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## The Evaluation of an Amino Acid- Oral Re-hydration Solution (Enterade®) to Improve Quality of Life in Solid Tumor Cancer Patients by Reduction of Chemotherapy Related Diarrhea

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Amino Acid- Oral Rehydration Solution to Reduce Chemotherapy Related Diarrhea and  
Improve Quality of Life in Solid Tumor Cancer Patients

Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Nursing  
Practice at the University of Kentucky

By

Holly Chitwood

Lexington, Kentucky

2021

## **Abstract**

**Background:** Chemotherapy related diarrhea (CRD) is a common adverse effect of many chemotherapy agents used to treat cancer. CRD negatively affects quality of life (QOL) for cancer patients and often results in treatment delays, hold, dose reductions, and hospitalizations affecting morbidity and mortality. Proper management of CRD with novel therapeutics is needed to improve the quality of life and patient outcomes for this population.

**Purpose:** The purpose of this study was to evaluate the use of a proprietary amino acid-oral rehydration solution (AA-ORS) known as Enterade® to reduce the severity of CRD, to improve patient reported QOL among patients over the age of 18, diagnosed with solid tumors, and receiving systemic chemotherapy, to reduce treatment holds, delays, dose modifications, prevention of weight loss, and subjective improvement of associated gastrointestinal mucositis physical symptoms.

**Conceptual Model:** Imogene M. King's Theory of Goal Attainment was utilized as the framework for this study.

**Methodology:** A quasi-experimental study without randomization in a single population with two separate measurements over time was performed in a National Cancer Institute (NCI) designated cancer center in the South-Central United States. The variables included sociodemographic data, cancer diagnosis, chemotherapy treatment regimens, Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade of diarrhea, stool consistency using the Bristol Stool Scale, use of antidiarrheals, associated gastrointestinal mucositis symptoms affecting QOL, and QOL measured with the Functional Assessment of Chronic Illness Therapy-Diarrhea survey (FACIT-D).

**Results:** A total of 22 participants enrolled in the study. Sixteen completed both the pre- survey and post survey. A statistically significant difference was not found between the patient's subjective report of quality of life when comparing pre and post survey responses. There was a statistically significant improvement from baseline in the QOL questions specific to bowel concerns due to diarrhea with a mean pre-survey response score of 35.3 versus a post survey score of 29.2 ( $p = .003$ ). There was a reduction in the CTCACE grade of diarrhea demonstrating a reduction in the frequency of stools per day ( $p = .001$ ) and a change in the consistency of stools moving from watery to more formed stools using the Bristol Stool Scale ( $p = .049$ ).

**Conclusion:** Use of AA-ORS in this study was found to be useful in the reduction of CRD in patients receiving systemic oncology therapies. This study needs to be replicated with a larger, more inclusive sample size to further support the use of AA-ORS in the reduction of CRD and QOL.

## **Acknowledgements**

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## **Dedication**

I would like to dedicate my Doctorate of Nursing Practice to my husband, son, daughter, and grandmother. Without their unwavering love, encouragement, and support, I would not have been able to pursue a DNP. I hope my own children will look back and view this accomplishment as an inspiration to achieve their own education goals. With permission from her family, I would like to dedicate my doctoral study to a beloved, pancreatic cancer fighter, Mrs. Verville who inspired me to focus on the quality of life in patients undergoing cancer therapy. In the short time I was her provider, she carried an infectious laugh and positivity while courageously fighting cancer. When she left this world, she left me with a desire to seek new knowledge to improve the care of patients experiencing toxicities associated with oncologic therapies. The lessons I learned from her are innumerable and I will hold her and her family close always as I seek to advance my practice.

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# Amino Acid- Oral Rehydration Solution to Reduce Chemotherapy Related Diarrhea and Improve Quality of Life in Solid Tumor Cancer Patients

## **Introduction**

Chemotherapy related diarrhea (CRD) is a toxicity of cancer therapy which contributes to decreased quality of life, weight loss, malnutrition, dehydration, and life-threatening electrolyte balances. CRD is estimated to affect up to 50-80% of patients receiving treatment for various cancers (Deng et al., 2017; McQuade et al., 2014; Lee et al., 2014; McQuade et al., 2016). CRD management often results in treatment holds, delays, and/or dose reductions affecting morbidity and mortality of this population while management is costly to the healthcare system.

While the data from 2020 and 2021 is incomplete, the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) projected that roughly 1.8 million people in the United States were to be diagnosed with cancer in 2020 (SEER, 2020). The most prevalent sites of cancer were projected to be cancers arising from the breast, lung, prostate, colon, and rectum accounting for 50 % of all new diagnoses (SEER, 2020). Lung, colorectal, pancreatic, and breast cancers accounted for nearly 50 % of all cancer related deaths (SEER, 2020). The SEER Cancer Statistics Review estimated 57,000 adults were projected to be diagnosed with pancreatic cancer, 42,000 with hepatobiliary, 27,000 with gastric cancer, and 147,000 with new cases of colorectal cancers in the United States in 2020 (SEER, 2020). Cancer of the pancreas, colon, rectum, liver & intrahepatic bile duct are among the eight deadliest cancer sites (SEER, 2020).

