A randomized, double-blind, comparative, effectiveness and safety study of Eleview vs. Hetastarch in subjects undergoing Endoscopic Mucosal Resection (EMR) of colonic lesions equal to or larger than 11mm

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Introduction:

EMR is a technique used for the removal of flat or sessile neoplasms confined to the superficial layers of the GI tract using a snare. Injection-assisted EMR is commonly used during resections of larger flat lesions as it provides submucosal lift of polyps, adenomas, other gastrointestinal mucosal lesions or early-stage cancers prior to EMR. This has been found to minimize mechanical or electrocautery damage to the deep layers of the gastrointestinal tract wall as the injectate provides a "safety cushion" as such between the area to be removed and healthy mucosal tissue (ASGE, 2008).

Several solutions are used today for injecting lesions including saline, hyaluronic acid, and hydroxyethyl starch (Hetastarch). Saline solution has been found to dissipate within minutes, which may result in a lower quality lesion lift. Hyaluronic acid provides a longer lift, but is expensive and is not readily available in the U.S (Hwang, 2015).

A new injectate known as Eleview has been developed for use in gastrointestinal endoscopic procedures and recently approved by the FDA. This injectate boasts a cushion of excellent height and duration through the use of an oil-in-water emulsion. However the initial cost of this material is quite high ($80 per 10 ml). Hetastarch, which is the current injectate used by Dr Rex, is a safe and considerably inexpensive solution that provides prolonged submucosal elevation and lowers procedure times (Fasoulas, 2012). Our study will aim to compare Eleview to Hetastarch in the hopes of finding the ideal submucosal injectate. This trial will focus on polyps of size ≥11 mm removed by snare EMR technique. Patients with lesions deemed not suitable for EMR due to features suggestive of sub-mucosal invasion will not be included.

Injectate randomization:

Study patients will be randomly assigned to the Eleview or the Hetastarch treatment group in a 1:1 ratio. Randomization will occur at the site using envelopes provided by the Investigator. The envelopes contents will specify the treatment assignment for each patient and opened by the research team (PI will be blinded).

We will monitor the safety and effectiveness data. The appropriate solutions will be injected into the submucosal space beneath the lesion(s) to be excised before the lesion(s) is/are removed. Subjects in both groups will receive the appropriate volume of injectate deemed necessary by the PI for the individual patient.

Objectives**:**
Primary objectives of the study are:

- To evaluate the effectiveness of Eleview injection in comparison to Hetastarch, for EMR. Effectiveness will be evaluated by the Sydney Resection Quotient (SRQ), which is defined as the size of the polyp divided by the number of pieces resected.

- To evaluate the safety of Eleview for EMR procedures in relation to adverse events and occurrence of complications during and after the EMR procedure in comparison to Hetastarch injectate.

*Secondary objectives***:**

- To collect other effectiveness data regarding the administration of Eleview in comparison to Hetastarch, such as injectate amount required for efficient lesion lift and complete removal.

End-points:

Primary endpoints:
- Effectiveness of Eleview in comparison to Hetastarch for EMR in terms of:
    - Sydney Resection Quotient
    - Number of subjects with *en bloc* resection of lesions.

- Safety outcomes as assessed by complications during or after the procedures including:
    - Intra-procedural bleeding (bleeding requiring therapeutic intervention during the EMR*)*.
    - Early (<24h) and delayed (≥24h post EMR) post-procedural bleeding (bleeding post procedure that necessitates transfusion or endoscopic hemostasis because of hematemesis or a decrease of Hgb concentration of more than 2 g/dL after EMR).
    - Perforation

- Post-Polypectomy Syndrome
- Hospital admissions for any clinically relevant complications post-procedure.

Secondary endpoints:

- Effectiveness of Eleview compared to Hetastarch in terms of:

  - Injected volume needed for initial lesion lift
  - Injected volume needed for complete removal of lesion
  - Number of re-injections (number of times the injection device is passed down the scope).
  - Number of resected pieces
  - Ease of use for polyp removal and fluid behavior combined, and rated on a 5-point scale for: very easy, easy, neutral, difficult and very difficult.
  - Time (in minutes) to remove the lesion completely (measured from the first injection to final excision of the lesion), and total time of procedure.
  - Need for additional treatments such as avulsion, coagulation or ablation.
  - Pathological reports for negative lateral and/or deep margins (lateral margins only accurately assessed in *en bloc* resections)
  - Presence and number of deep resections containing muscularis propria.
  - *En-bloc* resections histologically examined for free-margins.
  - Recurrent or residual neoplasia rates examined by biopsy (if applicable) at the follow-up visit.

