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The NEAT Study (Novel ElectroAcupuncture). Electroacupuncture After Laparoscopic Colon Cancer Resection: Thinking Outside The Box. Study Protocol.

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Abstract:

Introduction: *Colorectal cancer is the second leading cause of cancer-related death in the US; complete surgical resection is the only curative treatment for non-metastatic colorectal cancer (NMCC). Postoperative ileus (POI) frequently increases patient morbidity and healthcare costs. Enhanced recovery after surgery (ERAS) protocol is the standard of care in most institutions and has been shown to reduce postoperative complications, but there is no a completely effective treatment for this condition. Studies suggest that electroacupuncture (EA) can improve gastrointestinal tract function after surgery.*

Objective: *We aim to determine if including EA to the standard treatment of POI decreases the time to the first defecation, enhancing the return of normal bowel function after colon resection for NMCC.*

Methods: *We propose a phase II, single-center, randomized, triple-blinded, sham-controlled trial with two parallel arms and a 1:1 allocation ratio. Patients 40-80 years of age diagnosed with NMCC scheduled to undergo laparoscopic surgery for colon cancer resection will be included. The arms will be EA + standard treatment and sham EA + standard treatment. The standard treatment will follow the ERAS protocol.*

Discussion: *This will be the first randomized clinical trial to evaluate the impact of using EA along with the ERAS protocol for POI. This intervention may reduce patient morbidity and improve healthcare costs associated with the disease.*

Keywords: *Colorectal cancer, postoperative ileus, ERAS, electroacupuncture*

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Abbreviations:
NMCC: non-metastatic colon cancer
POI: postoperative ileus
ERAS: Enhanced Recovery After Surgery
EA: electroacupuncture
POD: Postoperative day

INTRODUCTION

Colorectal cancer is the second most common cancer in females and third in males, and the second leading cause of cancer-related deaths in the US (Siegel et al., 2020). The only curative treatment for non-metastatic colorectal cancer (NMCC) is complete surgical resection. Postoperative ileus (POI) symptoms such as abdominal

pain, delayed passage of stool and flatus, and intolerance of solid diet are usually present and tend to resolve within 2 to 3 days (Liang et al., 2019). Pharmacologic agents used to treat this condition have shown side effects, limited efficacy, and a high economic burden (Van Bree et al., 2012). A non-pharmacologic approach to enhance recovery is acupuncture, which can be manual, electroacupuncture (EA), or transcutaneous acustimulation (J. D. Z Chen et al 2018).

EA involves a combination of manual acupuncture and electric current stimulation (Hershman et al., 2018). The mechanism on how EA exerts its effect on the gastrointestinal tract is known to be through an increased vagal efferent activity (Carmichael et al., 2017).

Ng et al. studied 165 patients undergoing laparoscopic resection for colorectal cancer, assigned to EA, sham-EA, or control. They found that patients who received EA had a shorter time to defecation (P= 0.001) and length of hospital stay (P= 0.007) when compared to sham-EA and control, demonstrating EA's effectiveness (Ng et al., 2013). However, the authors recognized as a limitation the fact that they could not state with certainty whether the difference observed between the groups occurred due to the action of acupuncture on intestinal function directly or due to the lower dose of opioids required for pain control.

The Enhanced Recovery After Surgery (ERAS) protocol integrates evidence-based techniques to reduce postoperative stress and complications. It focuses on pre-admission, intraoperative, and postoperative strategies and is considered a standard of care during the early postoperative period (Gustafsson et al., 2018). We decided to compare the combination of EA + standard treatment based on the ERAS guidelines versus sham-EA + standard treatment. By basing our standard treatment on ERAS guidelines, all patients will receive healthcare interventions to decrease the risk of POI, minimizing ethical issues or any potential barriers for patients' willingness to participate.

This randomized trial protocol aims to evaluate whether the addition of EA to the standard treatment of POI decreases the time to the first defecation, enhancing the return of normal bowel function after colon resection for NMCC in the attempt to reduce POI. To our knowledge, this will be the first randomized clinical trial to evaluate the impact of using EA along with the ERAS protocol for POI.

