Effect of epinephrine on immediate post-polypectomy pain in colorectal lesions larger than 20 mm

NCT04065451

10/19/20

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Abbreviations
This page is optional. The list below includes some common abbreviations. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
IRB	Institutional Review Board
PI	Principal Investigator
US	United States

1.0 Background & Rationale

Polypectomy is an important aspect of colonoscopy for colorectal cancer prevention[1]. Large sessile polyps (≥20 mm in any dimension) are particularly challenging to remove. Endoscopic mucosal resection (EMR) is an effective therapy for patients with large laterally spreading colon neoplasms measuring greater than 20 mm[2]. Main complications of endoscopic resection include bleeding, perforation, transmural injury and recurrence[3].. Our anecdotal observation is that most patients with large colorectal lesions complain of pain immediately after polypectomy when using epinephrine.

Epinephrine is sometimes used as an additive to submucosal injection fluid primarily to reduce immediate (intra-procedural) hemorrhage[2]. The submucosal injection generally consists of non-allergenic viscous solution to raise the polyp away from the submucosa thereby reducing the chance of submucosal injury and perforation. Adding epinephrine to this solution is generally accepted and left to endoscopist discretion. We hypothesize that the complaint of pain in patients with polypectomy of colorectal lesions might be due to the use of epinephrine. Epinephrine reduces the propensity for immediate bleeding by contracting the blood vessels in the surrounding area where it's injected, causing a degree of ischemia. Any relative ischemia might be the cause of the patients' pain.

2.0 Objective

To identify if epinephrine use during EMR will result in a change in patient pain perception

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measure

The primary outcome measure is the mean of the two pain scores assessed on a visual analog scale (VAS, 10 cm vertical line, appendix 1) at 30 minutes and one hour after colonoscopy.

3.2 Secondary Outcome Measures

We will also collect information on the ease of polypectomy (Sydney resection quotient, *en* bloc resection, quality of mound) and frequency of immediate bleeding among both groups.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

1. Patients aged 18 years and over
2. Patients scheduled for treatment of large (≥ 20 mm) colorectal polyps
3. Able to sign informed consent

4.2 Exclusion Criteria

1. Patients previously enrolled in the study
2. Pedunculated polyps
3. Polyps not amenable to endoscopic resection
4. Patients allergic or sensitive to epinephrine

5. Patients with coronary artery disease who have had a myocardial infarction in the past year, or had coronary stenting in the past year, or had angina in the past year.
6. Patients electing anesthesia other than monitored anesthesia care with propofol (MAC) for colonoscopy