CRD is a symptom of gastrointestinal mucositis toxicity associated with a variety of cancer treatments such as chemotherapy, immunotherapy, and biologic monoclonal antibodies. CRD associated with chemotherapy has been reported among patients receiving alkylating

agents, (cisplatin, cyclophosphamide, oxaliplatin), antimetabolite agents (5-fluorouracil, capecitabine, gemcitabine, methotrexate), anthracyclines (doxorubicin), taxanes (docetaxel, paclitaxel), topoisomerase inhibitors such as irinotecan, oral therapies such as tyrosine kinase inhibitors, and other drugs such as monoclonal antibodies (Lexicomp®, 2021; McQuade et al., 2016). However, CRD is more common with agents such as irinotecan (CPT-11, Camptosar) used in combination with 5-fluorouracil (5-FU) which is often used to treat gastrointestinal tract malignancies arising from the stomach (gastric), pancreas, hepatobiliary (liver, bile duct), and colorectal cancers (Benson III et al., 2004; Ribeiro et al., 2016; Krishnamurthi & Macaron, 2019; McQuade et al., 2014). Irinotecan administered alone has been associated with early CRD in 43-51% and 7-22% experienced moderate to severe CTCAE grade III/IV CRD; whereas delayed or late CRD was reported in as high as 83-88% of patients with 14-31% experiencing grades III/IV CRD (Lexicomp®, 2021).

The pathophysiology of CRD is mediated by inflammation and cellular apoptosis of the epithelial lining of the gastrointestinal mucosa. Malabsorption occurs due to the retention of non-absorbable compounds resulting in an osmotic shift of water into the intestinal lumen which leads to increased secretion of electrolytes and fluids into the small intestines, and altered gastrointestinal motility (McQuade, et al., 2016; Krishnamurthi & Macaron, 2019; Gibson et al., 2013). CRD among pancreatic cancer patients is further exacerbated by exocrine pancreatic insufficiency post pancreaticoduodenectomy procedure, the location of the tumor, and/or pancreatitis contributing to bile salt malabsorption (Struyvenburg, et al., 2017). CRD is also exacerbated by surgical resection of the colon and radiation to the abdomen and pelvis in combination with chemotherapy.

Approximately 11% of cancer patients will experience mild grade I and/or grade II CRD, necessitating chemotherapy dose reductions and/or treatment delays with up to 45% of patients estimated to experience any-grade of CRD (Koselke & Kraft, 2012). Research has indicated the incidence of severe grades III and IV CRD has occurred in 21% of cancer patients receiving drugs such as fluorouracil and irinotecan as part of the FOLFIRINOX treatment regimen (Bossi et al., 2018; Conroy et al., 2011).

It is difficult to estimate the total cost of CRD in healthcare dollars as there is insufficient recent data regarding the economic impact of CRD. Severe grade III or IV CRD is costly to the healthcare system, with economic estimates demonstrating hospital stay of eight days for the management of grade III or IV CRD with intravenous fluids, electrolyte replacements, and anti-diarrheal medications (McQuade, et al., 2014). Dranitsaris, et al., (2005) conducted a cost of illness analysis of among colorectal cancer patients ( $n = 96$ ) receiving adjuvant or palliative chemotherapy which demonstrated that grade III/IV CRD developed after the first cycle of chemotherapy in approximately 54% of patients, resulting in dose reductions in 20% of patients, and therapy was delayed by a median of 7 days. This study demonstrated a statistically significant association with development of severe diarrhea requiring hospitalization after the first cycle of chemotherapy ( $p = 0.051$ ); 32% of those patients required hospitalization for supportive care management of CRD with an 8-day median length of stay (range of 2 to 28 days) (Dranitsaris, et al., 2005). In this study, the quantifiable economic impact of treating grade III/IV diarrhea was \$2559 per patient with a 95% confidence interval and a cost range from \$1665 to - \$3453 (Dranitsaris, et al., 2005).

Since the early 2010's, there has been increasing development, approval, and utilization of new oncologic drug therapies such as monoclonal antibodies targeting EGFR and VEGF,

immunotherapy checkpoint inhibitors, and oral tyrosine kinase inhibitors which are strongly associated with diarrhea in cancer patients. In contrast, other than the use of high dose steroids for less severe cases and expensive biologics such as infliximab or vedolizumab needed for higher grades of immunotherapy induced colitis, there has been very little new literature concerning cost associated with CRD. The rising cost of health care and medications required to treat diarrhea in immunotherapy-induced diarrhea has further increased the cost in managing this toxicity.

While it is important to consider the cost of CRD in using novel therapies, it is also important to consider targeting appropriate management strategies to reduce the risk of emergency room visits and hospital readmissions related to CRD for future reimbursement of care. The Tax Relief and Health Care Act of 2006 mandated the Hospital Outpatient Reporting Program (OQR) which requires hospitals to submit data regarding the quality of care provided in outpatient settings (Centers for Medicare & Medicaid Services [CMS], 2021). A specific measure, OP-35 Admissions (ADM) and Emergency Department (ED) Visits for Patients Receiving Outpatient Chemotherapy, was designed to assess the quality of care delivered and encourage performance improvement using a tool to calculate inpatient admissions and hospitalizations within 30 days of chemotherapy for conditions such as anemia, dehydration, diarrhea, emesis, fever, nausea, neutropenia, pain, pneumonia, or sepsis (CMS, 2021). Under this reporting program, hospitals report data for these standardized measures reflecting performance which affects the rate of reimbursement for healthcare services in the coming years (CMS, 2021).

## **Purpose**

The purpose of this study was to evaluate the use of a proprietary amino acid-oral rehydration solution (AA-ORS) known as Enterade® to reduce the severity of CRD, to improve patient reported QOL among patients over the age of 18, diagnosed with solid tumors, and receiving systemic chemotherapy, to reduce treatment holds, delays, dose modifications, prevention of weight loss, and subjective improvement of associated gastrointestinal mucositis physical symptoms.

The specific aims of this study were to:

1. Determine if there is a reduction in CRD with use of AA-ORS with or without the standard of care loperamide and/or diphenoxylate atropine to reduce the severity of CRD measured with the CTCAE Common Terminology Criteria for Adverse Events (CTCAE) v5.0 to grade severity and frequency of diarrhea, the Bristol Stool Scale to evaluate stool consistency, and in comparison, with concomitant use of the subjective pre and post use of anti- diarrheal medications.
2. Determine if the use of AA-ORS with or without standard of care loperamide and/or diphenoxylate atropine would improve patient reported QOL measured with patient reported responses to statements replicated from the Functional Assessment of Chronic Illness Therapy-Diarrhea questionnaire (FACIT-D) regarding the physical, pain, social, functional, and bowel concerns domains specific to diarrhea.
3. Determine if there is a reduction in treatment holds, delays, dose modifications, prevention of weight loss, and subjective improvement of associated gastrointestinal mucositis physical symptoms from pre and post use of regimen of 12-21 days use of AA-ORS with or without standard of care loperamide and/or diphenoxylate atropine.

