RESEARCH PROTOCOL
INVESTIGATOR INITIATED TREATMENT TRIALS
Document date 4/8/2021

Title of Project: Closure of mucosal and submucosal defects in the gastrointestinal tract using the novel X-Tack endoscopic suturing device

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Abstract

Background: Perforation rates following endoscopic submucosal dissection (ESD) of colonic lesions can be as high as 4% with delayed bleeding rates of up to 8%, resulting in significant patient morbidity. Endoscopic closure of resection defects is the least invasive method for closure of perforations or fistulas and has been shown to reduce delayed bleeding rates. The X-Tack is a new system for endoscopic suturing that has been designed to be use through the operating channel of standard endoscopes, as opposed to the previous standard of care (the Overstitch system) which needed to be loaded onto a separate endoscope.
Methods: Adult patients presenting for endoscopic closure of a gastrointestinal luminal defect will be enrolled and randomized 1:1 to closure of the defect with either the X-Tack system (the study group) or the Overstitch system (the control group.) Demographics, comorbidities, laboratory values, size of defect, time to close the defect, and the number of sutures to close the defect will be recorded. The primary outcome will be the time to closure of the defect. Secondary outcomes will include the rate of incomplete closures (as defined as either crossover to the other study group per endoscopist's discretion, or the need for additional modalities to close the defect such as endoscopic clips) as well as complications (bleeding, infection, perforation) and costs. Time to closure will be compared using the student T-test. To detect a 5-minute mean difference between the two groups at 80% power with an alpha of 0.05 and 1:1 randomization, 16 patients will be required in each group. Anticipating loss of subjects or data for technical or unanticipated reasons after randomization, we expect that 50 patients will need to be enrolled.

A. Specific Aims

The primary objective of the study is to compare the time required to close a defect or fistula in the gastrointestinal tract between the X-Tack system and the current standard of care (suturing with the Overstitch system.) The secondary objectives of the study will be to compare the rate of incomplete closures (as defined as either crossover to the other

study group per endoscopist's discretion, or the need for additional modalities to close the defect such as endoscopic clips) as well as complications (bleeding, infection, perforation) and costs between the X-Tack system and the current standard of care. We hypothesize that the X-Tack system will permit faster closure of endoscopic defects compared to the current standard, because the X-Tack does not require a different endoscope to use.

B. Background and Significance

Perforation rates with endoscopic submucosal dissection (ESD) of colonic lesions and early cancers can be as high as 4% with delayed bleeding rates up to 8%. Endoscopic closure of resection defects has been shown to reduce delayed bleeding rates in the colon and is the least invasive method for closure of perforations or fistulas. Current options for closure include through-the-scope (TTS) clips, over-the-scope clips (OTSC,) and endoscopic suturing with the Overstitch system. TTS clips frequently misdeploy or are dislodged during complex closures and are cumbersome for the closure of large defects. OTSC are limited to closure of ~2 cm defects but are unable to capture the entirety of larger defects. The Overstitch system can close defects of any size but requires the use of a double-channel endoscope that is wide in diameter and is often too short to reach the right colon. It also requires removal of the endoscope that is being used for the resection from the patient in order to introduce the double-channel scope for closure. The X-Tack system offers the ability to close large defects with endoscopic sutures but can be introduced through the instrument channel of any standard endoscope, filling the gap between clips and suturing.

