PROSPECTIVE RANDOMIZED TRIAL OF IMMEDIATE POSTOPERATIVE USE OF A REGULAR DIET VERSUS CLEAR LIQUIDS IN ELECTIVE COLORECTAL SURGERY.

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BACKGROUND. Offering patients, a low residue diet on the first postoperative day (POD1) after colorectal surgery is safe and improves surgical outcomes and postoperative hospital stay (Lau C, Phillips E, Bresee C, Fleshner P. Early use of low solid is superior to clear liquid diet after elective colorectal surgery. Ann Surg 2014; 260:641-649). We have recently demonstrated the feasibility and safety of the immediate use of a regular diet after elective colorectal surgery (Chough I, Zaghiyan K, Ovsepyan G, Fleshner P. A feasibility and safety study of the immediate use of a regular diet after elective colorectal surgery. Poster, Annual Meeting of the Southern California Chapter of the American College of Surgeons, Jan 2017 and Chough I, Zaghiyan K, Ovsepyan G, Fleshner P. Prospective study of the feasibility and safety of the immediate use of a regular diet after elective colorectal surgery. ePoster American Society of Colorectal Surgeons, June 2017). The purpose of this study is to prospectively evaluate whether providing a patient a solid diet from postoperative day zero is superior to clear liquids. The primary endpoint measured will be patient tolerability, as evidenced by absence of vomiting. The secondary endpoints measured will be duration of supplemental intravenous hydration needed, length of hospital stay and postoperative complications, and intestinal rate measured by Abstats (Gi Logic, Pasadena, CA).

AbStats™ (GI Logic; Pasadena, CA) is an FDA cleared wearable gastrointestinal biosensor system for functional assessment of the gastrointestinal tract. The device has been tested and validated for monitoring of gastrointestinal recovery after colorectal surgery (Kaneshiro et al. Postoperative Gastrointestinal Telemetry with an Acoustic Biosensor Predicts Ileus vs. Uneventful GI Recovery. J Gastrointest Surg 2016; 20:132-9; Spiegel et al. Validation of an Acoustic Gastrointestinal Surveillance Biosensor for Postoperative Ileus. J Gastrointest Surg. 2014; 10:1795-803). In these prior studies, Abstats has predicted postoperative ileus with a slower median intestinal rate 3.01/min compared with patients not developing ileus (median intestinal rate 4.46/min). However, in these studies, advancement of diet was not standardized and many patients were maintained NPO until return of flatus. A secondary aim of this study will be to compare intestinal rate measured by Abstats™ in patients offered immediate solid versus clear liquids after colorectal surgery to determine if Abstats™ can predict intolerance to feeding early on.

PROTOCOL

Protocol Title:	Prospective randomized controlled trial investigating commencement of low residue diet versus clear liquids on postoperative zero following elective colorectal surgery, with regards to patient tolerability, incidence of nausea and/or vomiting, and postoperative length of hospitalization stay.
Study Rationale	The purpose of this study is to evaluate whether giving a low residue diet immediately after elective colorectal surgery is superior to clear liquids with regards to patient tolerability in an elective colorectal surgery patient. Patient tolerability is evidenced by absence of vomiting.

Study Population:	Based on current literature, the incidence of postoperative nausea and vomiting varies widely and can reach up to 40% in abdominal surgery patients. Thus, patient tolerability to postoperative enteral feeds is taken as 60%. This is a superiority trial: Group I is the clear liquids group and patient tolerability in this group is taken to be 60%. Group II is the low residue diet group. Group II is assumed to be superior to group I with respect to patient tolerability. Group sample sizes are taken to be 50 in group one and 50 in group two, thus achieving an 80% power to detect a difference between the group proportions of 0.2451. The proportion in group one is assumed to be 0.6000 under the null hypothesis and 0.8451 under the alternative hypothesis. The proportion in group two is 0.6000. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is 0.0524.
Hypothesis	The primary hypothesis is that the incidence of postoperative ileus is not affected by the consistency of enteral diet given, and patients who are placed on low residue diet from postoperative zero do not have an increased risk of postoperative nausea and/or vomiting as compared to patients who are placed on clear liquids. The null hypothesis in this superiority trial design is that both group I (clear liquids group) and group II (low residue diet group) are equally tolerated by patients on postoperative day one following elective colorectal surgery. The alternative hypothesis is that both groups differ, and group II (low residue diet group) is superior to group I (clear liquids group) with regards to patient tolerability.
Study Design:	Single-center, prospective, randomized trial.
Intestinal Telemetry	Abstats™ consists of a disposable plastic device embedded with a microphone that adheres to the abdominal wall and connects to a computer measuring acoustic event rates. The monitor will be placed on the patient's abdomen 30 minutes prior to surgery in the preoperative holding area to obtain baseline intestinal rate. The monitor will be removed prior to surgery and replaced by the surgical team in the operating room and maintained until postoperative day 3. Daily intestinal rate will be calculated as mean and median acoustic events per minute. The raw data will be analyzed by an investigator blinded to the clinical data. Intestinal rates of patients offered immediate solid feeds will be compared with those offered clear feeds. In addition, patients not tolerating or consuming early solid meal will be compared with those who do to identify whether Abstat™ can be an early predictor of diet intolerance in patients undergoing colorectal surgery.