## **Theoretical Framework**

The Imogene King's Theory of Goal Attainment serves as the theoretical framework for this project. In this theory, the emphasis is focused on the three interacting systems; personal (individuals), interpersonal (groups), and social systems (society) needed to influence goal attainment between humans and their environment (King, 1991). King (1968) references communication and participation as the basis of interaction when building of an interpersonal relationship. The nursing assessment combined with the patient's subjective perception of health, influence the interactional and transactional processes contributes to participation in decision making toward goal attainment to improve quality of life (King, 1991; King, 1968).

Porter (1991) noted that the utilization of King's Theory of Goal Attainment allows for oncology nurses and practitioners in the ambulatory setting to engage in shared decision-making with oncology patients through assessment & monitoring while engaging and enabling individuals to understand their symptoms and management of symptoms with participation in development of mutual goals toward improvement. In King's theory, goals are achieved through concepts such as perception, communication, interpersonal relationships, health status, and social institutions (King, 1991; King, 1968). Furthermore, Porter (1991) references that by placing the personal system at the core of the framework, the patient and nurse are partners in the nursing process with the nursing actions dependent on the patient's participation and perception of perceived symptom severity and quality of life.

King's framework was used to guide, design, and implement this evidence-based study with aims to improve the quality of life by the reduction of diarrhea for patients experiencing CRD. The Theory of Goal Attainment provided the foundation for a stepwise approach of assessment, planning, implementation and evaluation with identification of a clinical opportunity

affecting perceived quality of life among cancer patients supporting the translation of research performed by Chauhan et al. (2018) to improve outcomes of patients experiencing CRD. The implementation involved forming a collaborative team of medical oncologists, advanced practice providers, nurses, and dietitians to identify patients, promote participation, and referral of participants for inclusion. Engagement of patients and caregivers was accomplished through education on a novel therapy targeting improvement of patient outcomes limiting dose reductions, delays and rescheduling therapy, and hospitalization, which increased workload and clinical coordination of care for all involved. In addition to guiding the implementation process, the Theory of Goal Attainment assessed the patient's perspective of the feasibility of the intervention while allowing for continued monitoring and outcome analysis with regard to clinical setting, staff, cost, and patient variables in the interpersonal and social systems (King, 1991).

### **Literature Review**

A comprehensive literature search was performed using CINAHL, MEDLINE, and PubMed databases. Keywords included in the search were chemotherapy related diarrhea, chemotherapy induced diarrhea, gastrointestinal mucositis, gastrointestinal cancer toxicities, management, treatment, and oral rehydration. Research studies, clinical practice guidelines, and published articles from other peer-reviewed sources were used. The search was filtered to include peer reviewed literature, in English language, and from 2014 to present, and focused on Level I and Level II articles on randomized control trials and systematic reviews of randomized control trials specific to the management of CRD.

There were no randomized control trials or systematic reviews to support the use of an AA-ORS in the management of CRD among pancreatic cancer patients. However, there were

two Level I systematic reviews of randomized control trials investigating agents in the management of CRD. There were three Level II randomized control trials; and two-Level IV retrospective cohort studies articles included in the synthesis of current management of CRD.

The evidence demonstrates few agents known to prevent CRD, but there may be agents that can lessen the severity and improve quality of life. Historically, clinical practice guidelines from the American Society of Clinical Oncology, the European Society of Medical Oncology, & Dana Farber suggest the best practice in the management of chemotherapy-induced diarrhea is first line use of loperamide (Benson III et al., 2004; Bossi et al., 2018; McQuade, et al., 2016). Second line therapy guidelines for CRD refractory to loperamide are alternating diphenoxylate/atropine with loperamide tablets (Bisanz et al., 2010), octreotide SC (Gibson et al., 2013) and deodorized tincture of opium although there is no evidence-based literature to support use (McQuade et al., 2016).

Use of the antidiarrheal agent loperamide was allowable and used concurrently in the systematic reviews and randomized control trials investigating long acting octreotide, probiotics, and elsiglutide. Prophylactic use of agents such as long acting octreotide (Deng, et al., 2017) probiotics (Mego et al., 2015), and loperamide (Jamil, et al., 2015) given prior to chemotherapy demonstrated a potential for a reduction in severity of CRD, but not useful for therapeutic management alone with the exception of loperamide. However, the use of loperamide and/or diphenoxylate/atropine for rescue concomitantly with prophylactic probiotics has demonstrated a mixed efficacy in the reduction of severity for Grade 2 or higher CRD with respect to severity and duration; but may place patients at risk for infection (Mego et al., 2015; Wang et al., 2016). The use of elsiglutide, a glucagon like peptide-2 analogue with antidiarrheal properties was found to not have a statistical significance in a multinational randomized control trial although



the severity of diarrhea was reduced in comparison to the placebo group receiving similar chemotherapy regimens (Karthaus et al., 2017). Octreotide LAR was evaluated for efficacy as a prophylactic agent in a systematic review, but failed to demonstrate a statistical significance in the severity and duration of CRD (Deng et al., 2017).

