Sucralfate as an Adjunct to Analgesia to Improve Oral Intake in Children With Infectious Oral Ulcers: A Randomized, Double-Blind, Placebo-Controlled Trial

Nidhi V. Singh, MD*; Giovanni A. Gabriele, BA; Matthew H. Wilkinson, MD, MPH

*Corresponding Author. E-mail: nvsingh@bcm.edu.

Study hypothesis: We hypothesized that sucralfate along with oral analgesics (acetaminophen or ibuprofen) administered in the emergency department leads to a clinically significant improvement in oral intake in children with acute infectious oral ulcers.

Methods: This was a randomized, double-blind, placebo-controlled trial of sucralfate versus placebo conducted between 2017 and 2018 in an urban pediatric emergency department. Children aged 6 months to 5 years with acute, infectious oral ulcers and poor oral intake received either acetaminophen at 15 mg/kg or ibuprofen at 10 mg/kg and were then randomized to receive sucralfate at 20 mg/kg per dose up to 1 g or a placebo solution. The primary outcome was oral fluid intake within 60 minutes of medication administration. The secondary outcomes were repeat ED visits, length of stay in ED, intravenous hydration rate, admission rate, adverse event rate, and emergency physician's determination of the adequacy of oral intake.

Results: One hundred subjects with mild dehydration (clinical dehydration score of 1) and a median age of 1.38 years were enrolled and analyzed (49 in the sucralfate group and 51 in the placebo group). Oral intake 1 hour after drug administration was similar in both the groups: the median intake in the sucralfate group was 9.7 mL/kg and 10.7 mL/kg in the placebo group (difference −1 mL/kg; 95% confidence interval [CI] −2.0 to 4.8). According to the emergency physician's report, the secondary outcomes were significant only for adequate oral intake: 71% in the sucralfate group versus 88% in the placebo group (difference −16.8%; 95% CI −32.2 to −1.4).

Conclusion: Sucralfate as an adjunct to oral analgesics was not superior to placebo in improving oral intake in children with acute oral infectious ulcers. [Ann Emerg Med. 2021;■:1-8.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Pediatric patients commonly present to the emergency department with decreased oral intake, fussiness, and fever owing to infectious oral lesions, including gingivostomatitis, herpangina, and hand-foot-and-mouth disease. These diagnoses are made clinically and managed symptomatically with the goals of controlling pain and improving oral intake to prevent dehydration.[1]

Despite the high incidence of these diseases in children, there is a paucity of literature on their optimal management. Acyclovir, which is used to treat herpes simplex and varicella virus ulcers, is ineffective in reducing pain and promoting oral intake.[2] Acetaminophen and ibuprofen are the most commonly used first-line analgesics in pediatric emergency departments.[3] Opioids, compounded topical suspensions (diphenhydramine, aluminum hydroxide, and magnesium hydroxide), and viscous lidocaine are used for more severe pain.[3-6] No data exist to support the efficacy of these compounded suspensions or lidocaine in the management of mucositis or oral ulcers.[7,8] Sucralfate, a basic aluminum salt of a sulfated disaccharide, is a topical agent that forms a protective barrier.[9] It is commonly used for treating ulcerative diseases of the gastrointestinal tract,[10-12] and chemotherapy-induced mucositis[13] or managing postoperative oral pain.[14-16] The efficacy of sucralfate as a topical analgesic for infectious oral ulcers in children is less well understood.

Editor's Capsule Summary

What is already known on this topic

Infectious oral lesions in children, without optimal pain management, can lead to dehydration requiring intravenous fluids.

What question this study addressed

When added to acetaminophen and/or ibuprofen, does topical sucralfate improve oral liquid intake?

What this study adds to our knowledge

In this randomized, double-blinded trial of 100 children, oral liquid intake at one hour was similar for sucralfate versus placebo.

How this is relevant to clinical practice

These results do not support the use of topical sucralfate for infectious oral ulcers in children. Use of acetaminophen and/or ibuprofen in the emergency department as well as at home should be encouraged to optimize oral fluid intake.

