A Randomized Clinical Trial of Recombinant Human Hyaluronidase-Facilitated Subcutaneous Versus Intravenous Rehydration in Mild to Moderately Dehydrated Children in the Emergency Department

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ABSTRACT

Background: Alternative treatment of dehydration is needed when intravenous (IV) or oral rehydration therapy fails. Subcutaneous (SC) hydration facilitated by recombinant human hyaluronidase offers an alternative treatment for dehydration. This clinical trial is the first to compare recombinant human hyaluronidase-facilitated SC (rHFSC) rehydration with standard IV rehydration for use in dehydrated children.

Objective: This Phase IV noninferiority trial evaluated whether rHFSC fluid administration can be given safely and effectively, with volumes similar to those delivered intravenously, to children who have mild to moderate dehydration.

Methods: The study included mild to moderately dehydrated children (Gorelick dehydration score) aged 1 month to 10 years. They were randomized to receive 20 mL/kg of isotonic fluids using rHFSC or IV therapy over 1 hour and then as needed until clinically rehydrated. The primary outcome was total volume of fluid infused (emergency department [ED] plus inpatient hospitalization). Secondary outcomes included mean volume infused in the ED alone, postinfusion dehydration scores and weight changes, line placement success and time, safety, and provider and parent/guardian questionnaire.

Results: 148 patients (mean age, 2.3 [1.91] years; white, 53.4%; black, 31.8%) were enrolled in the intention-to-treat population (73 rHFSC; 75 IV). The primary outcome, mean total volume infused, was 365.0 (324.6) mL in the rHFSC group over 3.1 hours versus 455.8 (597.4) mL in the IV group over 6.6 hours (P = 0.51). The secondary outcome of mean volume infused in the ED alone was 334.3 (226.4) mL in the rHFSC group versus 299.6 (252.3) mL in the IV group (P = 0.03). Dehydration scores and weight changes postinfusion were similar. Successful line placement occurred in all 73 rHFSC-treated patients and 59 of 75 (78.7%) IV-treated patients (P <
0.0001). All IV failures occurred in patients aged <3 years; rHFSC rescue was successful in all patients in whom it was attempted. Both treatments were well tolerated. Clinicians rated fluid administration as easy to perform in 94.5% (69 of 73) of the rHFSC group versus 65.3% (49 of 75) of the IV group (P < 0.001). Parents/caregivers were satisfied or very satisfied with fluid administration in 94.5% (69 of 73) of rHFSC-treated patients and 73.3% (55 of 75) of IV-treated patients.

Conclusions: In mild to moderately dehydrated children, rHFSC was inferior to IV hydration for the primary outcome measure. However, rHFSC was noninferior in the ED phase of hydration. Additional benefits of rHFSC included time and success of line placement, ease of use, and satisfaction. SC hydration facilitated with recombinant human hyaluronidase represents a reasonable addition to the treatment options for children who have mild to moderate dehydration, especially those with difficult IV access. ClinicalTrials.gov identifier: NCT00773175. (Clin Ther. 2012;34:2232–2245) © 2012 Elsevier HS Journals, Inc. Open access under CC BY-NC-ND license.

Key words: dehydration, pediatric, rehydration, recombinant human hyaluronidase, subcutaneous.

INTRODUCTION
Assessment and treatment of dehydration is one of the leading causes of emergency department (ED) use in the United States. Furthermore, dehydration is one of the most common reasons for hospitalizations in pediatrics nationwide. The current standard for treatment of dehydration is oral rehydration therapy (ORT) and intravenous (IV) therapy. However, both therapeutic techniques have advantages and disadvantages. Advantages of ORT include that it is a more “natural” way to rehydrate the patient because it uses the body’s inherent mechanism to maintain hydration (glucose sodium cotransport), is less expensive, takes less time, and can be performed outside of the medical environment. However, for success, a cooperative patient and family are needed. Studies have shown that there is an approximate 20% rate of inability to perform ORT. IV fluid therapy is obviously a mainstay of rehydration but requires IV access. It is known that placement of an IV line is not an easy process, particularly in a dehydrated pediatric patient. Research regarding difficult IV access has shown that children aged <3 years are at a greater risk for numerous IV attempts to obtain successful placement. The disadvantages inherent in these 2 techniques necessitate a reevaluation of the therapeutic options available for dehydrated patients. Subcutaneous (SC) hydration was established as safe and effective for adults and children with dehydration, and was commonly used for this purpose in the past but was not in widespread use at the time the trial discussed herein was conducted. SC hydration was shown to be even more effective with the use of hyaluronidase, an enzyme that breaks down hyaluronic acid. Hyaluronan is a mucopolysaccharide found in the intracellular matrix of most types of connective tissue that resists the spread of substances through the SC space. By temporarily increasing the permeability of hyaluronan, fluid can more readily be absorbed via the capillary and lymphatic systems after SC administration.