METHODS

Trial Design & Study Setting

This is a phase II, parallel-group, randomized, blinded, and sham-controlled superiority trial. Allocation concealment will occur in a 1:1 ratio to EA + standard treatment or sham acupuncture + standard treatment. The standard treatment will follow the ERAS guidelines.

The study will be conducted in an American hospital considered reference in laparoscopic colon cancer resection, where ERAS protocol is fully implemented. The adherence to ERAS recommendations aims to standardize anesthetic, surgical, and perioperative clinical management.

Randomization

Patients will be randomized to either control or experimental group through a web-generated randomization list provided by REDCap (Research Electronic Data Capture) software. An independent staff member will retain the software password to assess the randomization code. Consecutive allocation will occur at a 1:1 ratio to one of the groups at least four hours after the surgical procedure and right before the first EA session. Blocked randomization with random sequences of blocks (4 to 6) will be used to guarantee allocation concealment.

The randomization sequence will be secured by a password. Neither the surgeons nor any staff member involved in the study will have access to it. Every time a patient arrives in the postoperative ward, the acupuncturist will access the software, inform the password, and have the allocation known.

Blinding and Unblinding

This will be a triple-blinded study in which subjects, physicians, and outcome raters/statisticians will be unaware of allocation. A blinded investigator (independent physician) will evaluate study outcomes, and a staff member unrelated to the research team (independent nurse) will feed the data into a separate file. Only the acupuncturist responsible for the procedure will be aware of the subject group allocation.

Due to the controversial aspect of sham procedures for EA, a blinding assessment will be performed at the end of the study's follow-up. Subjects will be questioned to speculate their group allocation through a three-category response: "active", "control" or "do not know". This data will be evaluated by the Bang´s

blinding index (BI), in which successful blinding is zero (BI=0).

Unintentional unblinding from either the subjects, physicians or raters, is considered a protocol deviation. It will be reported and explained, irrespective of the reasons for its occurrence. However, in the name of integrity and safety of the subjects, the intention to treat principle will be held. Its advantages in the study include the reflection of the daily clinical practice, the intact holding of randomization, and maintenance of the study power.

Emergency unblinding

Acupuncture is not associated with moderate or severe adverse effects, so blinding is not likely to be broken. However, in exceptional cases of severe side effects, emergency unblinding will be performed and a 24-hour hotline will be available if immediate medical attention is needed. If unblinding is required, the principal investigator should report it in the emergency unblinding database, explaining the reasons. Patients and the research team should remain blinded.

Eligibility

Inclusion criteria:

- Patients 40 to 80 years of age
- Diagnosis of NMCC
- Scheduled to undergo elective laparoscopic surgery for colon cancer resection

Exclusion criteria:

- History of a major abdominal or pelvic surgery
- Pregnancy
- Experienced past acupuncture treatment
- Allergy to acupuncture needles
- Local skin infection/active skin lesions, or limb amputation/deformities in acupuncture treatment areas
- Sepsis or intra-abdominal abscess
- Intestinal obstruction
- Metastatic colorectal cancer
- Patient with stoma
- Bleeding disorder or on anticoagulants
- Chronic opioid use
- Impaired circulation and/or severe arterial disease
- Diagnosis of autonomic gastrointestinal dysfunction due to any comorbidities including but not limited to diabetes
- Inflammatory bowel disease
- Unstable epilepsy or history of unexplained seizures
- Previous stroke or spinal cord injury that alter the patient's sensitivity
- Pacemaker or implantable electronic devices
- Postoperative complications that require conversion to open surgery or ICU
- Regional anesthesia or analgesia (epidural catheters) using opioids in the perioperative period
- Preoperative radiation or chemotherapy

Recruitment Strategy

Participants will be recruited from the surgery department of the participating center. Surgeons will help to target potential candidates in both the inpatient and outpatient settings, providing a list of potential participants who fulfill the inclusion criteria. The research team will arrange a meeting with each patient and explain the study aim, benefits and risk of intervention and expected outcomes, and secure informed consent. The patient and family will get an opportunity to clarify any questions or concerns with the team. The patient will be given a brochure explaining the aim of the study, benefits, and risks of EA, the patient role and responsibilities in this study, and contact information of the research team. The research team will secure the informed consent document if the patient agrees to participate in the study. A copy of the information will be sent to the research team to double-check the adequacy of the recruited candidates. A copy of the consent form and a detailed information sheet will be provided to each participant included.