Importance

Oral infectious ulcers are a burden on both the health care system and families. Patients in the ED experience long lengths of stay because physicians emphasize oral intake, manage pain without opioids, and minimize trauma by limiting intravenous placement. Despite physicians' efforts, patients may require further observation or admission for continued intravenous fluid administration. Families face anxiety when their child is ill, caregivers lose time from work, and caregivers have unclear options for home management of the child's pain. Ultimately, developing a standard of care using a low-risk medication for oral infectious ulcers might lead to improved symptoms for such children in both the ED and at home. To date, no studies have evaluated the efficacy of sucralfate in children with oral infectious ulcers.

Goals of This Investigation

This randomized, placebo-controlled trial aimed to assess whether sucralfate leads to improved oral intake 60 minutes after its administration in children with oral infectious ulcers compared with a placebo in an ED setting. We chose sucralfate as the topical analgesic in this interventional study because it is commonly used for treating oral ulcers at our institution. A difference of 4 mL/kg in fluid intake was considered clinically significant.[8] The secondary goals were to evaluate the frequency of intravenous fluid administration, frequency of hospital admissions, frequency of 72-hour repeat ED visits, length of stay in the ED, physicians' perception of adequate oral intake, and adverse events.

MATERIALS AND METHODS

Study Design and Setting

The study was a double-blind, randomized, placebo-controlled trial conducted in an urban pediatric ED with approximately 80,000 annual visits, of which approximately 700 visits per year were due to oral infectious ulcers. The study was approved by the university's institutional review board. The trial was registered with ClinicalTrials.gov: NCT03241030. A more detailed version of the trial protocol can be found in Appendix E1 (available at http://www.annemergmed.com.)

Selection of Participants

This was a convenience sample based on the availability of study staff. The eligibility criteria for participants were 6 months to 5 years of age; presentation of oral infectious ulcers, such as gingivostomatitis, herpangina, or hand-foot-and-mouth disease; history of poor oral intake of both solids and liquids according to the parents or guardians; and English- or Spanish-speaking parents or guardians. We excluded patients who appeared toxic and required immediate resuscitation; were exclusively breastfed; had preexisting upper airway obstruction or swallowing difficulties; had dental disease, mouth trauma, or active malignancy; had received intravenous fluid within the previous 24 hours; or had received both acetaminophen and ibuprofen within 4 hours before enrollment.

Interventions

The study subjects were randomized to receive treatment with either the experimental drug (sucralfate) or placebo after the research staff obtained consent from them. The research pharmacist performed randomization using a computerized randomization process and maintained the treatment arm allocation key until enrollment ended, and the data were reviewed for completeness. The placebo's volume was equal to the volume of the weight-based sucralfate suspension, and the sucralfate suspension and placebo were similar in color, taste, and smell. Both the treatments were dispensed by the pharmacy using amber-colored syringes to conceal any minor differences in appearance. The participants, caregivers, treating staff, and research staff were blinded to the treatment allocation.

We collected data on demographics, analgesia before arrival (medication, dose, and time before arrival), and

triage vital signs, and further clarification of the severity of the decreased oral intake was assessed by asking the parents or guardians about the number of days of the decreased oral intake and decreased urine output. Given the recall bias associated with parental reports and for a more objective measure of dehydration, we calculated a clinical dehydration score, a previously validated tool with moderate interobserver reliability.[17-20] All patients in the ED received either acetaminophen at 15 mg/kg or ibuprofen at 10 mg/kg, depending on prior analgesic use and at the discretion of the treatment provider.

Patients assigned to the experimental arm received oral sucralfate (20 mg/kg, maximum dose 1 g).[21] Patients assigned to the placebo arm received a solution of water combined with a syrup commonly used as a vehicle for compounded medication. The medications were administered by nurses, with redosing if the child spit up the medication within 5 minutes.