<u>Sample size and Statistical Analysis</u>

At least 200 patients will be enrolled. 100 of these patients will be randomized to Eleview injectate and 100 will be given the standard of care, Hetastarch injectate only. Efficacy and safety of Eleview injectate has only been reviewed in one previous study. Therefore, the planned sample size was not calculated using a statistical power analysis, but was regarded as sufficient to repeat the objectives of the COSMO study (2017) and satisfy the exploratory purposes of the present study. Study personnel will carry out a simple randomization using a commonly used online generator. Randomization assignments will then be sealed until day of procedure until patient eligibility has been confirmed. The Principal Investigator will remain blinded and will perform all data analysis after completion of the study.

Data will be summarized and compared using classic descriptive statistics, i.e. mean, standard deviation, coefficient of variation (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative

variables.
The Sydney Resection Quotient will be compared between treatment groups using a Wilcoxon Rank-Sum test. The proportion of subjects with *en bloc* resection of all endoscopically visible lesions will also be compared between treatment groups using a Fisher's exact test. A nominal alpha level of 0.05 will be used for both the comparisons.
No formal comparison will be performed for the secondary endpoints.

Selection criteria

Inclusion criteria:

1. Sex and age: men and women > 18 years old
2. Subjects referred for EMR of polyps of size ≥11 mm
3. ASA score 1, 2 or 3.
4. Contraception: Women of childbearing potential must have a negative pregnancy test (one is provided as the standard of care) or sign a waiver. Post-menopausal women must have been in that status for at least 1 year (per standard of care).
5. Subject is willing and able to participate in the study procedures and to understand and sign the informed consent

Exclusion criteria:

1. Age: Subjects is under 18 years old
2. Consent: Vulnerable subjects including those who are unable to consent
3. Pregnancy: Pregnant or breastfeeding women
4. ASA score <3
5. Physical findings: Abnormal physical findings that may interfere with the study objectives

Excluded lesions:

- Lesions less than 11 mm in largest dimension
- Lesions involving the muscularis propria (T2 lesions)
- Ulcerated depressed lesions (Paris type III) or pathology proven invasive carcinoma
- Proven malignant disease locally advanced or with metastasis
- Active inflammatory bowel disease lesion, e.g ulcerative colitis, Crohn’s disease

6. Endoscopic appearance of invasive malignancy
7. Previous partial resection or attempted resection of the lesion
8. Allergy: Proven or potential allergic reaction to study products or history of anaphylaxis to drugs
9. Severe liver disease.

10. Known or suspected gastrointestinal obstruction or perforation, active diverticulitis, toxic megacolon,
11. Inflammatory bowel disease e.g ulcerative colitis or Crohn's disease
12. Hemostasis disorders (eg Von Willebrand disease, factor V Leiden thrombophilia or haemophilia), known clotting disorder (INR>1.5).
13. Subject with any other current serious medical conditions that would increase the risks associated with taking part in the study.
14. Patients must be advised to stop anticoagulation medications prior to the procedure per local practice guidelines and should re-start as clinically indicated after the procedure.

Visit 1 will be a screening appointment where the patient will be educated about the study and the informed consent document will be completed. The patient medical history will then be recorded, as well as current medications taken. The patient will also undergo a physical exam as standard of care. This visit can be combined with Visit 2 (Day of Procedure).

During *Visit 2*, inclusion and exclusion criteria will again be confirmed and after the lesion has been measured and found to be ≥11mm and suitable for EMR, the patient will be randomized to the injectate. Polyps will be documented by photographic record prior to randomization. The injectate will be prepared out of sight from the investigator performing the EMR so that the investigator will remain blinded to the injectate. Patient vital signs including BP, HR and SpO2 will be recorded prior to, during, and after the procedure. Once the lesion has been injected, only Boston Scientific Captivator snares measuring 15-20mm will be used to resect the polyps, however additional treatment modalities required will also be recorded.

Visit 3 will consist of a follow up phone call 30 days±7 later. The occurrence or persistence of any adverse events will be recorded.

Data integrity and safety:

All paper charts pertaining to the patient will be kept under lock and key in coordinators office away from the endoscopy area. The data entry will be performed into an excel file which will be stored on an internal network drive with encryption and password security. Regular quality control checks of the data will be performed. Only approved personnel by the IRB will have access to the file storage. This file will also not have any identifiable information (name, DOB or

mrn). A study log with the identifiable information will be kept in a separate folder (also encrypted) 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 data and safety will reviewed annually in addition to the continuous PI monitoring. Protocol revisions will be proposed, if needed, based on the results of the safety review including, but not limited to, stopping the randomization process.

References:

COSMO (2017). A randomized, double-blind, comparative, effectiveness and safety study of SIC 8000 in subjects undergoing Endoscopic Mucosal Resection (EMR) of colonic lesions equal to or larger than 2 cm