Timeline

The trial´s timeframe will begin on the day the initial consent is signed and will last until the subject completes the study. The intervention will start on postoperative day (POD) 1 and will be performed twice for 30 minutes daily, until POD 3 or primary outcome, whichever occurs first. Follow-up will last until POD day 10. For both primary and secondary outcomes, there will be a continuous evaluation. The total time for the trial completion is expected to be 2 years **(Figure 1)**.

Adherence

The main approach to maximize adherence will be through patient education and open communication with participants. During the recruitment phase, individualized educational training will be given to all participants, to make sure they fully understand the study protocol. The research team will undergo special training regarding adherence-promoting behaviors to

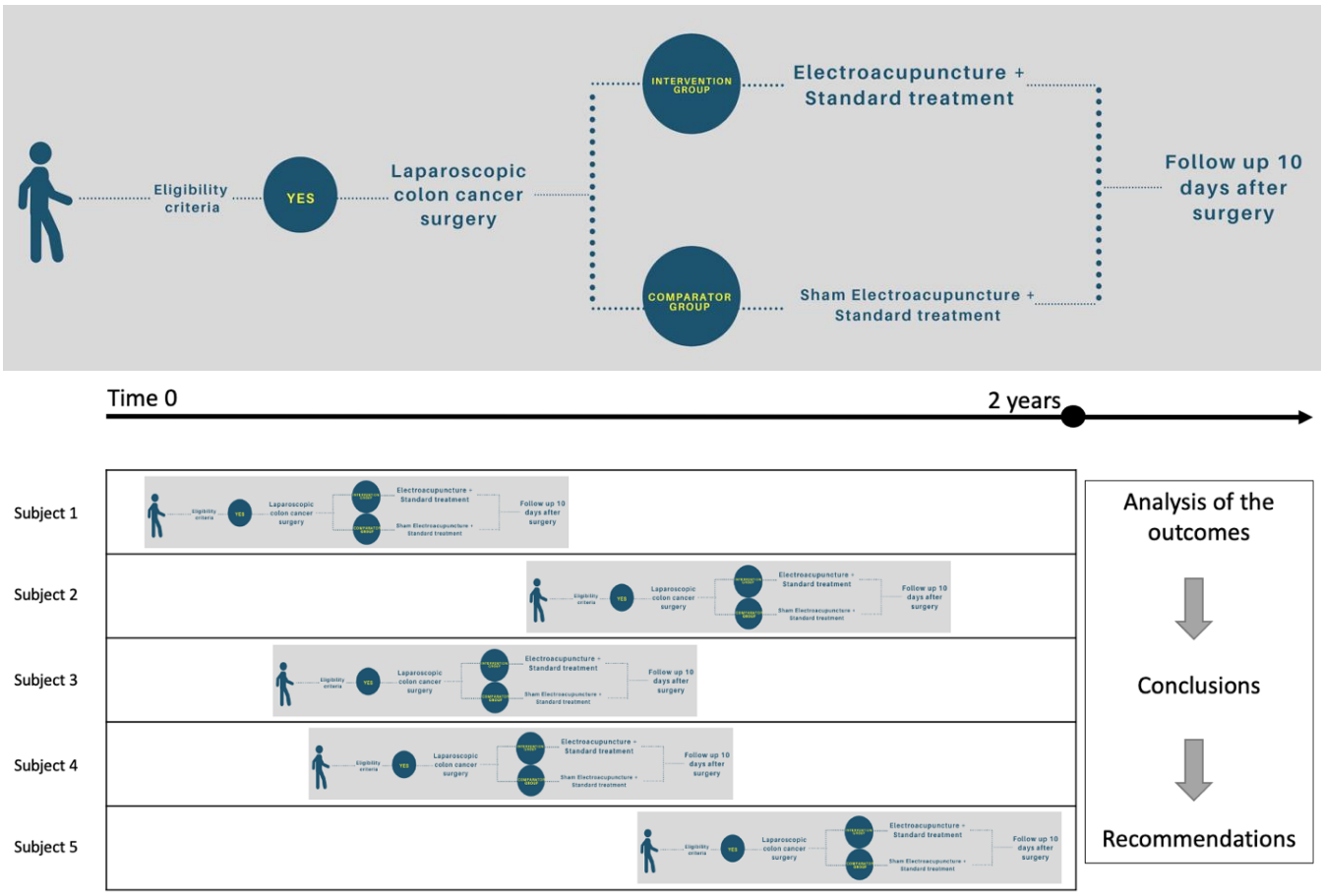

Figure 1. Timeline

raise awareness about the impact of a good patient-provider relationship in attaining adherence.