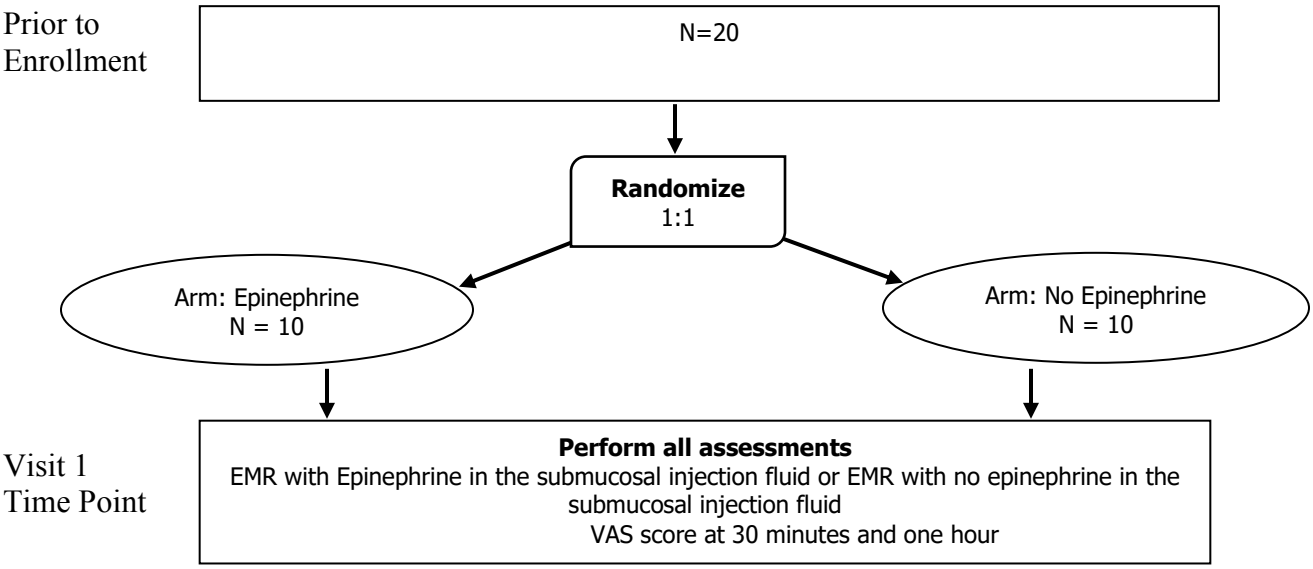
5.0 Study Design

All patients scheduled for the resection of a colorectal polyp ≥ 20 mm in diameter under MAC with propofol will be approached and explained the purpose of the study. If the patient is eligible, and willing to participate in the study and signs an informed consent, patient will be enrolled in the study. Randomization will be performed after Dr. Rex measures the polyp as ≥ 20 mm in diameter and decides on employing EMR for polypectomy.

If EMR is not employed, the patient will not be randomized and will be excluded from the study. Randomization is computer generated using a 1:1 ratio for the two arms in the study.

Patients in the epinephrine arm will receive a submucosal injection of hetastarch and indigo carmine dye with diluted epinephrine (1:200,000, 5μg/ml) [5]. Patients in the no epinephrine arm will receive submucosal injection of hetastarch and indigo carmine dye but no epinephrine. Submucosal injection will be prepared by a registered nurse in the technicians' area away from the endoscopy room and the endoscopist will not be aware of the randomization. The endoscopist will administer the submucosal fluid. The total volume of injected fluid will be

determined by the lesion and the need for fluid volume to achieve adequate lift before snare resection, and will not exceed 100 ml.



6.0 Enrollment/Randomization

The subject will be randomized to one of the 2 arms – Epinephrine arm and non-epinephrine arm after the PI inspects the polyp for EMR potential. The research coordinator at this point will break the randomization by opening a sealed envelope. The PI will be blinded to the injection solution throughout the study.

7.0 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 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 injecting submucosal fluid till the patient is discharged**.**

8.0 Data Safety Monitoring

The PI, Dr. Rex has a large practice of resecting large polyps and we hope to recruit the 20 patients as quickly as possible. Although this is a randomized trial, both arms of the study are currently commonly used in clinical practice and both are within the standard of care. Dr. Rex also uses both approaches in his practice. The use of epinephrine (1:200,000 as generally used in colon polypectomy) does not add significantly to the cost of the procedure and doesn't raise important safety issues. All safety precautions for large polyp resection will be followed. Dr. Rex will monitor adverse events including delayed hemorrhage, post-polypectomy syndrome and perforations.

9.0 Study Withdrawal/Discontinuation

Any patient who likes to withdraw from the study at any point can do so. The data collected until the patient withdraws consent will be used to maintain data integrity.

10.0 Statistical Considerations

We hope to recruit 10 patients into each arm of the study. Our anecdotal observation is that using epinephrine dramatically increases the post-procedure pain perception of patients. To our

knowledge, there is no literature comparing these two groups with pain outcome measure. The visual analog score is widely used for pain during colonoscopy procedures but there are no relevant publications testing whether epinephrine affects pain after EMR. We calculated that the total sample size of 20 will have 90% power to detect a 50% decrease in mean pain scores at a 2-sided type 1 error rate of 0.05 using a student's t-test (a decrease of mean VAS from 90 with epinephrine to 45 without epinephrine, with a standard deviation of 30 in each group). Sydney resection quotient and quality of mound will be analyzed using Wilcoxon rank sum tests. The proportion of patients who have an en bloc resection and immediate bleeding will be compared using chi-square tests.

11.0 Statistical Data Management

Primary data will be collected via paper charts and stored electronically on the S-drive located on IUSM Gastroenterology servers. Access will be limited and password controlled. Data on S-drive is backed up continuously and copies transferred to secure storage every 30 days. We will use Microsoft Excel for data entry and storage. Paper charts will be stored in the administration area away from the endoscopy suite. Charts will be stored for a period of 5 years from the end of the study recruitment. As part of quality control, Excel file will be checked for data entry errors at recruitment of 10 patients.

12.0 References

1. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144:74-80 e1.
2. Committee AT, Hwang JH, Konda V, et al. Endoscopic mucosal resection. Gastrointest Endosc 2015;82:215-26.

3. Klein A, Bourke MJ. How to Perform High-Quality Endoscopic Mucosal Resection During Colonoscopy. Gastroenterology 2017;152:466-471.
4.
5. World Health Organization. Epinephrine (for use with local anaesthetics). Model Prescribing Information: Drugs Used in Anaesthesis, Geneva, 1989:33