After the study drug's administration, the subjects were provided with oral hydration supplements in the form of an age-appropriate formula, an oral rehydration solution, water, apple juice, or popsicles. There was no standardized amount of fluid that was provided to the subjects; however, the study staff recorded the volumes provided to calculate how much was ingested at the end. The study staff had 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 checked at 30 minutes to make sure that the parents were trialing fluids and offering alternative fluids if needed. Following the completion of the experimental stage at 60 minutes, the patients received standard care therapy at the emergency physician's discretion.

Methods of Measurement

At 60 minutes, the staff documented fluid intake. The volume (in mL) was measured by the research staff based on the volume listed on the container or calculated measurements of the dispensed fluids. If the patient did not consume the full amount of the fluid in the container, the staff measured the remaining amount using a syringe and subtracted it from the full amount listed on the container or the dispensed amount. In addition, they recorded the dose and timing of analgesics provided in the hospital, an updated set of vital signs, and whether there were any side effects, such as nausea, vomiting, abdominal pain, or rash. The ED providers were asked to subjectively report (yes or no) whether the patient had a successful oral challenge during the 1-hour trial period. Both the treatment providers and the parents or guardians were asked to provide their best guess regarding treatment assignment to assess the adequacy of the blinding.

After discharge, the study staff recorded whether the subjects had received intravenous fluid hydration, length of stay in the ED, and final disposition. The research staff contacted each family approximately 72 (72 to 96) hours after the initial visit to inquire about repeat ED visits to other locations and assessed our ED records for additional visits. We chose a 72-hour revisit period because this is a standard quality metric for our institution and many other pediatric facilities.[22,23]

Outcome Measures

The primary outcome was the amount of fluid ingested within 60 minutes of the administration of the study drug, expressed in milliliters per kilogram. Oral intake was chosen because dehydration and decreased oral intake are common complaints with this disease process. The secondary outcomes were percentage of patients receiving intravenous fluid, percentage of patients hospitalized, length of stay in the ED in minutes, percentage of patients with repeat ED visits within 72 hours, percentage of patients with adverse events, and percentage of patients who had adequate oral intake according to the ED provider's report.

Primary Data Analysis

In accordance with a previous study with a similar endpoint, we calculated our sample size assuming a baseline fluid intake rate of 8.4 mL/kg and a mean difference of 4.3 mL/kg between the sucralfate and placebo groups, with a standard deviation of 7 mL/kg ingested during a 60-minute fluid trial.[8] A panel of experts from this previous study deemed an effect size of 4 mL/kg to be clinically meaningful.[8] Based on these data, with an alpha of 0.05 and a beta of 0.20, the sample size calculation yielded 50 per group (100 in total).

An intention-to-treat and a per-protocol analysis were performed for the primary outcome of oral fluid intake in milliliters per kilogram. For the intention-to-treat analysis, a sensitivity analysis was performed, in which the 2 excluded subjects were included and assigned both the smallest and largest values of oral intake, which did not change the results of the primary endpoint. The Stata "cendif" function was used to calculate 95% CIs for median differences in the primary outcome and secondary outcome variables.[24] Following the primary analysis,

multivariable linear regression (version 13.0; StataCorp, College Station, TX) was employed to evaluate the effect of baseline differences (age, sex, race, presence of fever, administration of analgesics at home, clinical dehydration score, parental report of decreased oral intake, and administration of analgesics at the ED) between the sucralfate and placebo groups on the primary endpoint. Additionally, a post hoc analysis was performed to quantify the volume that physicians deemed as adequate oral intake.

RESULTS

Characteristics of the Study Subjects

Between July 2017 and July 2018, 254 children were assessed for inclusion (Figure 1), 102 were enrolled, and 2 were later excluded from the analysis (1 for not having oral lesions and 1 for not receiving analgesics), resulting in 100 subjects being eligible for the analysis (Table 1), of whom 49 received the intervention. The children in both the groups were mildly dehydrated, with a median clinical dehydration score of 1 (interquartile range [IQR] 0, 2). In addition, herpangina was the most common clinical diagnosis, with 25 (51%) in the sucralfate group and 24 (47%) in the placebo group.