During the follow-up period, an assigned research team member will monitor the patient's symptoms through a daily telephone call while maintaining a symptom diary until POD 10, a time in which all patients are expected to have the outcome. The contact number will be provided to the participants to ensure effective communication with the research team, as well as a notebook in which the patient will write down the exact time of defecation.

Interventions

Eligible patients will be randomized in a 1:1 ratio between EA of bilateral ST36, ST37, and SP6 acupoints + standard treatment **(Figure 2)** or sham acupuncture + standard treatment. The intervention will be based on the Traditional Chinese Medicine technique, performed by a qualified acupuncturist with more than five years of experience. The team of acupuncturists will be composed of two experts on the field available 24h. Disposable sterile acupuncture needles will be used (length, 25 mm; diameter, 0.22 mm; Hwato; Suzhou Medical Appliance Factory, Suzhou, China) with an estimated insertion depth of 20mm for each point until muscle twitch or deqi according to Massachusetts General Hospital Acupuncture Sensation Scale (MASS). Deqi describes the subjective sensations felt by the patients during acupuncture treatment.

Needles will be connected to the ES-160 6-channel programmable EA device (Ito Company, Ltd, Tokyo, Japan). Electric stimulation will be set at 100Hz for 30 minutes. The first session will be delivered eight hours (+/- 2 hours) after the surgery's conclusion and repeated every 12 hours until defecation to a maximum of 6 sessions. We have established a maximum of 6 sessions based on evidence generated by previous studies, which found that 6 is the number of sessions needed to generate a bowel movement (Liu Y. et al., 2018).

The sham procedure will be performed using a blunt tip needle with 0.30 mm in diameter and 25 mm in length that does not puncture the skin at the original acupoints (ST36, ST37, SP6), and an adhesive pad of