There are studies currently evaluating the use of a proprietary amino acid-oral rehydration solution (AA-ORS) at Vanderbilt University (NCT04073017) and at the University of Kentucky Markey Cancer Center (NCT03722511) currently enrolling neuroendocrine carcinoma and carcinoid syndrome patients with quality of life limiting diarrhea to assess the use of AA-ORS in improving intestinal absorption and overall patient-reported quality of life (NIH U.S. National Library of Medicine, ClinicalTrials.gov [NIH], 2021). Chauhan (2018) evaluated an AA-ORS drink (Enterade®) in a retrospective cohort study of small bowel and pancreatic neuroendocrine tumor patients. The patients were instructed to consume 8 ounces of AA-ORS twice daily either 30 minutes before or 1 hour after meals. It is important to note the neuroendocrine patients participating in these studies were not receiving chemotherapy, and the diarrhea is a result of excess hormone secretion with neuroendocrine tumors. However, the patients reported an improvement within 6 days of initiating use with a 50% reduction in number of stools per day (Chauhan, 2018).

Chauhan et al. (2020) performed another retrospective chart review over four months among solid tumor cancer patients who received AA-ORS (Enterade®). Patients were instructed to consume one 8-oz bottle of AA-ORS twice a day for at least one week in addition to standard of care antidiarrheal medications for chemotherapy or immunotherapy-induced diarrhea (Chauhan, et al., 2020). In this study, 46 patients were offered AA-ORS. Seventeen patients

reported an 80% subjective reduction in diarrhea frequency after consuming AA-ORS, with 50% reporting a reduction in diarrhea after only 3.6 days of use of AA-ORS (Chauhan, et al., 2020). The evidence demonstrates there has been limited new research within the past five years on the management of CRD and research dedicated to the management of CRD among pancreatic cancer patients receiving chemotherapy is lacking. Best practices in the management of CRD currently remain with first line use of loperamide and second line refractory to loperamide with or without alternating diphenoxylate atropine. The Level I systematic reviews and Level II randomized control trials evaluated prophylaxis with long acting octreotide, loperamide, elsiglutide, and probiotics with some benefit in reduction of severity, but failed to demonstrate improvement in quality of life or for use as a single agent for CRD therapeutic management (Deng, et al., 2017; Jamil, et al., 2015; Mego et al., 2015; Karthaus et al., 2017). The two-Level IV retrospective cohort studies demonstrated that prophylactic loperamide and AA-ORS may be useful in the reduction of CRD (Jamil et al., 2015; Chauhan, 2018). The research has not demonstrated statistically significant evidence to make practice changes. However, emerging therapies such as AA-ORS offer potential to hydrate intestinal epithelial cells and reduce the severity of CRD among cancer patients thereby improving quality of life.

## **Methods**

### **Design**

The study was a quasi-experimental study without randomization, in a single population with two separate measurements over time.

### **Setting/Agency Description**

The study was performed in a National Cancer Institute (NCI) designated cancer center, as a part of a Magnet designated, academic medical center, in the South-Central United

States. Participants were recruited from the three outpatient clinics and four outpatient infusion clinics of the cancer center. All policies and safety protocols with respect to COVID-19 pandemic in place at the academic medical center and cancer center were followed by the primary investigator and study personnel to ensure safety and prevent transmission of COVID-19 to participants (i.e. universal masking with all contact, daily screening for COVID-19 symptoms, maintaining social distancing at all times, and proper disinfecting of all electronic devices used to complete surveys).

### **Sample**

A convenience sample of participants was recruited through identification by the physician, advanced practice provider, or nurse of patients experiencing CRD. Inclusion criteria included adult participants, over the age of 18, who were being treated at the institution's cancer center, diagnosed with a solid tumor, receiving systemic oncologic therapy, and experiencing at least grade 1 CRD. Participants were excluded from participation if they were thought to have gastrointestinal illness or active infections contributing to diarrhea such as *Clostridium difficile*, diagnosed with a hematologic malignancy, were pregnant, had a known allergy to the artificial sweetener Stevia, and/or were receiving hospice care. Participants were also excluded if they had an ECOG (Eastern Cooperative Oncology Group (ECOG) Performance Status less than 2 as this performance status score is used to determine ability of patient to tolerate therapies in serious illness, specifically for chemotherapy.

### **Procedures**

Approval for this study was granted from the Institutional Review Board (IRB) affiliated with the primary investigator's university. Approval was also granted through the cancer center's protocol review and monitoring committee, and registered with the NCI Clinical Trials

Reporting Program (CTRP). Documentation of informed consent was obtained by the primary investigator or study personnel from each participant during clinic visits with oncology provider or during infusion clinic visits. After informed consent was obtained, participants were provided with education on the use of antidiarrheal medications loperamide and/or diphenoxylate atropine, the recommended serving of two, 8-ounce bottles of AA-ORS daily, and a free supply of twelve bottles of AA-ORS. A pre-survey was administered at that time and the post survey was performed between days 12 and 21 dependent upon the number of days in the participant's chemotherapy regimen cycle.

### **Measures and Instruments**

The primary investigator used the medical record to verify and document the grade of diarrhea using the CTCAE v5.0 ranging in severity from mild, grade I to severe, life threatening grade IV diarrhea. Other data obtained from the medical record included the cancer diagnosis, chemotherapy treatment regimen, the participant's weight in kilograms, and identified whether there were dose reductions, holds, or delays in therapy on the same day the participants completed the pre and post surveys. All other subjective data was collected from participant responses in a Research Electronic Data Capture (REDCap) survey.

