Sucralfate to Improve Oral Intake in Children with Infectious Oral Ulcers: A Randomized, Double-blind, Placebo-Controlled Trial

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I. Objectives/Hypothesis

Specific Aim 1: To evaluate comparative effectiveness of sucralfate versus placebo on the improvement of oral fluid intake (in ml/kg) 60 minutes post administration in children between 6 months and 5 years of age with oral infectious ulcers presenting to an urban pediatric emergency departments with concern for decreased oral intake or dehydration.

Hypothesis: Sucralfate will lead to a clinically significant improvement in oral intake relative to placebo in pediatric patients diagnosed with oral infectious ulcers and a history consistent with poor oral intake or dehydration presenting to the emergency department.

Specific Aim 2: To explore the difference in the rates of intravenous fluid (IVF) administration, admission rates, ED length of stay, rates of unscheduled visits and physician perception of adequate oral intake in children between 6 months and 5 years with oral infectious ulcers treated with sucralfate versus placebo.

Hypothesis: Pediatric patients receiving sucralfate will have decreased rates of IVF administration, hospital admission, unscheduled return visits, as well as shorter ED length of stay compared to the placebo group.

II. Methods

Study Design and Setting

The study will take place in an urban pediatric ED with approximately 80,000 visits per year, of which about 700 visits per year are due to oral infectious ulcers. This study will be a double-blind, randomized, placebo controlled trial comparing sucralfate to placebo for improving oral intake in children with oral ulcers. Due to lack of benefit from clinical trials, and the potential for harm, placebo was chosen as a comparator over combination diphenhydramine, aluminum hydroxide, and lidocaine. A randomized control trial will be the best study to determine efficacy of the therapy, while minimizing bias.

Selection of Participants

This will be a convenience sample based on study staff availability. Subjects will be identified in triage based on a history of oral ulcers or by physicians during examination. They will be screened and enrolled by a member of the study team.

<u>Subject Eligibility:</u>

Inclusion:

- Age ≥6 months and <5 years of age
- Present with oral infectious ulcers such as gingivostomatitis, herpangina, or hand, foot and mouth disease
- History of poor oral fluid intake by parent or guardian
- English or Spanish speaking parents or guardians

Exclusion:

- Severely dehydrated or toxic, requiring immediate resuscitation
- Exclusively Breastfed
- Dental disease
- Mouth trauma

Active Malignancy
Preexisting upper airway obstruction or swallowing difficulties
Received IVF within 24 hours
Administration of BOTH acetaminophen AND ibuprofen within 4 hours of enrollment

Interventions

After consent is obtained from the parents or guardians, study patients will be randomized to receive treatment with either the experimental drug (sucralfate) or placebo. Simple randomization allocation will be performed with a computerized randomization process. The research pharmacy will maintain a treatment arm allocation key. The pharmacist will send an amber colored syringe with a number and no other identifying factors. This will blind patients, family, nurses, physicians and study staff from the assignment.

Subsequently, the study personnel will collect baseline data from the patient's guardian. Data will be recorded on a standardized form and will include subject demographics (including age, ethnicity, and sex), historical information about prior analgesia at home (medication, dose and time prior to arrival), duration of current symptoms, an initial set of vital signs (temperature, heart rate, blood pressure and peripheral pulse oximetry), and the baseline clinical dehydration score. The Clinical Dehydration Score (CDS) will be used since prior research exhibited moderate inter-observer reliability(23) and it has been previously validated for the evaluation of dehydration(24-26).

All patients will receive analgesia, either acetaminophen 15mg/kg or ibuprofen 10mg/kg depending on medication administration prior to arrival in the ED and the discretion of the treating physician. Some patients may receive these medications in triage if they are febrile, the rest of the participants will receive analgesia as part of the study protocol.

Patients randomized to the experimental arm will receive therapy with oral sucralfate. Administration will be by the treating nurse using a measured syringe provided by the pharmacy to the oral cavity, aiming to cover the inflamed mucosa and ulcerative lesions. Given the young nature of the patients in the study, the swish and swallow method is not feasible. A weight based dose of sucralfate will be administered - 20mg/kg/dose up to 1g, consistent with published recommendations for other indications (27). Studies have shown doses from 15-50mg/kg/dose to be relatively safe in the pediatric population(15-17). If a patient spits the medication out within 5 minutes of administration, the dose will be re-administered.