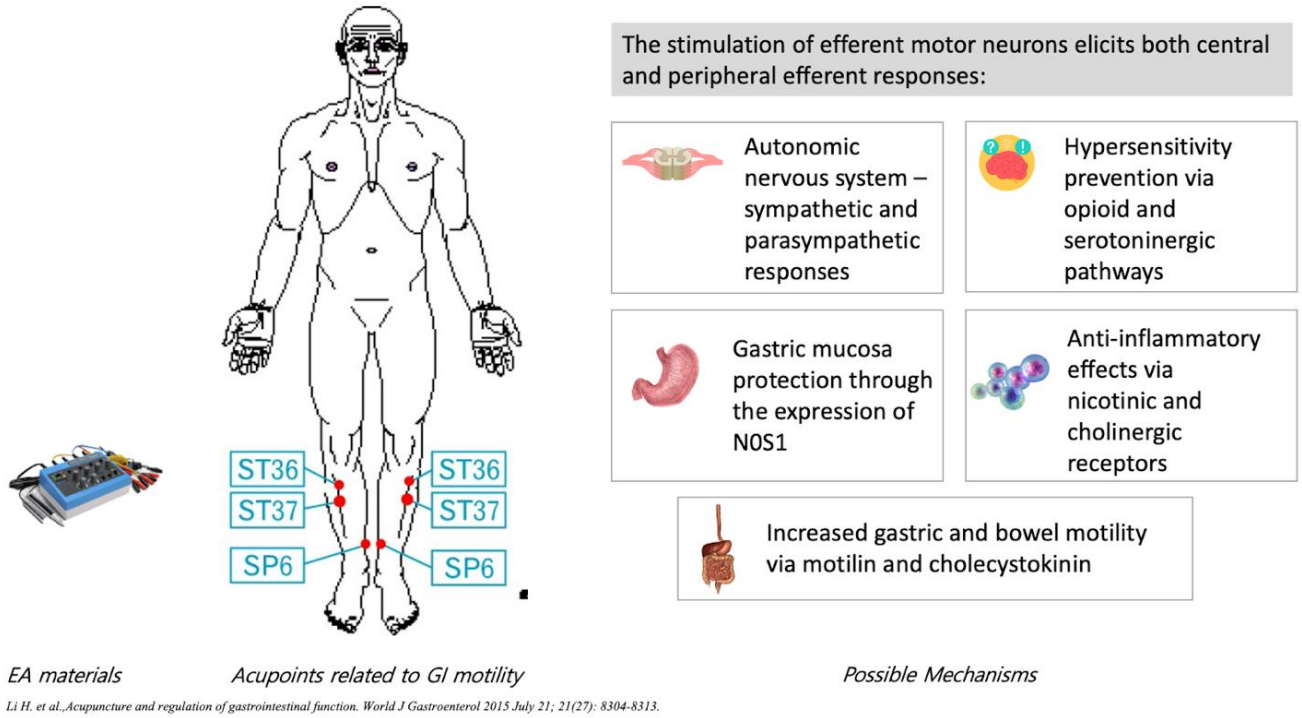

Figure 2. EA points and main physiologic effects

sterile cylindrical polyethylene foam with double-sided adhesive tape at the bottom. The pad has the function of fixing the placebo needle at the acupoint and blinds the patient; it will be used in both EA and sham procedures (Liu B et al.,2014). After placing the placebo needle, it will be connected to the switched wires to not generate any electrical stimulation and will follow the same schedule as the EA.

Modification/Discontinuation

If stimulation frequency of 100Hz is not tolerated, it will be reduced according to tolerance. The session will be performed for 30 minutes, and the protocol modification will be recorded and analyzed. Treatment will be discontinued when the primary outcome or the maximum number of sessions is achieved, whichever happens first.

Based on previous studies, we do not expect adverse events, including pain, with EA. If we encounter the rare circumstance that a patient experiences intolerable pain related to the procedure, they can have a short break and continue with the session. A complete session is defined as a session in which the patient has received at least 25 minutes of EA. Patients that did not undergo at least 25 minutes of EA due to pain, discomfort, or any other reason will be excluded from the analysis.

Outcomes

The primary outcome is time to first defecation (in hours), starting when the surgery ends. The research staff will instruct the patients to record the time of their first defecation and notify immediately to the nursing staff, which will document it on the medical records. Also, as part of the follow-up done by the research staff, information about the time of defecation will be added to the symptom diary. If the patient is not at the hospital at the time of the outcome, they will be asked to record the exact time at home. Research staff will make daily calls to monitor if the outcome has happened and will be reminding those who have not defecated yet to record the time when it happens. Daily calls will be made until the occurrence of the primary outcome. This outcome was chosen based on its objectivity and relevance to the clinical management of patients.

The secondary outcomes are the length of hospital stay in hours, time to first flatus in hours, and the total opioid usage measured by morphine equivalent in milligrams. They will be measured during hospitalization; the information will be collected from the patient's chart. They will be asked to register the time of the first flatus and to notify the nursing staff.

Data Management

An electronic data capture (EDC) system record (REDCap) will be completed for each subject enrolled in the clinical study. The investigator will review, approve, and lock each EDC record. The investigator's record locking serves as an attestation of the responsibility for ensuring that all clinical data entered on the EDC is complete, accurate, and authentic.

The medical records and the patients' symptom diary will be considered Source Data and will contain the clinical findings and observations, and other information collected during the clinical trial.

All data will be stored on encrypted, password-protected computers, and stored securely within REDCap. Only the PI, data manager, and researchers specific to this study who have been granted access to the data by the PI will be able to view the data of the protected folder. When data is sent out to be analyzed the data will be de-identified. The data will contain subject identification numbers, which are linked to the medical record numbers on a separately secured spreadsheet. The data will be labeled by assigning each subject an identification number and removing any identifiable information. The code will be secured by the PI and Study Coordinator on encrypted and password-protected computers. The code that links information that can identify the subject to the data collected for this research will be kept separate from their protected health information. All research related records will be kept for 10 years after the completion of the study.

