Project Title: Tolerability of an Amino Acid-based Oral Rehydration Solution in Children with Short Bowel Syndrome

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Study Site: Boston Children's Hospital (BCH)

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1. Background

Intestinal failure (IF) is defined as a critical reduction of the gut mass/function below the minimum needed to absorb nutrients and fluids required for adequate homeostasis, growth and development. It is a condition in which severe malabsorption results in the need for lifesaving parenteral nutrition (PN) or enteral nutrition (EN) (1). In neonates, the most common cause of IF is surgical short bowel syndrome (SBS), which is defined as the need for prolonged parenteral nutrition following surgery for congenital or acquired gastrointestinal disorders. SBS is characterized by a compromised bowel absorptive capacity because of a reduced mucosal surface, which if left untreated can result in diarrhea, fluid and electrolyte imbalance, and malnutrition. Limiting the duration of PN by promoting enteral autonomy has been shown to decrease complications and improve survival for pediatric patients with IF (2).

When possible, the gastrointestinal tract is preferred for feeding because it is the most physiological and safest way to provide nutrition. Enteral feeding tolerance in SBS is evaluated by measuring stool or ostomy output, by the observation of clinical signs of intolerance, as well as serum electrolyte concentrations (3). Standard oral rehydration solutions are commonly used in the management of excessive intestinal fluid loss, as adjunctive therapy to enteral nutrition.

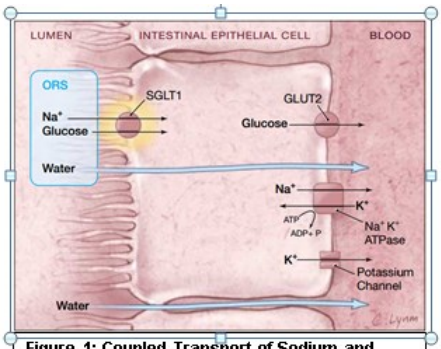

Figure 1: Coupled Transport of Sodium and Glucose in Intestinal Epithelial Cells.

In children with intact intestinal tracts presenting with diarrhea, oral rehydration solution (ORS) is a simple cost-effective solution containing glucose and electrolytes that can be used to prevent and treat dehydration due to diarrhea of any cause across all ages (4). Standard ORS takes advantage of a glucose-coupled sodium transport mechanism with absorption of molecules across the luminal membrane being facilitated by the protein sodium glucose co-transporter 1 (SGLT1) (figure 1). To take advantage of this Na-glucose co-transport, WHO and UNICEF currently recommend a glucose-based ORS with a total osmolarity of 245 mmol/L for the management of childhood diarrhea (5). In the past few decades, different formulations and substrates including sucrose (6), glycine (7), alanine and glutamine (8), of the standard WHO-ORS have been attempted.

There is limited data regarding the use of oral rehydration solutions in the setting of SBS with bowel resections involving the different parts of the small and/or large bowel. Studies in adults confirm that ostomy output is highly correlated with ostomy sodium concentration (9), and treatment guidelines generally recommend replenishment of ostomy losses with oral glucose electrolyte solutions (10). . In infants and young children, there is only a single case series that evaluated ORS use in infants who had undergone diverting ostomy. Five infants (3 with intestinal atresias, one with colonic aganglionosis and one with midgut volvulus) were treated with Orosal 65 (an ORS containing Na 65 mmol/L, glucose 20 g/L and osmolality 281 mOsm/kg)

in a volume that replaced ostomy losses (range 45-105 ml/kg/day) (11). Although improvements were claimed, no detailed data were presented on serial electrolytes, ostomy output or clinical outcomes.

Thus there is very little published data on ORS in children with SBS, and a need to measure and document outcomes. This preliminary study will evaluate tolerability and palatability of enterade® among pediatric patients with SBS and help inform a future single-center, cross-over randomized control trial between enterade® and a glucose-based ORS (ie. Pedialyte/Gatorade).

Specific Aim

1. To monitor tolerability of enterade® compared to current ORS (as measured by stool output, consistency, frequency).
2. To measure palatability of enterade® compared to current ORS.

Hypothesis

1. Enterade® will be better tolerated compared to current ORS with less frequency of abdominal distension, stool and emesis frequency.
2. Enterade® ORS will be comparable to current ORS with similar taste ratings.

2. Methods

We propose an open label single center pilot study to evaluate the tolerability and palatability of an amino acid-based ORS, enterade® (advanced oncology formula), among patients with SBS.

Enterade® (advance oncology formula) contains no glucose, but does contain five amino acids (AA) that can function as sodium co-transporters (Table 1). The amino acids in enterade® were selected based on the optimization of the following functions: 1) Amino acids that showed significant coupled sodium absorption; 2) Amino acids that decreased paracellular permeability; 3) Amino acids that did not stimulate electrogenic chloride secretion; 4) Amino acids that increased crypt number, proliferation, and increase in villous height or surface area of absorption (12). Enterade® (advance oncology formula) is commercially available.