Patients randomized to the placebo arm will receive therapy with a solution of water and ora-sweet syrup. Using prepared syringes from the pharmacy, the nurses will administer a placebo volume that will be equivalent to the volume of the weight based sucralfate suspension. Ora-sweet syrup is essentially a sweet base, normally used as a vehicle for other pediatric suspension medications. The ingredients glycerin, sorbitol, sodium saccharin, xanthan gum, flavoring, buffered with citric acid, sodium citrate and preservatives provide a solution similar in color, taste, and smell. Both will be dispensed in amber syringes to conceal any minor differences

in appearance. Similar ingredients have been used in other studies as placebo, and have not impeded the ability to demonstrate efficacy of sucralfate(3, 19).

After the administration of the study drug, subjects will be actively encouraged to drink fluids. The study staff or nursing staff will provide oral hydration supplements in the form of age appropriate formula or pedialyte (instead of breastfeeding), apple juice, Gatorade or popsicles. The study staff will have a script of instructions explaining to the family the importance of encouraging oral intake with small sips every few minutes, which is the current standard of care at our institution. The study staff or nurses will check in at 30 minutes post administration to make sure parents are trialing fluids and offer alternative fluids if patient prefers.

At 60 minutes post administrations, the study staff will document the volume of the fluids in ml. Fluid amount ingested will be measured by research staff according to calculated measurements of cups, other containers, and syringes in the ED or packaged frozen rehydration solution. In addition, they will record the dose and timing of analgesia provided in the hospital, an updated set of vital signs (temperature, heart rate, blood pressure and peripheral pulse oximetry), and any side effects. Physicians will be asked if they feel the oral intake is sufficient per their impression. Both the treating physician and parent/guardian will be asked their best guess of treatment allocation to assess the adequacy of blinding.

Following completion of the experimental stage as detailed above, patients will be released to receive standard of care therapy as determined by the assigned attending ED physician. After the patient is discharged from the ED, study staff will record the need for further IV hydration, ED length of stay, the final disposition, and whether or not a prescription for sucralfate is provided. The research nurse will contact each family approximately 72 (72-96) hours after initial visit to inquire about unscheduled visits elsewhere, and ED records will be reviewed for any unscheduled return visits.

Methods of Measurement and Outcome Measures

The primary outcome will be the amount of fluid ingested within 60 minutes of administration of the study drug, expressed in milliliters per kilogram.

The secondary outcomes measured will include (1) whether the oral intake is deemed adequate at 60 minutes (as determined by the treating clinician); (2) whether patient required fluid administration by intravenous line (oral hydration failure); (3) whether participant required hospital admission; (4) duration of stay in the ED; (5) incidence of unscheduled visits.

Sample Size

The treatment groups will be analyzed on an intention-to-treat basis. The only prior study in the literature with a similar endpoint of fluid intake between 2 treatment groups (viscous lidocaine versus placebo) with oral infectious ulcers demonstrated a baseline fluid intake rate of 8.4 ml/kg, mean difference of 4.3ml/kg and SD 7ml/kg ingested during a 60-minute fluid trial. A panel of experts convened for the study design deemed an effect size of 4 ml/kg to be clinically meaningful(12). Using this data, with an alpha of 0.05 and beta of 0.20, sample size calculations

yield n=50 per group (100 total). No allowance is made for loss to follow-up because of the short timeframe of this study. The calculations were performed using STATA (version 13.0; Statacorp, College Station, TX).

Statistical Analysis

Baseline group characteristics will be summarized in a table with means and standard deviations for continuous data, percentages for categorical data, and medians with interquartile ranges for ordinal data.

The primary outcome of oral fluid intake in milliliters per kilogram will be compared between the two groups using a two-tailed t-test, or non-parametric equivalent if the data is non-normally distributed. The data will be presented with mean intake in each group and its standard deviation, with comparison between the groups presented as a difference in means and its 95% confidence interval, and resultant p value.

Secondary outcomes for this study will include IVF administration rates, hospital admission rates, ED LOS, rates of unscheduled visits, and physician perception of adequate oral intake. Analysis of these variables will be completed using appropriate statistical analysis depending on the nature of the data (t-test for continuous, chi square of Fisher's exact test for categorical, and Mann-Whitney U test for ordinal). Non-parametric tests will be used when appropriate.

Finally, if significant baseline difference in the groups occur, linear multivariable regression analysis of the primary endpoint will be performed to adjust for potential confounders.