Sample Size

A sample size of 190 with 95 participants for each of the two groups was estimated using Stata/IC v.16.1 (StataCorp - College Station, TX, USA) considering the findings from Ng et al. (2013). Their trial is a landmark paper for EA after laparoscopic surgery for colorectal cancer, presenting a correlation with two of the three EA points used in this protocol. Thus, their finding in time to defecation of 85.9 hours ± 36.1 in the EA group, and 122.1 hours ± 53.5 when given standard therapy, determined our expected effect size. Sample size calculation considered an alpha level of 0.05 with a two-sided hypothesis, 90% power, and assuming 20% dropout. Such a high dropout rate is expected due to the need to follow up after discharge from the hospital, which could decrease patient adherence.

Statistical Analysis

The significance level will be set at 0.05 considering a two-tailed hypothesis, comparing control and intervention groups. Primary and secondary outcomes will be analyzed using two-sided unpaired T-tests. Multivariable regression analysis will be performed to account for possible confounders.

Missing Data

As a balance through randomization is maintained, it will be included in the analysis considering the group they were first allocated into, thus using an intention to treat protocol.

Missing data for mean time to the first defecation, length of hospital stay, first flatus, and total morphine milligram equivalents per day will be addressed with multiple imputation. We will replace missing values with imputed ones from the regression model constructed with baseline characteristics.

We will report the reasons for each of the missed observations and compare those qualitatively between groups but also quantitatively to see if the missing values are balanced across groups. A sensitivity analysis will be conducted to estimate the impact of each missed value to better identify missing values not at random, comparing the results from multiple imputation against complete case analysis.

DISCUSSION

The NEAT study aims to determine the potential effects of using EA as an add-on to the ERAS protocol following laparoscopic NMCC resection, to enhance intestinal function recovery. EA is a novel, non-pharmacological intervention, without major adverse effects, that has proven to be feasible in the postoperative period. Previous RCTs and meta-analyses addressed EA effects on POI and showed controversial results (Deng et al., 2013; Meng et al., 2010; Ng et al., 2013; Liu et al., 2018).

POI is associated with prolonged patient recovery (Person; Wexner, 2006), hospitalization, increased healthcare costs, and worse postoperative quality of life (Kehelt, 2008; Langenhoff et al., 2001). Furthermore, pharmacological agents used to treat POI have limited efficacy (Van Bree et al., 2012). Therefore, EA might be a potential adjuvant in the management of POI.

Interestingly, this would be the first RCT to evaluate EA following the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations in standardized postoperative management following the ERAS guidelines. Moreover, this study applies a previously validated sham procedure, a common source of bias

associated with a hard outcome, minimizing our risk of bias.

As a phase two trial, our study presents some limitations. It adopted narrow eligibility criteria and excluded patients with significant postoperative complications, which might limit the generalizability of the findings. Likewise, the exclusion of fragile patients may result in a smaller frequency of POI than previously estimated in the literature (Greco et al., 2013), affecting the power of the study.

Our biggest challenge was to determine an adequate control group. Considering the balance between aiming to exclude the placebo effect from the lack of sham group and the incidental physiological effect of the sham procedure, we adopted a very well-validated technique proposed by Liu et al. 2014, which found no statistically significant differences in the experience between the active and sham groups.

Nevertheless, we firmly believe our sham will be masked and will not have a significant effect; we decided to assess blinding's success at the end of the trial due to controversial studies using sham acupuncture techniques. We think this analysis will reinforce the chosen sham's validity and generate hypotheses according to our findings. Furthermore, independently of our primary analyses results, the blinding assessment will provide valuable insights into this research field.

Failing to show significance in our primary analysis will not invalidate the study's purpose or hypothesis. Despite a negative result, we think this could be relevant due to the scarcity of robust and well-designed trials that assess acupuncture for ileus. There is still controversy on whether this intervention is effective; thus, a negative result of a well-designed study can shed light on this matter.

Results according to our hypothesis may positively impact the application of EA in clinical practice decreasing the incidence of POI and the duration of postoperative recovery time and consequently reducing the need for medications, patient morbidity, and ultimately minimizing health expenditures per patient.

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Conflict of Interest

None

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