The pre-survey included sociodemographic data related to age, marital status, if they had financial concerns related to CRD, and ethnicity of participants. The post survey measured the participants' compliance with the number of servings per day of AA-ORS and the number of days per week AA-ORS was consumed. The post survey also included an item where participants were asked to indicate if they felt the use of AA-ORS improved QOL by reduction of watery stools, reduction in the frequency of stools, and/or prevented treatment delays, holds, or dose modifications. In both the pre and post surveys, participants were asked to provide

information to measure consistency of stools using the Bristol Stool Scale borrowed from the Bowel and Bladder foundation (2016), describe their current antidiarrheal use with choices of “loperamide,” “diphenoxylate atropine,” “both loperamide and diphenoxylate /atropine,” or none; and subjectively identify which associated physical symptoms they were experiencing with CRD. In addition, participants were asked to provide subjective responses in both the pre and post survey of physical, social, functional and specific bowel related concern statements on a Likert scale ranging from “0-not at all,” “1-a little bit,” “2-somewhat,” “3-somewhat” “4-quite a bit,” to “5-very much” replicated from the Functional Assessment of Chronic Illness Therapy - Diarrhea (FACIT-D) version 4 (FACIT, 2020) (see Figure 1).

The FACIT-D quality of life statements reflective of physical attributes consisted of “lack of energy,” “having nausea,” “trouble meeting family needs,” “feeling ill,” and “spending time in bed.” Having pain was also from physical domain, but measured independently in its own category. The only quality of life statement reflective of the social well-being was “I am satisfied with how I am coping with my illness.” The quality of life statements in the functional domain were concerning the “ability to work,” ability to enjoy life,” “sleeping well,” “enjoying things they usually do for fun,” and “contentment with current quality of life.” The statements specific to bowel concerns in relation to diarrhea were “having control of bowels,” “moving bowels more frequently than usual,” “fear of being away from the toilet,” “having to limit social activity because of diarrhea,” “having to limit physical activity due to diarrhea,” “embarrassment by having diarrhea,” “experiencing abdominal cramping or discomfort due to diarrhea,” diarrhea keeping them from sleep at night,” and “moving bowels more frequently to avoid accidents.”

## **Data Collection**

Participants were provided a unique identification number to access survey, participate in the study, and to secure patient health information (PHI). Participant data was collected from responses from the REDCap pre and post surveys. The participants were provided a link by email or an iPad with a link to complete surveys during clinic or infusion appointment.

## **Data Analysis**

Descriptive analysis including means, standard deviations or frequency distributions were used to summarize sociodemographic data such as age, marital status, financial concerns related to CRD, ethnicity, cancer diagnosis, and treatment regimens of the study population. A paired *t*-test was used to determine change from pre and post survey data from the physical, pain, social, functional, bowel concern QOL domains, the CTCAE grade of diarrhea, and consistency of stools using the Bristol Stool scale. SPSS version 26 was used to analyze data with statistical significance defined as a *p* value less than or equal to .05. A McNemar Test with paired data was used to determine if there was a significant difference in treatment holds or delays, dose reduction modifications, and significant changes in weight between the pre or post survey data.

The physical QOL scale scores were reverse coded with a potential range of scores from 5-25, with higher scores indicating a decrease in physical health correlating with worse QOL and poor physical condition. The physical attribute of pain had a potential range of scores from 0-5 with higher score indicating increased pain. In the social QOL domain, the single statement regarding “satisfaction with coping of illness” had a potential score of 0-5 with a higher score indicating with higher level of satisfaction with coping. The functional QOL scale responses also had a potential range of 5-25 with a higher score indicted a higher functional status and

better QOL. The bowel function concerns were reverse coded with a range of 5-45, with a lower response demonstrating worse QOL due to bowel function concerns.

## **Results**

### **Demographics**

A total of 22 participants were enrolled in the study over a period of 5 months. Sixteen participants completed both the pre-survey and the post survey. The average age of participants was 55 years of age (SD =13; see Table 1). The majority of the participants self-identified their race /ethnicity as White Caucasian (93%, n=14), one participant identifying as Other/Hispanic, and the remainder choosing to not respond to question (32%, n=7). Approximately 67% of those who provided data indicated they were married. Among the 22 participants who participated, only 19% identified as having financial concerns related to CRD.

Roughly, 38% (n=8) of the participants were diagnosed with colorectal cancer, followed by lung at 33% (n=7), and pancreatic at 14% (n=3) (see Table 2). The most common treatment regimen associated with the patient experience of CRD was a combination of 5-fluorouracil regimen with irinotecan and without or without oxaliplatin (FOLFIRINOX, FOLFIRI, FOLFOXIRI) at 27% (n=6), with 5% (n=1) receiving a 5- fluorouracil Regimen with both irinotecan and the monoclonal antibody panitumumab. The next most common regimen was a 5-fluorouracil based regimen without irinotecan (mFOLFOX, 5-flourouracil alone, or FOLFOX) at 18% (n=4), and 5% (n=1) were receiving a 5-flouracail based regimen without irinotecan, but with the addition of the monoclonal antibody panitumumab (see Table 2). Participants receiving regimens used for lung, esophageal and sarcoma cancers containing taxane agents such as paclitaxel, docetaxel made up another 24% (n=5), with 14% (n=3) of those combined with carboplatin, followed by tyrosine kinase inhibitors (10%), and only one patient each receiving

capecitabine, single agent irinotecan unknown if liposomal), and a combination regimen of carboplatin, pemetrexed, and pembrolizumab.

## **Findings**

When comparing the pre and post survey QOL responses, there was not a statically significant improvement in the physical, pain, social responses related to satisfaction with coping of illness, or functional domains (see Table 3). The pre-survey physical QOL domain score mean was 13.6 and the post- survey mean was 11.8 ( $p = .078$ ). The mean pre-survey mean for pain was 3.5 and post survey mean was 3.3 ( $p = .546$ ). The pre-survey satisfaction with coping of illness mean was 3.3 and the post survey mean was 3.6 ( $p = .369$ ). The pre-survey functional QOL domain score mean was 12.5 and the post survey mean score was 14.2 ( $p = .133$ ).

There was a statistically significant improvement from pre- survey QOL questions specific to bowel concerns with diarrhea with a mean pre-survey score of 35.3 and a post survey score of 29.2 ( $p = .003$ ) (see Table 3.). The reduction in the CTCAE grade of diarrhea demonstrated a reduction in the frequency of stools per day ( $p = .001$ ), and a change in the consistency of stools moving from watery to more formed stools was seen using the Bristol Stool Scale ( $p = .049$ ) (see Table 3; Figure 1.; Figure 2).