Main Results

The amount of fluid ingested in 60 minutes was similar in both the groups (Figure 2). The median amount of oral intake in the sucralfate group was 9.7 mL/kg (IQR 3.9, 19.4) and 10.7 mL/kg (IQR 7.2, 17.1) in the placebo group (difference −1 mL/kg; 95% CI −2.0 to 4.8) (Table 2). The regression analysis adjusted for the baseline differences between the groups and presence of fever did not change the significance of the difference in the primary endpoint (Table 3).

The secondary outcomes were similar in both the groups (Table 2), except for the emergency physicians' report that 71% in the sucralfate group versus 88% in the placebo group had adequate oral intake (difference −16.8%, 95% CI −32.2 to −1.4). A post hoc analysis determined that the value that the emergency physicians deemed "adequate" was 13.2 mL/kg (IQR 7.9, 19.3) and the value deemed "inadequate" was 1.4 mL/kg (IQR 0.3, 6.6). Five patients (10%) in the sucralfate group and 1 (2%) in the placebo

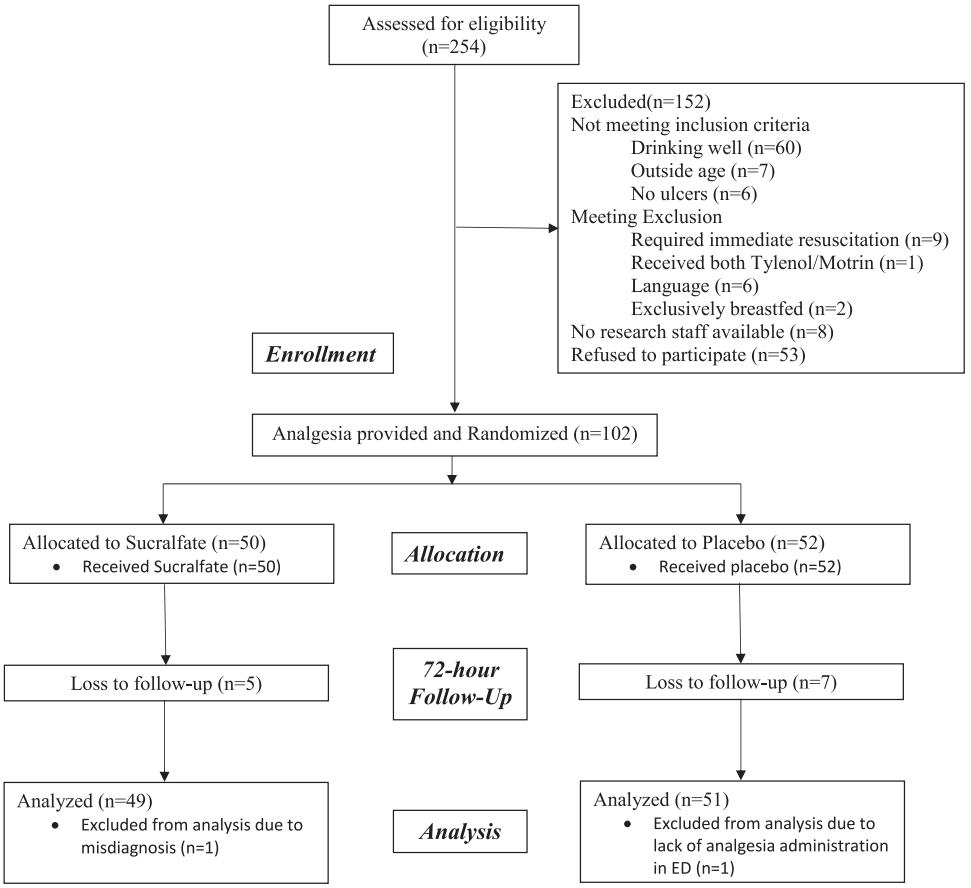

Figure 1. Study flow chart in consolidated standards of reporting trials format.

