adenomas when compared to our control of no treatment.

2.2 Secondary Objective

Time it takes to apply each respective treatment (APC or STSC)

Number of complications for each randomization arm. Examples include bleeding, perforation, pain or post polypectomy syndrome.

Cost analysis detailing the effectiveness of the treatment versus the cost of each therapeutic device (argon probe vs. snare).

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

Primary outcome is the recurrence rate of adenomas at the site of any qualifying, previously resected lesions at the first follow-up colonoscopy. At the first follow-up the endoscopist will view the polypectomy scar with a high definition colonoscope under white light and NBI for any suspicious polyp tissue. The scar will be biopsied. All polyps noted as recurrent by the endoscopist at colonoscopy and/or by the pathologist based on histopathology will be considered a recurrent polyp.

3.2 Secondary Outcome Measures

Time it takes to apply each treatment will be recorded by a research assistant during the index procedure using a stop watch. During the colonoscopy the

treatment time will be recorded as the time, after initial polyp resection, that the randomized treatment instrument comes into view until before clips are applied. Complications will be assessed during the follow-up call simply by asking the patients if they experienced any adverse events. We will use the following definitions to ascertain complications:

Bleeding: severe bleeding event that required hospitalization, a blood transfusion, a colonoscopy, surgery, or any other invasive intervention to control bleeding, and that occurred after the patient left the endoscopy unit and within 30 days after completion of the colonoscopy

Perforation: iatrogenic full thickness defect in the colon wall diagnosed within two weeks of the procedure

Pain: Any pain perceived by the patient after they left the endoscopy unit and within 30 days after completion of the colonoscopy

Post polypectomy syndrome: Abdominal pain, fever, leukocytosis and peritoneal inflammation in the absence of perforation within two weeks of the procedure

Our cost analysis will then take all of these endpoints into account to report which method we found to be more affective. As stated, this will be based on the instrument cost, treatment time, polyp recurrence, and reported complications.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- 25 years and older
- Ability to provide informed consent

- Undergoing colonoscopy for screening, surveillance, diagnostic reasons, or removal of a lesion

4.2 Exclusion Criteria

- Pedunculated lesions
- Inflammatory bowel disease
- Inability to provide informed consent
- Lesions less than 15mm in largest dimension

5.0 Study Design and procedures

A member of the research team will approach a potential subject to discuss participation in the study, including background of the proposed study, inclusion and exclusion criteria, benefits and risks of the procedures and follow-up. If this is of interest to the subject, the informed consent document will be discussed and presented. The subject must sign the consent form prior to enrollment. This form will have prior approval of the study site's Institutional Review Board (IRB). Failure to obtain informed consent renders the subject ineligible for the study.

Patients who have provided informed consented and are scheduled to undergo endoscopic mucosal resection (EMR) of lesions 15mm and larger will be enrolled in the study. During the procedure randomization will be performed by approved study staff once the colonoscopist confirms the eligibility (at least one sessile polyp greater than 15 mm in the largest dimension measured by the snare size). The three arms of randomization are STSC (80 W, Effect 5) vs APC (preferred settings) vs No Treatment of the perimeter of the EMR site. The randomization list,

which will include 645 randomized treatments, will be generated by our biostatistics department by George Eckert. These selections will then be printed and placed into sealed envelopes pertaining to the patient numbers and will be opened following confirmation that the patient is study eligible. Randomization will occur on a per procedure basis.

All randomized subjects will receive a 30-day post procedure follow-up phone call (+ 7 days) and be scheduled, as per the standard of care, to receive a standard follow-up colonoscopy procedure after the initial procedure. The follow-up window for the primary endpoint has been extended beyond 6 months due to procedure delays caused by the COVID-19 pandemic. We will measure the rate of recurrence by endoscopic visualization of the EMR site at the first follow-up using endoscopic magnification and electronic chromoendoscopy, as well as systematic biopsy of the scars. Additionally we will look for the presence of scarring and any clips retained.

6.0 Enrollment/Randomization

All colonoscopies in the study will be performed by Dr. Douglas Rex or one of the Sub-Investigators listed above. Patients will be 25 and older and will be randomized to one of the aforementioned arms of the study. Blinding of the PI will be maintained until the end of the polypectomy procedure at the primary procedure. Further blinding is not possible due to the nature of the study.

Screen failure: any patient enrolled in the study but not randomized because of not satisfying polyp size or other exclusion criteria discovered during the procedure.

7.0 Study Calendar

Index procedure will be the day of colonoscopy where one of the intervention arms or the control arm is administered. Patients will receive a follow-up phone call at 30-days (+ 7 days) to ascertain any complications as previously described. Patients will also receive a follow-up colonoscopy (standard of care for large polyp removal) where the polypectomy site is observed for any recurrence.

	Index procedure	Follow-up phone call	Follow-up colonoscopy
	Day 1	Day 30 + 7 days	Approximately Day 180
Study Procedures	Colonoscopy with one of the intervention arms or control	Phone call to ascertain complications	Colonoscopy to observe for recurrence at polypectomy site

Lost to follow-up: All patients who are randomized to one of the interventions but fail to complete the required follow-up colonoscopy. Failure to contact at 30 days will not be considered lost to follow-up (complications information in such cases will be deemed acceptable if collected at the first follow-up but an accurate accounting of the number of such patients will be kept and reported to the DSMB).

8.0 Reportable Events

All adverse events meeting prompt reporting criteria will be reported to the IRB within 5 business days of the study team becoming aware of the event. An adverse event meeting prompt

reporting criteria for this study is defined as any event assessed by the PI, or appropriately trained and qualified designee, as (1) unexpected, (2) related or possibly related to study participation, AND (3) suggesting that the research places subjects or others at greater risk of harm than was previously known. The period for assessing AE's will be from the point of inserting the colonoscope until 30 days after the index colonoscopy.