Primary Efficacy Endpoint:	Patient tolerability, as evidenced by development of vomiting on postoperative day two.
Secondary Endpoints:	1. Whether ordered diet was consumed and % consumption on POD0 2. Time to flatus. 3. Time to first bowel movement 2. Length of postoperative stay. 3. Quality of life measures, recorded by self-administered questionnaire. (Please see appendix A for the questionnaire.) 4. Duration of supplemental intravenous hydration. 5. Need for insertion of nasogastric tube. 6. Postoperative complications, including surgical site infections. 7. GI motility patterns as assessed by ABStats 8. Composite of patient reported nausea, vomiting, abdominal distention or bloating, belching, heartburn, eructation, gas pain, constipation, diarrhea, halitosis, aspiration, pneumonia, regression of feeding to NPO or liquid feeds, intraabdominal abscess or anastomotic leak, insertion of NG tube, fecal impaction, small bowel obstruction, postoperative use of laxative
Safety Endpoints:	Enteral feeds or nil by mouth advice the patient would have otherwise received.
Sample size:	The study is powered ($\alpha = 0.05$, $B = 0.80$) to detect a 24.5% difference in proportion of patients developing nausea and/or vomiting; 50 patients per arm are required.
Interim Analysis	There will not be an interim analysis.
Key Inclusion Criteria:	1. Able to freely give written informed consent to participate in the study and have signed the Informed Consent Form; 2. Males or females, >18 years of age inclusive at the time of study screening; 3. American Society of Anesthesiologists (ASA) Class I-III; 4. Colorectal surgery (open and/or robotic/laparoscopic); 5. Elective Surgery.

Key Exclusion Criteria	1. Mentally incompetent or unable or unwilling to provide informed consent or comply with study procedures. 2. Children <18 years of age. 3. Pre-operative clinical diagnosis of intestinal obstruction. 4. Pre-existing known upper gastrointestinal disorders including hiatus hernia, gastroesophageal reflux disease, peptic ulcer disease. 5. Pre-existing oropharyngeal disorders such as stomatitis, altered taste sensations. 6. Colorectal surgery with concomitant re-sectional surgery of the stomach or proximal jejunum (small bowel). 7. Pregnant patients. 8. Bedbound or moribund patients. 9. Pre-existing history of clinical depression. 10. Epidural analgesia. 11. Surgical procedures completed after 4pm 12. Patients taking narcotics prior to elective colorectal surgery After randomization: 1. Postoperative diagnosis of intra-abdominal sepsis, including anastomotic leaks. 2. Postoperative complications requiring early reoperation within the same hospital stay.
Treatment Regimen/ Duration:	Patients will be assigned into one of two groups: Group I - Clear liquids on postoperative day zero immediately upon return to the floor and subsequent days' advancement of enteral diet to regular diet is as per discretion of the attending physician. Group II - Regular diet from postoperative day zero immediately upon return to floor and onwards. Three questionnaires assessing quality of life are to be completed by the patient, during his/her hospital stay. On postoperative day one, a self-administered questionnaire is to be completed by the patient. Please see appendix A for the questionnaire details. The same questionnaire is administered on postoperative day two and again on the last day of hospitalization.

Treatment Failure/ Discontinuation Criteria:	Patients will be discontinued from the trial at any time as a result of any other event that in the opinion of the investigator warrants discontinuation from the trial. Additionally, patients will be excluded after randomization if: 1. Intraoperative complications require postoperative use of nasogastric tube; 2. Postoperative complications require early re-operation or a planned second operation within the same hospital admission. 3. Prolonged unanticipated need for intravenous opioids beyond postoperative day five.

Statistical Analysis Plan

Based on current literature, the incidence of postoperative nausea and vomiting varies widely and can reach up to 40% in abdominal surgery patients. Thus, patient tolerability to postoperative enteral feeds is taken as 60%. This is a superiority trial: Group I is the clear liquids group and patient tolerability in this group is taken to be 60%. Group II is the low residue diet group. Group II is assumed to be superior to group I with respect to patient tolerability. Group sample sizes are taken to be 50 in group one and 50 in group two, thus achieving an 80% power to detect a difference between the group proportions of 0.2451. The proportion in group one is assumed to be 0.6000 under the null hypothesis and 0.8451 under the alternative hypothesis. The proportion in group two is 0.6000. The test statistic used is the two-sided Z test with pooled variance.