Table 1. Baseline characteristics and illness characteristics of case and control patients.

Variable	Sucralfate (n=49)	Placebo (n=51)
Age, y, median (IQR)	1.48 (1, 2.3)	1.28 (0.9, 1.9)
Sex, male, no. (%)	24 (49)	23 (45)
Race or ethnicity, no. (%)		
Hispanic	39 (79.6)	42 (82.4)
White	9 (18.4)	5 (9.8)
Black	1 (2)	4 (7.8)
Degree of dehydration		
Decreased oral intake, d, median (IQR)	1 (1, 2)	1 (1, 2)
Decreased urinary output, d, median (IQR)	1 (0, 1)	1 (0, 1)
Clinical dehydration scale, median (IQR)	1 (0, 2)	1 (0, 2)
Clinical diagnosis, no. (%)		
Herpangina	25 (51)	24 (47.1)
Hand-foot-and-mouth disease	18 (36.7)	16 (31.4)
Ulcerative stomatitis/pharyngitis	1 (2)	7 (13.7)
Oral ulcers	3 (6.1)	3 (5.9)
Gingivostomatitis	2 (4.1)	1 (2)
Analgesia in previous 24 h, no. (%)		
Ibuprofen	20 (40.8)	14 (27.5)
Acetaminophen	13 (26.5)	17 (33.3)
None	15 (30.6)	19 (37.3)
Unknown	1 (2)	1 (2)
Analgesia before arrival, h, median (IQR)	5 (3.5, 7)	4.5 (2.5, 7)
Analgesia in ED, no. (%)		
Ibuprofen	29 (59.2)	38 (74.5)
Acetaminophen	17 (34.7)	12 (23.5)
Both	3 (6.1)	1 (2)

IQR, Interquartile range; *ED*, emergency department.

group required intravenous fluid hydration, although the difference was not statistically significant. No patients experienced adverse events during their stay in the ED.

In the assessment of blinding, 56% of physicians and 52% of family members correctly guessed the allocation arm, indicating adequate blinding.

LIMITATIONS

Our study had limitations. First, the population included in this study was a convenience sample based on the availability of research staff. Second, this was a single-center trial, limiting the generalizability of our results. In addition, oral challenges are effort-dependent, and there was likely patient/family variability among the patients and family members in encouraging fluid intake. The coaching provided by the staff might also have been variable. We used a hydration script to standardize the coaching provided by the staff to the families as well as randomization to avoid introducing a bias. Furthermore, we instructed the research staff to bring an adequate amount of oral hydration to each subject but did not specify the amount or type, which may have been another limitation.

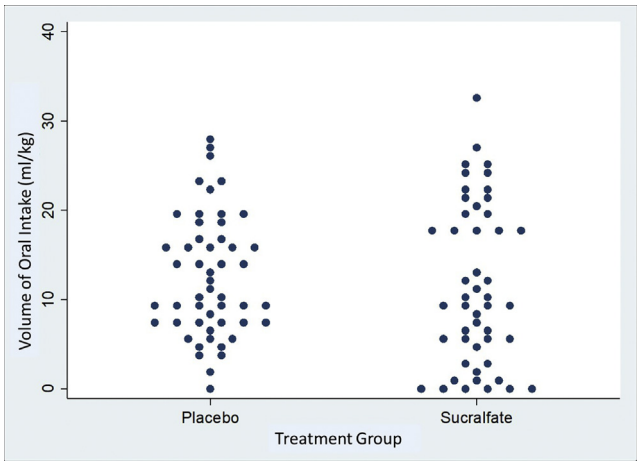

Figure 2. Dot plot of each participant's oral intake.