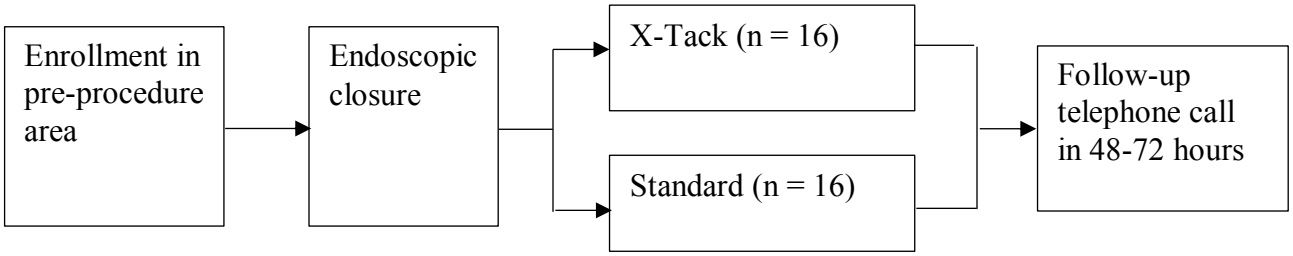
C. Preliminary Studies/Progress Report

The X-Tack is currently FDA cleared on the basis of similarity to previous suturing devices, though human data is pending. Preclinical animal data primarily compared the X-Tack to through-the-scope (TTS) clips. In the 24 X-Tack cases, 21 could be closed with just one X-Tack device, while a second device was used in 3 cases. Technical closure of defects in the animal model was successful in 24/24 cases using the X-Tack, versus just 13/16 cases using TTS clips. On necropsy, the time to complete healing of the defects was comparable between the X-Tack and TTS clip cases. On this basis, the investigators concluded that the X-Tack achieved expected levels of tissue healing and higher technical success rates than the current standard of care.

D. Research Design and Methods

Currently, the community standard is that gastroenterologists who are familiar with Overstitch start using the X-Tack without additional training. However, a hands-on demonstration session with the X-Tack device in a "dry lab" has been conducted with each endoscopist in the trial prior to the study in order to familiarize them with device before enrollment. Each endoscopist has also participated in a "wet lab" using an explant (porcine stomach) to simulate in vivo closure of defects using the X-Tack system. The device operates in a similar fashion compared to previous suturing devices, which are

used frequently by all endoscopists involved in this study. On this basis, all endoscopists in the study report comfort and familiarity with the X-Tack system, and the "break-in" period is not anticipated to affect safety or results during the study. The primary study visit will be comprised of the endoscopic procedure at the time of defect closure and a telephone call 48-72 hours later to assess for complications. Patient will be enrolled in the pre-procedure area. If the patient has a pre-procedure visit, they may be notified of their potential for enrollment in the study at that time, though not all patients have a pre-procedure visit in our practice. Patients will be randomized to closure with the X-Tack system versus closure with the Overstitch system prior to their procedure using a centralized computer-generated randomization. Technical success of closure, time of closure, number of sutures required, need for alternative modalities for closure, and any intraprocedural complications (bleeding, perforation) will be recorded. Any patient with possible periprocedural perforation will receive antibiotics at the endoscopist's discretion. At the endoscopist's discretion, the patient may cross over during the procedure to the other group if they believe that their current closure strategy is failing to safely close the defect. Alternate methods of closure (TTS clips, over-the-scope clips) may be used in either group if required by the endoscopist for safe closure of the defect. After the procedure, most patients are observed in the recovery area for 1-2 hours for any signs of complications before they are discharged home.



E. Statistical Methods

Time to closure will be compared using the student T-test. To detect a 5-minute mean difference between the two groups at 80% power with an alpha of 0.05 and 1:1 randomization, 16 patients will be required in each group (32 patients in total.) Anticipating loss to follow-up and patient dropout, we expect that a total of 50 patients will be required. Categorical variables will be compared using the chi squared test.

F. Gender/Minority/Pediatric Inclusion for Research

Women and minorities will be included in the research protocol.

G. Human Subjects

1. Provide number, age range, and health status of the subject population. List criteria for inclusion or exclusion.

We anticipate enrolling 50 patients in total.

Inclusion criteria: Patients > 18 years of age undergoing closure of a gastrointestinal luminal defect for which a suturing device would be otherwise indicated.

Exclusion criteria: INR > 2, platelets < 150, ongoing anticoagulation not meeting ASGE Antithrombotic Guidelines (Acosta RD et al, The Management of Antithrombotic Agents for Patients Undergoing GI Endoscopy, Gastrointest Endosc, 2016; 83(1): 3-16,) hemodynamic instability, ongoing or anticipated pregnancy

2. Identify sources of research material in the form of specimens, records or data.

Records and data will include chart data including demographics and comorbidities, laboratory values, endoscopy reports, and video acquired during endoscopy.

3. Describe plans for recruitment and consent procedures to be followed.

The endoscopist performing the procedure will meet the potential subject in the pre-procedure holding area. The endoscopist will review the consent documents with the potential subject. The subject will be provided time to review the entirety of the document and ask any questions of the endoscopist that they have. If they are amenable to proceeding, they will sign the consent and the procedure will be performed. No additional recruitment or inducement (i.e. advertising) is anticipated.