Among the participants ( $n = 16$ ) who provided data in the post survey after using AA-ORS (Enterade®), only 13% ( $n=2$ ) of the participants reported compliance with the appropriate recommended use of two, 8-ounce servings of AA-ORS, 7 days per week. Nineteen percent of participants ( $n=3$ ) reported using half of the recommended serving of only one, 8-ounce bottle of AA-ORS, 7 days per week and 31% ( $n=5$ ) reported using 1-2 bottles of AA-ORS per day ranging from one to seven days per week. Thirty eight percent ( $n=6$ ) reported they did not use AA-ORS at all during the study.



In addition, 31% of participants subjectively reported they felt the use of AA-ORS resulted in a reduction in the number of watery stools and 15% reported a reduction in the frequency of stools. Eight percent of participants indicated they felt the use of AA-ORS prevented delays, dose modifications, or holding their cancer treatments related to their CRD, and 23% felt the AA-ORS aided in prevention of weight loss. However, after data analysis, there was no associated statistically significant improvement in prevention of dose modifications ( $p = .508$ ), holds or delays in cancer treatment regimens ( $p = .625$ ) or prevention of weight loss (see Table 4).

Subjective use of anti- diarrheal medications, associated physical symptoms and objective electrolyte disturbances were studied before and after use of AA-ORS. Of those who provided subjective information concerning anti-diarrheal use, there was no significant change from the pre- survey where 35% of participants reported use of single agent loperamide, and 39% in the post survey. Thirteen percent of the participants reported using single agent diphenoxylate /atropine (Lomotil), in comparison to 5.6% in the post survey (see Table 5). However, there was increased use of the combination regimen of standard of care loperamide (Imodium ad- over the counter) and diphenoxylate /atropine (Lomotil) reported among 33 % of participants in the post survey in comparison to pre-survey use of 26%. Nausea, abdominal pain, weight loss, muscle weakness, muscle cramping, dehydration, decreased appetite, hypomagnesemia, and hypocalcemia were decreased in frequency in comparison from the pre-survey (see Table 6). Hypokalemia was the only associated electrolyte variable in the post survey found to have subjectively increased in frequency.

## Discussion

Oncology treatment related diarrhea is associated with poor quality of life, resulting in treatment holds or delays, and/or dose reductions affecting morbidity and mortality of this population while treatment is costly to the healthcare system. The purpose of this study was to determine if the use of a proprietary amino acid-oral rehydration solution (AA-ORS) known as Enterade® could be used to reduce the severity of treatment related diarrhea and to improve patient reported QOL among adult oncology patients receiving systemic cancer therapies. The study demographics in regard to cancer diagnosis and treatment regimens were as expected with the majority receiving regimens that included irinotecan (CPT-11, Camptosar) used alone or in combination with 5-fluorouracil (5-fu), in pancreatic and colorectal cancer regimens as well as panitumumab, tyrosine kinase inhibitors, and taxane drugs consistent with regimens known to cause CRD.

In this study, there was no association with improvement in the physical status, pain, satisfaction with coping of illness, or functional domains with respect to QOL with the use of AA-ORS. There is no recent literature evaluating the use of AA-ORS in reduction of CRD in solid tumor cancer patients to improve QO/L. As previously discussed, Chauhan et al. (2018) evaluated an AA-ORS drink “Enterade” in a retrospective cohort study among small bowel and pancreatic neuroendocrine tumor patients who reported an anecdotal improvement within 6 days of initiating use with a 50% reduction in number of stools per day (Chauhan, et al., 2018).

In another pilot study, Chauhan et al. (2018) evaluated the use of AA-ORS for anti-diarrheal properties among neuroendocrine tumor patients; they found that 73.9% of patients reported an improvement in diarrhea and 52.2% reported a greater than 50% reduction in the frequency of diarrhea. AA-ORS is being currently being studied in a phase II study evaluating

the ability of AA-ORS to reduce bowel frequency in neuroendocrine tumor (NET) patients with carcinoid syndrome and non-carcinoid syndrome (NCT04073017) at Vanderbilt University. The University of Kentucky Markey Cancer Center is currently enrolling participants in a prospective Phase II study among neuroendocrine carcinoma and carcinoid syndrome patients with quality of life limiting diarrhea to assess the use of AA-ORS in improving intestinal absorption and overall patient-reported quality of life (NCT03722511) (NIH U.S. National Library of Medicine, ClinicalTrials.gov [NIH], 2021).

This study found the majority of participants were diagnosed with a CTCAE grade II or higher treatment related diarrhea at baseline. This is consistent with data in previous studies where approximately 11% of cancer patients will experience mild grade I and/or grade II CRD, and up to 45% of patients estimated to experience any-grade of CRD (Koselke & Kraft, 2012). The incidence of severe grades III and IV CRD has been associated with up to 30% of cancer patients (Benson et al., 2004; Deng et al., 2017; McQuade et al., 2014; Lee et al., 2014; McQuade et al., 2016). As with this study, patient receiving drugs such as fluorouracil and irinotecan as part of a treatment regimen are at higher risk for CRD (Bossi et al., 2018; Conroy et al., 2011).

This study used measurement tools such as the FACIT-D, Bristol Stool Scale, and CTCAE v 5.0 to compose the pre and post surveys question specific to diarrhea. Use of AA-ORS was associated with an improvement in bowel concerns with diarrhea affecting QOL, a reduction in the CTCAE grade of diarrhea demonstrating a reduction in the frequency of stools per day, and a change in the consistency of stools moving from watery to more formed stools. This finding is consistent with the previous research findings of Chauhan et al. (2020) demonstrating a subjective reduction in diarrhea frequency after consuming AA-ORS.