In other studies, sucralfate was administered by the swish-and-swallow method, which was not feasible in our study group because of the young age of our patients. This may have limited the ability of the substance to fully coat the mouth and ulcers and, thus, provide the barrier intended. We instructed the families to wait for at least 5 minutes after medication administration to start with the oral intake. This length of time may not have been sufficient for the substance to coat the ulcers. The method of swishing and swallowing for 1 to 5 minutes demonstrated efficacy in reducing postoperative pain,[14-16] and the medication remained in the mouth even 2.5 hours after its administration.[25]

Finally, we did not quantify the severity of the disease in terms of the number of the ulcers. Instead, we attempted to define the severity based on family reports of the number of days of decreased urine output and oral intake and clinical dehydration score as a more objective measure to reduce the recall bias. However, our study population had mild dehydration, limiting our understanding of the effect of sucralfate in more dehydrated patients or the effect based on the quantity of ulcers.

Table 2. Results of primary and secondary outcomes.

Outcome	Sucralfate (n=49)	Placebo (n=51)	Difference (95% CI)
Oral fluid intake, mL/kg, median (IQR)	9.7 (3.9, 19.4)	10.7 (7.2, 17.1)	−1.0 (−4.8 to 2.0)
Physician's perception of adequate intake, %	71.4	88.2	−16.8 (−32.2 to −1.4)
LOS in ED, min, median (IQR)	218 (176, 295)	215 (162, 255)	3 (−13 to 44)
IVF hydration, %	10.2	2.0	8.2 (−1.1 to 17.5)
Repeat ED visit in 72 h, %	8.2	11.8	−3.6 (−15.3 to 8.1)
Admitted, %	2.0	4.1	−2.1 (−8.8 to 4.6)

CI, Confidence interval; *LOS*, length of stay; *IVF*, intravenous fluid.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, we found that there was no statistically significant difference in oral intake 1 hour after administration between children with oral infectious ulcers administered sucralfate and those administered placebo. There were no significant differences in the secondary outcomes of intravenous hydration, hospital admission, length of stay in the ED, and 72-hour repeat ED visits. The rate of intravenous fluid hydration was 6% in our cohort, with 5 (10%) patients in the sucralfate group and 1 (2%) in the placebo group, which was lower than the rates reported in other studies.[5,8] The overall admission rate was 3%, which is lower than the 10% admission rate reported in other studies.[8,26] It is possible that these rates were lower than those in other studies because our patients had very mild dehydration, as shown by the median clinical dehydration score.

Analgesics are a vital part of the management of oral infectious ulcers and were included as a part of our protocol. Commonly, medication given at home may be underdosed, or there may be a significant recall bias in the time of the last administration. Thus, we standardized the protocol for all the patients to receive analgesics in the

Table 3. Results of regression analysis for primary outcome.

	Univariable Analysis			Multivariable Analysis		
Outcome	**β**	**95% CI**	***P* value**	**Adjusted β**	**95% CI**	***P* value**
Sucralfate	−1.02	−4.17 to 2.13	.523	−0.26	−3.46 to 2.94	.873
Age	−1.48	−3.38 to 0.43	.127	−1.73	−3.73 to 0.27	.089
Male sex	−0.83	−3.99 to 2.33	.604			
Race or ethnicity						
White	Ref			Ref		
Hispanic	1.93	−2.62 to 6.47	.402	1.26	−3.33 to 5.86	.587
Black	5.98	−2.20 to 14.16	.150	6.83	−1.53 to 15.19	.108
Temperature at triage	−0.47	−1.32 to 0.37	.269			
Analgesia at home						
None	Ref					
Ibuprofen	−0.60	−4.57 to 3.38	.766			
Acetaminophen	−0.30	−4.10 to 3.49	.875			
CDS	0.58	−0.67 to 1.83	.359			
Analgesia in ED						
Ibuprofen	Ref					
Acetaminophen	−0.51	−4.05 to 3.03	.776			
Both	4.19	−3.93 to 12.30	.308			
Days of decreased oral intake	0.57	−0.61 to 1.75	.343			

CDS, Clinical dehydration score.