Development of a recombinant human hyaluronidase has renewed interest in SC delivery. Recombinant human hyaluronidase is a human, DNA-derived, hyaluronidase enzyme that has up to 100 times greater purity than the reference standard, animal-derived formulation, on the basis of enzymatic activity. Recombinant human hyaluronidase-facilitated SC (rHFSC) rehydration is safe and well tolerated, with no reports of serious hypersensitivity reactions. Not only did the addition of recombinant human hyaluronidase increase gravity-driven SC flow rates ~4-fold to ~400 mL/hour, but the fluid was absorbed into the systemic circulation better than in the control group who received SC hydration without recombinant human hyaluronidase. In the first study of rHFSC fluid administration, a single-arm, open-label treatment study in mild to moderately dehydrated children (Increased Flow Utilizing Subcutaneously-Enabled Pediatric Rehydration I [INFUSE-Peds I]), fluid administration was well tolerated, and 94.1% of the 51 patients studied were rehydrated successfully via the SC route. Potential advantages of rHFSC rehydration compared with IV rehydration are that it expedites and simplifies parenteral access, requires fewer staff resources, and is less distressing to parents and patients. rHFSC fluid therapy may be particularly useful for patients with difficult IV access. The US Food
and Drug Administration (FDA) had approved recombinant human hyaluronidase and issued the same class label as the existing animal-derived product. One labeling restriction was that there was a limit of 200 mL of fluid that could be administered subcutaneously in infants and children <3 years old. This low amount of fluid would not be particularly helpful in rehydrating patients; therefore, the investigators designed the Increased Flow Utilizing Subcutaneously-Enabled Pediatric Rehydration II (INFUSE-Peds II) study to evaluate whether rHFSC fluid administration can be given safely and effectively, with volumes comparable with those delivered intravenously, in mild to moderately dehydrated children. The FDA removed the fluid restriction while the clinical trial was in progress. The primary outcome was total fluid administered at a single location. Secondary outcomes included mean fluid volume administered in the ED, dehydration scores, fluid administration times, pain measures, and line placement success and questionnaires of the parent/guardian and health care provider.

METHODS

Study Design

This was a Phase IV, prospective, randomized, industry-sponsored, multicenter, open-label, parallel-group, noninferiority clinical trial comparing rHFSC with IV rehydration. The trial was conducted in 24 US hospitals with pediatric EDs and 1 urgent-care center between November 2008 and December 2009. All investigators received written institutional review board approval.

The authors chose a noninferiority design to demonstrate that SC hydration is an appropriate alternative to IV hydration. There are inherent benefits to SC hydration over IV hydration. If the trial could demonstrate that SC therapy rehydrates children as well as IV therapy then the clinician may be willing to use this option in the future. It would have been inappropriate to try to demonstrate that SC therapy is superior to IV therapy because the IV method is considered the “gold standard” for rehydration. SC hydration may be as effective and at least as well tolerated as IV hydration but with fewer potential complications and advantages in terms of ease of administration; SC hydration may thus be preferred for appropriately selected patients. Because SC hydration, compared with IV hydration, requires less skill to implement and can be delivered in more patient care settings (eg, settings outside the hospital), it may also have an impact on the cost of health care.

During the course of this study, the FDA approved several labeling changes for recombinant human hyaluronidase that included removal of the upper limit of fluid volume (200 mL) per SC administration to children <3 years of age. Based on the new labeling, the protocol was amended to include children up to 10 years of age so that the study results could better represent the pediatric population in whom SC rehydration is most likely to be used.

Treatments

Patients meeting inclusion and exclusion criteria (Table I) were randomly assigned to treatment by using a validated computerized interactive response system that could be accessed by telephone or an Internet Web page; patients were stratified according to dehydration severity and weight. They were randomized 1:1 to rHFSC or IV fluid administration to 1 of 6 different strata. Strata included: weight <10.0 kg and mildly dehydrated; weight <10.0 kg and moderately dehydrated; weight 10.0 kg to <20.0 kg and mildly dehydrated; weight 10.0 kg to <20.0 kg and moderately dehydrated; weight >20.0 kg to ≤30.0 kg and mildly dehydrated; or weight >20.0 kg to ≤30.0 kg and moderately dehydrated. Isotonic fluids were administered at 20 mL/kg during the first hour, with additional fluids administered for up to 72 hours based on the investigator’s ongoing evaluation of the patient’s hydration status. Follow-up telephone assessments occurred on days 2 and 7 after patient discharge.

Outcome Measures

The primary outcome was mean total fluid volume (in milliliters) administered at a single infusion site from start to cessation of fluid administration (ED plus inpatient hospital stay). The goal was to assess outcomes from the ED stay alone as well as the entire encounter (ie, both the ED and inpatient stay combined), if applicable. Prespecified secondary outcomes for ED alone and ED plus inpatient hospitalization included total fluid volume and administration times. Objective improvement in dehydration was assessed by using a dehydration score (Gorelick 10-item scale) and weight change at the end of infusion. Successful hydration was also subjectively assessed by a health care provider (HCP) survey at patient discharge. Num-
ber of attempts and time required for catheter placement were measured. Pain was assessed by using the FLACC\textsuperscript{19} scale (Face, Legs, Activity, Cry, Consolability scale; for those \(<3\) years old) and the FACES Pain Rating\textsuperscript{20} scale (for those \(\geq 3\) years old). HCP and parent/guardian satisfaction with therapy were assessed via a simple questionnaire administered by the study site investigator at the end of rHFSC or IV rehydration. Treatment-related events, including pain and swelling, were noted after catheter placement and hyaluronidase administration but before fluid infusion. A serious adverse event (SAE) was defined as any event that was fatal or life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or caused a congenital anomaly/birth defect. Investigators had a scale on which to grade relatedness of SAE to treatment, including “no, not related,” “unlikely,” “possibly,” “probably,” and “yes, related.” The National Cancer Institute’s Terminology Criteria for Adverse Events and Common Toxicity Criteria, a standard for clinical trials, was used in this study.