9.0 Data Safety Monitoring

See Data and Safety Monitoring Board Charter for information about DSMB. Briefly, the data safety monitoring board comprises 4 members: Charles J. Kahi MD (Indiana University), Huiping XU PhD (Indiana Universtiy), Cyrus Piraka MD (Henry Ford Hospital), and Joseph B. Elmunzer MD (Chair), (Medical University of South Carolina). None of the board members are involved with the current study in any capacity. Additionally, Dr. Rex's research team will provide him up to date information regarding the status of patients and any reportable events.

The data collected at sites other than IU will be de-identified before being sent to us. Each site will enter their data in to a secure web application (REDCap), which will then be accessed at the primary site. Only de-identified data from external sites will be added to the database (no HIPAA identifiers will be collected from external sites besides procedure dates and de-identified images of study lesions). Any other communication that is not patient related will be done over email or phone. Variables that will be transmitted from the other site include:

- Information from the procedure to remove the large polyp
    - This includes information about meeting inclusion/exclusion criteria, procedure date, randomization envelope number/randomization treatment, age, gender, race,

ethnicity, whether a fellow was involved in the procedure (and which parts of procedure, if applicable), procedure times, study polyp characteristics, de-identified study lesion images, resection times, information about the resection such as snare/ injection fluid usage and number of resected pieces, treatment times, other additional treatments used, clipping times, number/type of clips used, type of colonoscope used, Boston Bowel Preparation Score, whether fibrosis was present, whether there were any prior attempts at resection, information about procedural complications (if any), and study polyp pathology results

- Information from the 30 day follow up call
  - This includes information about whether the follow-up phone call was made successfully, date subject was reached by phone, and whether patient reported experiencing adverse events (and if so, information about the adverse event).
  - Information from the first follow-up procedure
  - This includes information about the previous EMR site, date of follow-up procedure, pathology results from residual or recurrent polyp tissue found at previous EMR site (if applicable), and pathology results from biopsies obtained from previous EMR site

10.0 Study Withdrawal/Discontinuation

Any subject who wishes to withdraw from this investigation on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the Investigator may decide for reasons of medical prudence, to withdraw a subject. In either event, the Investigator will clearly document the date and reason(s) for the subject's

withdrawal from this investigation in the CRF and should indicate whether or not he considers it was related to the study interventions.

11.0 Statistical Considerations

Assuming a 25% recurrence rate of the control arm, and a reduction to 10% in both of the treatment arms, we estimate that a sample size of 115 subjects per arm will be needed to demonstrate that APC and STSC are superior to no treatment for reduction of recurrence rate after EMR, based on 80% power and a two-sided 5% significance level for comparison of independent proportions with one interim analysis. The no treatment arm will be used as our control. In order to account for drop-outs, an extra 35 patients will be enrolled into the study to ensure sufficient data will be included in the analysis. Therefore, a sample size of 380 subjects will be enrolled in this study.

Once a polyp has been identified and its size fits within the targeted range, each subject will be randomized in a 1:1:1 ratio using a computer generated randomization sequence. Enrollment into the study will be competitive with the possibility for each site outside of IU to randomize up to 100 patients. Not all 645 randomization numbers generated will be used in the study. Instead each external site will continue to enroll until a total of 380 patients have been randomized study-wide with a potential to randomize up to 100 patients. Randomization numbers will be assigned as follows: IU will be assigned numbers 001 – 095 and 496 - 526; AdventHealth Orlando will be assigned 096 – 145 and 446 - 470; The Johns Hopkins Hospital will be assigned numbers 146 – 195; Dartmouth-Hitchcock Medical Center will be assigned numbers 196 – 245; NYU Langone Medical Center will assigned numbers 246 – 295 and 471 - 495; the Mount Sinai

Hospital will be assigned 296 – 345, Sibley Memorial Hospital will be assigned 346 – 395, the University of Kansas Medical Center will be assigned 396 – 445, and Penn State Health Milton S. Hershey Medical Center will be assigned 546 - 595. The proportion of subjects with recurrence will be compared between study arms using chi-square tests. The number of complications will be compared among treatment arms using negative binomial regression. Treatment times and costs will be compared between the APC and STSC arms using Wilcoxon Rank Sum tests. A 5% significance level will be used for all tests.

Interim analysis and stopping rule:

The interim analysis will be conducted after half of the subjects have completed the study, using an O'Brien-Fleming spending function with alpha levels 0.003 and 0.049 at the interim and final analyses. Any results will be considered significant at a p-value of <=0.003 at the interim analysis and the DSMB will make a decision about stopping the study based on those results.

12.0 Statistical Data Management

Primary data will be collected via case report forms. All paper charts pertaining to the patient will be kept under lock and key in coordinators office away from the endoscopy area. Each site will enter their data in to a secure web application (REDCap). Virtual data will be stored on an internal network drive with encryption and password security. Only approved personnel by the IRB will have access to the file storage. This file will also not have any identifiable patient information. A study log with the identifiable information will be kept in a separate folder to enable the investigators to assist in any research audit. No procedural data except the date of examination will be entered into this log.

The storage location on IU servers will be backed up automatically and continuously. Quality assurance steps will include built in range checks for age, procedure duration, lesion size, total resection time, treatment time, clipping time on REDCap and remote study site visits after completion of the study by 190 patients.

Remote study site visit:

Before interim analysis and after completion of the study by 190 patients, 10% of case report forms from each site will be verified with the site's electronic medical system information via a video based call from the central data site (IU). Any patterns of systematic errors will trigger the verification of all case report forms for that particular site.

13.0 References

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3. Tate DJ, Bahin FF, Desomer L, et al. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. Endoscopy 2018;50:52-62.