Table 1: Composition Enterade® ORS (Advanced Oncology)

Aspartic Acid (g/L)	1.06
Threonine (g/L)	.95
Tyrosine (g/L)	.21
Valine (g/L)	1.17
Serine (g/L)	1.05
Sodium (mEq/L)	42.25
Potassium (mEq/L)	10
Citrate (mEq/L)	3.35
Magnesium (mEq/L)	1.2
Calcium Chloride (mEq/L)	1.2
Osmolarity (mOsm/L)	162.2

3. Preliminary data

Enterade® (advanced oncology formula)has been demonstrated to reduced gastrointestinal symptoms in patients with gastrointestinal toxicity in the setting of chemotherapy.

In a preliminary study, enterade® (advanced oncology formulation) was provided to 139 cancer patients experiencing gastrointestinal chemotherapy and radiotherapy induced toxicity such as diarrhea, nausea, vomiting, dehydration, weight loss, and malaise. After a 2-week observation, 118 subjects completed toxicity forms and were therefore eligible for evaluation; 60 patients used enterade® >7 days, 43 patients used enterade® for <7 days, and the remaining 15 patients did not use enterade®.The severity of initial

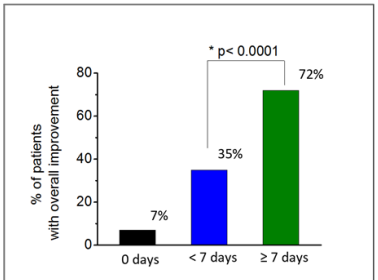

Figure 2. Overall Fraction of Patients with Symptom Improvement Based on enterade® Usage. Benefit included diarrhea, nausea, dehydration, weight loss, and malaise. *p<0.0001.

symptoms and age ranges were similar in all groups. As shown on Figure 3, statistical difference (p=<0.001) was appreciated in reduction of gastrointestinal symptoms (diarrhea and nausea) in patients who consumed enterade® product for greater than 7 days. Weight loss, a difficult clinical problem, was assessed as an individual endpoint and reached statistical significance. Patients who used the product for >7 days had a 69% improvement, compared to 13% in <7 days, and 0% improvement on those who did not use enterade® (p=0.024). Dehydration improvement was significance among patients who used enterade >7 days, compared to patients consuming enterade® <7 days.

A recent published study among mice with irradiation induced gastrointestinal toxicity evaluated the mechanism of enterade® (advanced oncology formula) and altered gastrointestinal function demonstrating an increase in crypt progenitors compared to saline (12). Mice treated with enterade® (advanced oncology formula) were also appreciated to have a significant difference in villous length and crypt count compared to saline treated mice (Figure 3).

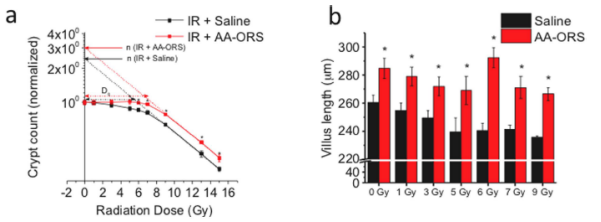

Figure 3. AA-ORS (enterade® oncology formula) increased crypt count and villus length following irradiation. *Indicates statistically significant difference (P

4. Experimental Design

Study Design: This is a single center, open label pilot study among short bowel syndrome (SBS) patients at a major national pediatric intestinal rehabilitation referral center. Patients with SBS will participate in a 14-day trial measuring the tolerability and palatability of an AA-ORS, enterade® (advanced oncology formula), in addition to their regular diet. Eligible intestinal rehabilitation patients will be identified through the Center for Advanced Intestinal Rehabilitation (CAIR) CAIR clinic at Boston Children's Hospital.

The CAIR program was one of the first multidisciplinary programs for intestinal failure established in the United States in 1999. The Center cares for more than 300 patients with IF and has pioneered novel surgical and nutritional therapies for this condition (1, 3, 13-18). In addition, the PI has led numerous trials that evaluate the safety and efficacy of ORS (4, 19-22).

Inclusion criteria:

- Male and female patients with a diagnosis of short bowel syndrome (as defined by surgical therapy for congenital or acquired gastrointestinal disease) between the ages of 1-17
- Patients who are in intestinal continuity or with diverting ileostomy, jejunostomy
- Patients must be on a stable enteral nutrition regimen with oral rehydration fluids that are taken orally.
- Stable GI medication regimen (e.g., loperamide, cholestyramine, SBBO regimen)

Exclusion criteria:

- Patients receiving IV antibiotics within the previous 72h.
- Patients with a primary diagnosis of a motility disorder (e.g., chronic intestinal pseudo-obstruction) or epithelial cell disorder (e.g., microvillus inclusion disease)
- Malnourished (as defined by WHZ <-2)

Sample Size: We propose a pilot study using a sample of 5 patients with short bowel syndrome who are currently outpatient.