2. SCHEDULE OF EVENTS/ DATA COLLECTION

	Group One: Control arm. Clear liquids from postoperative day zero
Visit Number	Admission
Informed Consent	✓
Demographics	✓
Height	✓
Medical History[1]	✓
Inclusion/ Exclusion Criteria Review	✓
Previous /Concomitant Medications	✓
Physical Exam[2]	✓
Vital Signs[3]	✓
Body Weight	✓
Placement of ABStats[7]	✓
Volume of oral intake on postoperative day zero (ml)	✓
Adverse Events[4]	✓
Quality of Life Assessment[5]	✓
Hospital Discharge or Early Termination Visit[6]	✓

	Group Two: Low Residue diet arm. Low Residue diet from postoperative day zero.
Visit Number	Admission
Informed Consent	✓
Demographics	✓
Height	✓
Medical History[1]	✓
Inclusion/ Exclusion Criteria Review	✓
Previous /Concomitant Medications	✓
Physical Exam[2]	✓
Vital Signs[3]	✓
Body Weight	✓
Placement of ABStats[7]	✓
Volume of oral intake on postoperative day zero (ml)	✓
Adverse Events[4]	✓
Quality of Life Assessment[5]	✓
Hospital Discharge or Early Termination Visit[6]	✓

Both arms:	
Postoperative Data	
Open or Laparoscopic	✓
Reason for surgery (benign or cancer, palliative intent or curative intent.)	✓
Type of Surgery (LAR, APR, IPAA, etc)	✓
ASA Score	✓
Level of anastomosis (less than 5 cm from anal verge)	✓
Neoadjuvant chemotherapy	✓
Neoadjuvant radiation therapy	✓
Intraoperative Fluid Volume (mL)	✓
Intraoperative Blood Loss (mL)	✓
Intraoperative and/or Postoperative Blood Transfusion	✓
Preoperative Bowel preparation	✓
Diverting stoma	✓
Antibiotic therapy more than 24 hours postoperatively	✓
Total Hospital stay Morphine equivalent (mg)[8]	✓
Quality of Life assessment[5]	✓
ABStats[7] motility data	✓

1. Medical History information will be collected via medical records at index admission including: Hypertension, Lung Disease, Diabetes
2. Comprehensive physical exam information will be collected from medical records at index admission
3. Vital Signs will be collected form medical records (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) at index admission.
4. Adverse events (AEs) will be recorded at every visit post screening. AEs will be followed until resolution.
5. Quality of Life assessment will be obtained on postoperative day one, postoperative day two and the last day of hospitalization (Appendix A)
6. Early Termination visits are used when a patient withdraws from the study (i.e., prior to hospital discharge).
7. ABStats motility data using the Acoustic Gastro-Intestinal Surveillance Biosensor (AGIS, GI Logic, Inc. Pasadena CA)
8. Morphine equivalent: 7 mg ≈ 1 mg hydromorphone

	Group I: Clear liquids arm	Group II Low residue diet arm
Clinical Endpoints		
Patient tolerability: - Development of nausea and/or vomiting from postoperative day one, two and three.	✓	✓
Need for insertion of nasogastric tube.	✓	✓
Return of bowel function; return of flatus as surrogate measure.	✓	✓
Length of postoperative hospital stay.	✓	✓
Number of postoperative days on supplemental intravenous hydration.	✓	✓
Surgical site infection	✓	✓
Other infective complications: - pneumonia. - Urinary tract infections.	✓	✓
Anastomotic Leak.	✓	✓
ABStats motility data[7]	✓	✓

APPENDIX A
Quality of Life Assessment Visual Analogue scale.

ABDOMINAL PAIN

Please identify how much *abdominal pain* you are having by drawing a vertical line across the horizontal line at the location that best describes the level of abdominal pain that you are currently experiencing.

NO PAIN		**WORST PAIN IMAGINABLE**

NAUSEA

Please identify how much *nausea* you are having by drawing a vertical line across the horizontal line at the location that best describes the level of abdominal pain that you are currently experiencing.

NO NAUSEA		**WORST NAUSEA IMAGINABLE**

ABDOMINAL BLOATING

Please identify how much *abdominal bloating* you are having by drawing a vertical line across the horizontal line at the location that best describes the level of abdominal pain that you are currently experiencing.

NO BLOATING		**WORST BLOATING IMAGINABLE**

FOR STUDY STAFF

I confirm that the above survey was completed by patient __ __ __ on date ___ ___ ___:

Subject ID:__ __ __