4. Describe risks and assess likelihood and seriousness.

The primary potential risk of this research is device failure (i.e. failure to close defect or complications of closure, such as bleeding or perforation.) Device failure is expected to be uncommon. Most device failures are expected to be minor (i.e. perhaps requiring an additional device to complete closure of the rest of the defect, but no immediate harms or risks to the patient besides longer procedure time.) Serious complications (i.e. bleeding or perforation attributable to the device and requiring hospitalization) are expected to be very rare.

5. Describe procedures for protecting against or minimizing potential risks.

Because the research device will be used for defect closure during the same period of sedation as the current standard of care, participants should not perceive any difference in their procedure beyond signing an additional consent form. Patients with a propensity for bleeding i.e. thrombocytopenia or coagulopathy will be excluded to avoid adverse events.

6. Describe potential benefits and importance to the subjects and others.

Participants could potentially benefit from a faster defect closure with reduced anesthesia time. The ease of deployment of the X-Tack device also might make clinical success more likely. If the X-Tack device proves to be a faster, safer way to close mucosal defects or fistulas, future patients undergoing endoscopic submucosal dissection or fistula closure could benefit from less anesthesia time and a better chance at clinical and technical success.

7. Discuss why risks are reasonable in relation to benefits.

The risks and side effects of closure with the X-Tack system are anticipated to be identical to those of the Overstitch system. Given that the Overstitch is the current standard of care, and the X-Tack is anticipated to be faster and more user-friendly, the benefits of introducing the X-Tack outweigh the risks.

H. Data and Safety Monitoring Plan

1. Data and Safety Monitoring Plan (DSMP)

a. reporting mechanisms for adverse events to the IRB, FDA, and NIH.

Adverse events will be tracked and reported to the IRB at the time of interim analysis and final analysis (anticipated study time is less than one year.) Adverse events will be defined as bleeding, infection, or perforation occurring within 72 hours of the procedure. Severe adverse events will be reported to the IRB at the time of occurrence. Adverse events will be defined using the ASGE Adverse Event Lexicon (Cotton PB et al, A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc, 2010; 71(3): 446-454.) Severe adverse events in this lexicon are considered any adverse events resulting in hospital admission >10 days, ICU admission > 1 night, surgery for an adverse event or permanent disability. Severe adverse events will be reported using the OHR online portal.

b. adverse event (AE) grading

Adverse events will be graded according to the ASGE adverse event lexicon.

c. plan for unanticipated AE reporting

Severe adverse events will be reported to the IRB at the time of occurrence.

d. plan for annual reporting of AEs

The anticipated study time is less than one year, thus all reporting will occur at the time of interim analysis and final analysis.

e. interim efficacy analysis where appropriate

Perforation rate and complications related to inadequate closure (leak, fistula, peritonitis, bleeding) will be monitored. Perforation or complications related to inadequate closure > 50% compared to control group will lead to

stoppage of the trial. Interim analysis will be performed at the midpoint of enrollment (25 patients.) For instance, if after 25 patients have enrolled, 2 patients in the control group experience a complication, yet 4 experience a complication in the X-Tack group, the results will be reviewed with the independent safety monitor for possible stoppage of the trial pending discussion with the IRB.

2. If applicable, describe the Data and Safety Monitoring Board (DSMB) that will be responsible for monitoring the study.
An independent reviewer has been selected within the Jefferson Division of Gastroenterology who is outside of the investigator group who will review the interim analysis.

I. Literature Cited

1. Kothari ST., Huang RJ, Shaukat A et al. ASGE review of adverse events in colonoscopy. Gastrointest Endosc 2019;90:863-76
2. Pohl H, et al. Clip Closure Prevents Bleeding After Endoscopic Resection of Large Colon Polyps in a Randomized Trial. Gastroenterology 2018;157:977-984.
3. Qumseya BJ, Wolfsen C, Wang Y, et al. Factors associated with increased bleeding post endoscopic mucosal resection. J Dig Dis 2013;14:140–146.
4. Cotton PB et al. A lexicon for endoscopic adverse events: reports of an ASGE workshop. Gastrointest Endosc 2010;71(3):446-454.

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