ED.[27,28] Some patients had received acetaminophen or ibuprofen at home and then received another dose of analgesics in the hospital. Despite randomization, more subjects in the sucralfate group than those in the placebo group had received analgesics at home before arrival. Even with this advantage, sucralfate did not show significant improvement compared with the placebo. Furthermore, more subjects in the placebo group than those in the treatment group received ibuprofen. Some studies have shown ibuprofen to be more effective than acetaminophen for pain control, which may have resulted in a bias toward the null.[29,30]

The only statistically significant secondary outcome was the physicians' perception of adequate oral intake: 71% in the sucralfate group versus 88% in the placebo group (difference −16.8%; 95% CI −32.2 to −1.4). This finding should be considered exploratory because there was no adjustment for a multiple hypothesis testing. The median fluid intake deemed "adequate" was 13.2 mL/kg (IQR 7.9, 19.3), similar to that reported in previous studies. In contrast, the median intake deemed "inadequate" was 1.4 mL/kg (IQR 0.3, 6.6), which was much lower than that reported in previous studies.[31] The ability to tolerate adequate oral intake is a major cause of ED disposition. These data suggested that the physician gestalt was fair at ascertaining fluid intake without measuring the exact volume of the fluid.

The median oral intake in both the groups was slightly higher than the oral intake reported in a study evaluating the efficacy of lidocaine for treating oral infectious ulcers.[8] The oral intake might have been higher in our study because the patients' oral intake was not as poor or they were not as dehydrated as the parents felt, as documented by the mild clinical dehydration score. Additionally, the oral intake might have been higher in our study because even the slightest coaching provided by the staff might have encouraged the families and patients to improve oral intake. Furthermore, both the sucralfate and placebo suspensions had sorbitol to give it a sweet taste, which may have served as an appetite stimulant.[32,33] This may have contributed to the improved oral intake in both the groups, thus obscuring any difference.

There is no standard formulation of these topically compounded solutions, and there is significant heterogeneity in the diphenhydramine–antacid mixtures, with or without lidocaine, with the substitution of bismuth subsalicylate by aluminum hydroxide and the inclusion of nystatin or hydrocortisone. We considered using a diphenhydramine–antacid compound for comparison; however, because of the lack of evidence of the efficacy of this compound in improving oral intake,[7] we opted for a placebo for comparison instead. The efficacy of these alternatives could be an area of further research. There is room for further research on the optimal time needed for sucralfate to exert a topical effect on the mucosa when administered orally or by the swish-and-swallow method.

We administered acetaminophen or ibuprofen to all our subjects to make this an ethical study. It would be inappropriate to only give a placebo to a patient with fussiness and pain. It is possible that appropriate weight-based doses of acetaminophen and ibuprofen may have masked the effect of sucralfate. Based on our clinical experience, we know that parents frequently underdose analgesics at home.[28,34] Additional studies could be devised to better elucidate whether analgesia alone improves oral intake. We believe that analgesia played a significant role in our study. Studies could be devised to compare improvement with nonnarcotic analgesics, such as acetaminophen and ibuprofen, and opioid medications. There are still many institutions that use opioids for the treatment of oral ulcers.[3] If nonnarcotic medications are shown to be equally effective, these results might lead to decreased prescription of narcotics during the current opioid epidemic.

In conclusion, this study found no difference between sucralfate and a flavored placebo suspension for improving oral intake in otherwise healthy preschool-aged children with acute oral infectious ulcers. We believe that the focus for these patients should be on optimizing oral analgesics and coaching their parents about oral fluid administration.

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Author affiliations: From the Department of Pediatric Emergency Medicine, Baylor College of Medicine, Houston, TX (Singh); the Dell Children's Medical Center, Austin, TX (Gabriele); and the Department of Pediatric Emergency Medicine, University of Texas Austin Dell Medical School, Austin, TX (Wilkinson).

Author contributions: NVS and MHW conceived the study, designed the trial, and obtained research funding. NVS and GAG supervised the conduct of the trial, data collection, and recruitment. MHW provided statistical advice on study design and analyzed the data. NVS drafted the manuscript, and all authors contributed substantially to its revision. NVS takes responsibility for the paper as a whole.

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