The surveys sampled questions from each domain of the FACIT- D, but did not use the entirety of the measurement tool in the pre and post surveys which limits reliability and validity of actually measuring QOL. The CTCAE grading criteria was used to document the severity of diarrhea from mild, grade I to severe, life threatening grade IV toxicities related to cancer related therapies. However, it's use alone in evaluation of stools, would have affected the validity and reliability in determining if AA-ORS is useful in reducing CRD (NCI CTCAE v5.0, 2017). Therefore, a combination of patient-reported stool consistency using the Bristol Stool Scale combined with the CTCAE grading to document severity and frequency of stools was used to increase validity and reliability in this study (Bowel & Bladder.org, 2016). In future, this measurement can be improved upon by having the patient complete the entirety of the FACIT- D to measure specific bowel concerns related to quality of life.

### **Implications for Practice, Education, Policy, and Research**

This study has demonstrated a statistically significant improvement in the quality of life questions specific to bowel concerns due to diarrhea, the reduction in the CTCAE grade of diarrhea demonstrating a reduction in the frequency of stools per day, and a change in the consistency of stools moving from watery to more formed stools using the Bristol Stool Scale. This study has demonstrated there is a distinct need for more verbal and written education regarding use of alternating anti-diarrheal medications and AA-ORS. There was not a statistically significant difference in pre and post use of anti-diarrheal medications, but there was a subjective increase in use of both single agent diphenoxylate and alternating both loperamide and diphenoxylate atropine in the post survey. This may have been a coincidence or could be confounded by the written and verbal education given to the patient at the time of informed consent on the best use of alternating anti-diarrheal medications and AA-ORS.

Further research is needed with larger studies to ascertain the efficacy of AA-ORS in reduction of CRD and improvement of QOL and to advocate for cost saving measures such as insurance coverage for the AA-ORS product. As studies demonstrate efficacy, insurance companies may be willing to cover the cost of the product to improve patient outcomes and drive the cost of CRD management down. In order for insurance to provide coverage, it would be ideal to design studies to limit confounding variables, bias found in subjective surveys, with addition of randomization to either preoperative patients versus post-operative patients or comparison of outcomes of those who refuse AA-ORS to those that agreed to trial AA-ORS. Research could also be aimed at offering AA-ORS as first line before escalating to addition of diphenoxylate atropine with first line loperamide or as prophylaxis before beginning cancer treatment to better assess efficacy. In addition, AA-ORS could be used in less severe grades I and II CRD before making dose modifications to ascertain if use of AA-ORS helped to prevent dose modifications. Future research could also evaluate retrospective hospitalizations among participants who used AA-ORS to reduce CRD.

### **Limitations**

This study had several limitations for translation into research-based evidence. The study sample was limited by the small size, representation of diversity in ethnicity, and lack of data collection on gender. The small convenience sample limited the ability to be inclusive and diverse resulting in the majority of the sample being White Caucasian, and it which is unknown if results would be transferable to other ethnicities and across gender differences. The second limitation was participation. Although, the study accrued 22 participants, only 16 provided post survey data due to reasons such as difficulty using the survey, time required to take survey, unexpected illness, hospitalization, and decision to no longer participate. In addition, the data

was largely collected from subjective responses allowing for the possibility of bias and misunderstanding when completing surveys.

Another significant study limitation was poor compliance with use of the AA-ORS solution. Among the participants who provided post survey data, only 13% (n=2) of the participants reported compliance with the appropriate recommended use of two, 8-ounce servings of AA-ORS, 7 days per week; whereas up to 25% reported using less than the recommended dose, and 58% of participants reporting they did not use any of the AA-ORS at either half the serving or the recommended serving on any day per week. There were various reasons reported for compliance issues such as nausea, taste aversions, not “wanting to have to take one more thing,” sudden resolution of diarrhea with use of anti-diarrheal, and the cost of the product. Although the participants were provided with free product, through a private funding grant, the cost for one box containing twelve, 8-ounce servings of the AA-ORS is \$59.64 and the product is not typically reimbursable by medical insurance as it is deemed a “medical food that provides select amino acids and electrolytes” (Entrinsic Health Solutions, 2020).

### **Conclusions**

In this study population, the use of AA-ORS was not found to improve the QOL of participants experiencing CRD. However, the data demonstrated that AA-ORS is useful in the reduction of CRD among patients receiving systemic oncology therapies. It is recommended that this study be replicated with a larger, more inclusive sample size to further support the use of AA-ORS in the reduction of chemotherapy related diarrhea and associated quality of life.

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**Table 1.** *Sociodemographic Variables of Participants (n=22)*

<b>Variable</b>	<b>Mean (SD) or n (%)</b>
<b>Age Mean (SD)</b>	
	54.7 (13)
<b>Race/Ethnicity n (%)</b>	
White/Caucasian	14 (64%)
Other (Hispanic, Asian, Native American, or another ethnicity)	1 (5%)
No Response	7 (32%)
<b>Marital Status</b>	
Married	10 (45%)
Not Married	5 (23%)
No Response	7 (32%)
<b>Financial Concerns Related to Chemotherapy Related Diarrhea</b>	
Yes	10 (45%)
No	5 (23%)
No response	7 (32%)