Methods and materials

The design of the trial is influenced by several pertinent clinical features of patients with short bowel syndrome. Each patient with SBS has unique anatomic and demographic factors that affect absorptive function (e.g., age, residual bowel length, underlying diagnosis of SBS). Oral rehydration solution frequency and quantity will be tailored to each individual participant based on current ORS volume tolerability. It will be administered orally in addition to their regular diet. Enterade® will be distributed in 8 ounce sealed bottles by the research team, free of cost, to participating patients.

Eligible participants will document daily fluid intake, stool output and other subjective intestinal parameters of tolerability on a daily dairy (Refer to Appendix A, B, D).

(1) Stool output: For patients with ostomies, we will obtain total daily ostomy output (mL) during each 14-day ORS study period. Patients in intestinal continuity will measure frequency and consistency of stool (see Appendix C).
(2) Measures of feeding intolerance will be monitored by frequency of emesis or abdominal distension.
(3) Patients will rate the palatability of their current ORS on day 1, and Enterade® on day 14 utilizing the facial hedonic method (23).

We will obtain and record the following patient information: demographic information, medical and surgical history, residual bowel length, anthropometrics (length, weight), specifics of parenteral nutrition support, and type and feeding rate of enteral nutrition at time of enrollment (Table 1). Palatability facial hedonic measurements and symptom log sheets will be mailed back on pre-labeled enveloped supplied during enrollement.

Table 1: Schedule of Events

		Week 1		Week 2	
Recruitment	**Day 0**	**Day 1-6**	**Day 7**	**Day 8-14**	**Day 15**
Weight (Kg)	x				
Pre-solution data collection	x				
Enterade solution		x	x	x	
Phone call			x		x
Symptom Diary		x	x	x	
Palatability scale		x			x

5. Analytical approach

The primary outcome will be tolerance of enterade®, as measured by frequency of abdominal distension, emesis as well as changes in stool frequency and consistency from baseline. Exposure viable is the change in ORS to enterade®.

The secondary outcome will be each participants rating of enterade® taste as measured on a 100-mm visual analog scale (worst (0mm), best taste (100mm)).

6. Risks & Benefits

Risks:
The risks associated with enterade® are anticipated to be minimal. Enterade® (advanced oncology formula) is an oral rehydration solution that is commercially available (https://enterade.com/) and generally regarded as safe.

Questionnaires are brief and will not have personal identifiers. Confidentiality of subjects will be preserved at all costs. All patient identifiers will be removed from the study record and secured.

Benefits:
Our cumulative discoveries from five patients have the potential to aid in our understanding of outcomes while on an amino acid based oral rehydrating solution in children with SBS. During our pilot trial, tolerance and palatability data will be documented. Collected data will be instrumental in the design of a more definitive study using a randomized controlled crossover trial that compares enterade® to pedialyte among patients with SBS.

7. Statistical approach

We will compare continuous outcomes (average stool frequency, consistency and ostomy output) between current ORS and enterade® with t-tests (for normally distributed data) or Wilcoxon tests (for non-normally distributed data). Taste score differences among solutions will compare mean distance in visual analog scale between solutions

Univariate descriptive statistics for our population will include: 1) baseline SBS disease information (age, sex, underlying diagnosis, length of residual bowel); and 2) mean daily stool output prior to and after enterade® exposure. Categorical variables will be compared with chi square analysis (or Fisher exact test if cell size is less than 3), and continuous variables will be compared with t-test (or non-parametric testing if they are not normally distributed).

8. Confidentiality

For those patients meeting inclusion criteria, the study purpose, procedures, costs, risks, benefits and alternatives to participation will be thoroughly explained and presented to the patient and their family. Once patients and families have had enough time to consider participation and have expressed a willingness to participate, informed consent will be obtained from the parents or legal guardian and child assent when appropriate based on age and IRB requirements. Enrolled patients in this study will be given a code (or number) that is not derived from or related to information about the individual and is not otherwise capable of being translated to identify an individual. The link between this code and any information that identifies the patient will be kept in a password protected electronic file accessible only by the study researcher. In addition, any data that we obtain from the patient's medical record will have any and all personally identifiable information removed.

9. Clinical Significance

SBS is a devastating disease with a significant associated morbidity stemming from poor enteral function. Understanding outcomes relating to alternative regimens, such as enterade®, could potentially help reduce dehydration secondary to diarrhea by enhancing fluid absorption with ultimately a reduced need for PN and decreased duration of in-patient admissions leading to improved morbidity and cost-effective care.

10. Financial Relationship

Manufacturers of enterade® (Entrinsic Health Solutions) will only be providing participants with free samples of enterade®, and will not be covering the cost of the trial or involved with participants in study.

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