**Table 2. Cancer Diagnosis and Treatment Regimen for Participants (n =22)**

	<b>Mean n (%)</b>
<b>Cancer Diagnosis</b>	
Colorectal	8 (38%)
Lung	7 (33%)
Pancreatic	3 (14%)
Esophageal	1 (5%)
Sarcoma	1 (5%)
Other	2 (9%)
<b>Cancer Treatment Regimen</b>	
5 fluorouracil regimen with irinotecan (+FOLFIRINOX, FOLFIRI, FOLFOXIRI, +mAB)	6 (27%) * (1 (4.5%) with mAB)
5 fluorouracil Based Regimen without irinotecan, 5FU alone or FOLFOX, + mAB)	4 (18%) * (1 (4.5%) with mAB)
taxane plus carboplatin (paclitaxel/docetaxel)	3 (14%)
taxane alone (paclitaxel/docetaxel)	2 (9%)
tyrosine kinase inhibitor, EGFR antagonists, VEGF inhibitor	2 (9%)
capecitabine based regimen	1 (4.5%)
irinotecan Only	1 (4.5%)
carboplatin, pemetrexed, pembrolizumab	1 (4.5%)
Other	2 (9%)

**Table 3.** Pre and Post Data Comparison of Quality of Life QOL Domains from Functional Assessment of Chronic Illness Therapy -Diarrhea (FACIT-D), Pain, Grade of Diarrhea, and Consistency of Stools (n =16)

	<b>Potential Range</b>	<b>Pre-intervention Mean (SD)</b>	<b>Post-intervention Mean (SD)</b>	<b>p</b>
Physical function	5-25	13.6 (4.1)	11.8 (4.0)	.078
Functional status	5-25	12.5 (2.8)	14.2 (3.6)	.133
Bowel Function	5-45	35.3 (9.0)	29.2 (10.1)	<b>.003</b>
Satisfaction with Coping	0-5	3.3 (1.4)	3.6 (1.2)	.369
Pain	0-5	3.5 (1.2)	3.3 (1.0)	.546
CTCACE Grade of Diarrhea	0-4	2.6 (0.8)	1.7 (0.7)	<b>.001</b>
Bristol Stool Scale (Consistency of stools)	1-7	5.4 (0.9)	4.6 (1.4)	<b>.049</b>

**Table 4.** Comparison of Treatment Holds, Delays, Dose Modifications, and Patient Weight from Baseline and After Use of AA-ORS (Enterade®)

	<b>Pre (Baseline)</b>	<b>Post</b>	<b><i>p</i></b>
Treatment Holds or Delays Due to CRD	18% (4)	32% (7)	.625
Dose Modification/Reductions due to CRD	27% (6)	38% (8)	.508
Change in Weight			
Weight Increased or Stable		50% (11)	
Weight Loss		32% (7)	



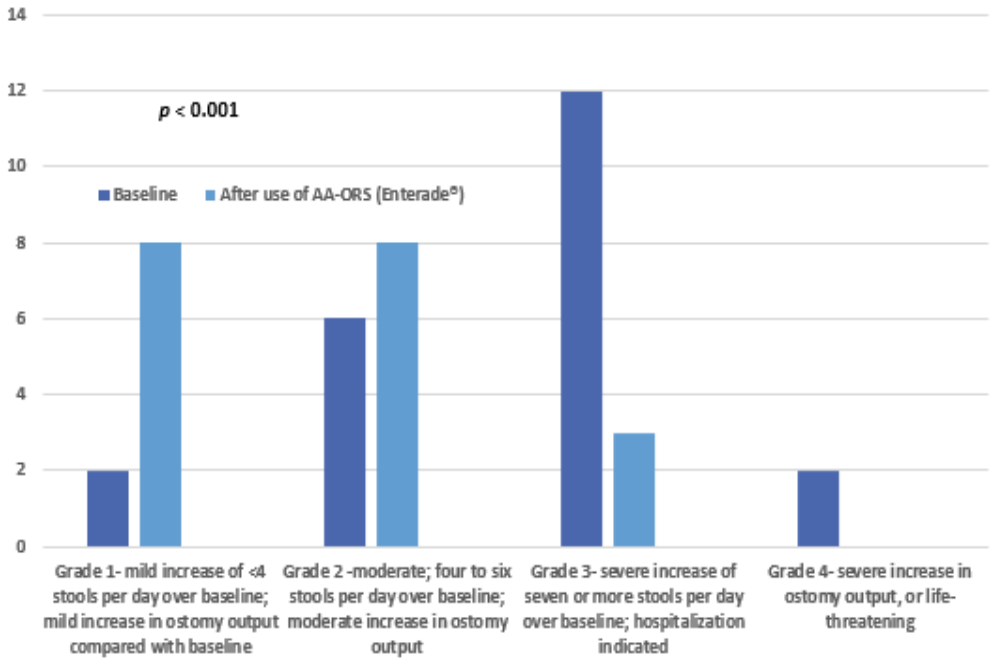
**Table 5.** *Pre and Post Data Comparison of Subjective Anti-diarrheal Use among Participants*

Anti- diarrheal medication	<b>Pre</b>	<b>Post</b>
Loperamide (Imodium ad- over the counter)	34.8%	38.9%
diphenoxylate /atropine (Lomotil prescribed by provider)	13%	5.6%
Both Loperamide and Diphenoxylate /atropine	26.1%	33.3%
None	26.1%	22.2%

**Table 6.** *Pre and Post Data Comparison of Subjective CRD Associated Symptoms*

<b>Symptom or Electrolyte Disturbance</b>	<b>Pre</b>	<b>Post</b>
Nausea	56.5%	36.8%
Abdominal pain	47.8%	26.3%
Weight Loss	60.9%	52.6%
Muscle Weakness	34.8%	26.3%
Muscle Cramping	17.4%	15.8%
Dehydration	65.2%	21.1%
Decreased Appetite	65.2%	47.4%
Hypokalemia	39.1%	42.1%
Hypomagnesemia	39.1%	31.6%
Hypocalcemia	17.4%	10.5%

**Figure 1.** Common Terminology Criteria for Adverse Events v5.0 (CTCAE) from Baseline (Survey 1) and after use of AA-ORS (Survey 2) (n=19)



**Figure 2.** Change in Stool Consistency Using the Bristol Stool Scale from Baseline (Survey 1) and after use of AA-ORS (Survey2) (n= 17)