At investigator’s discretion, patients could be switched (“rescued”) to the other treatment after at least 1 failed attempt. Rescued patients were considered successfully treated if discharged from the ED or, if admitted for further rehydration, received all additional fluid via the rescue route.

Table I. Inclusion and exclusion criteria for the Increased Flow Utilizing Subcutaneously-Enabled Pediatric Rehydration II (INFUSE-Peds II) study.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>● Children aged from 1 month to (&lt;10) years</td>
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<tr>
<td>○ No more than 20% of enrolled patients will be (&gt;3) years of age</td>
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<tr>
<td>● Patients presenting at the ED, inpatient pediatric unit, and/or outpatient urgent-care facility with mild to moderate dehydration (mild = 1–2; moderate = 3–6 [based on the score using the Gorelick assessment of dehydration status]) who failed to improve or are not candidates for oral rehydration therapy or are otherwise candidates for parenteral rehydration provided that:</td>
</tr>
<tr>
<td>○ No more than 70% of enrolled patients have a diagnosis of mild dehydration</td>
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<tr>
<td>○ The child is healthy except for the underlying etiology for dehydration (eg, viral gastroenteritis)</td>
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<tr>
<td>○ Prehydration weight (\geq 5)th percentile for age</td>
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<tr>
<td>○ Parents or legal guardian(s) available to provide written informed consent</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Patients with body weight (\geq 30) kg</td>
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<tr>
<td>● Shock or life-threatening situation (life expectancy (&lt;10) days)</td>
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<tr>
<td>● Requirement for IV access for any indication other than for treatment of dehydration</td>
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<td>● Indwelling IV catheter, except if intended only for collection of laboratory specimens</td>
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<tr>
<td>● Any condition precluding SC infusion or infusion-site evaluation in all possible anatomic locations, including the upper back, anterior thighs, abdomen, and other potential areas for SC therapy</td>
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<tr>
<td>● Any reason (before study enrollment) for a hospital admission or an extended stay in the ED for other than dehydration</td>
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<tr>
<td>● Known hypersensitivity to hyaluronidase or any ingredient in the study formulation of recombinant human hyaluronidase</td>
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<tr>
<td>● Known hyponatremia ((&lt;130) mEq/L), hypernatremia ((&gt;155) mEq/L), or hypokalemia ((&lt;3.0) mEq/L)</td>
</tr>
<tr>
<td>● Any medical condition likely to interfere with the patient’s ability to fully complete all protocol-specified interventions, the ability to undergo all protocol-specified assessments, or likely to prolong the patient’s need for medical attention beyond that required for rehydration</td>
</tr>
<tr>
<td>● Participation in a study of any investigational drug or device within 30 days before enrollment in this study</td>
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</tbody>
</table>

ED = emergency department; IV = intravenous; SC = subcutaneous.
Statistical Analysis

This noninferiority study was powered to test the null hypothesis that rHFSC therapy is inferior to IV therapy (ie, mean volume infused subcutaneously was ≤85% of volume delivered intravenously for fluids delivered for up to 72 hours). Assuming that fluids could be administered equivalently via the rHFSC or IV route and the coefficient of variation for fluid volume administered was 35%, rHFSC administration would not be deemed clinically inferior if the volume infused via the rHFSC method was ≥85% of volume infused by the IV method. A sample size of 74 patients per group would provide ≥80% power at a 1-sided 0.025 level of significance for establishing noninferiority of rHFSC versus IV. A P value of <0.05 rejects the null hypothesis of inferiority.

Descriptive statistics and/or frequency counts for efficacy measures were analyzed according to: (1) randomized route of administration (all patients) or intention-to-treat (ITT) population; (2) randomized route of administration (excluding those switched to another route before start of infusion) or per-protocol population; and (3) patients switched to another route before start of infusion (rescued population). For some end points, the second and third analysis groups were combined to yield a comprehensive “treatment-received” group. This comprehensive treatment-received group was created post hoc because it was noted that this was left out of the original analysis plan. This post hoc group did not change any of the results; however, the authors felt it was a more true representation of the 2 treatment groups and that the data would be informative for readers. There were no adjustments for multiplicity of testing of the same variable(s) being conducted on multiple populations. The results are presented based on the ITT population to maintain research integrity; however, the other 2 populations are discussed as well for completeness.

ITT Analysis

The ITT population represents all patients randomized to receive either rHFSC or IV treatment. According to ITT principles, patients were analyzed according to randomized treatment even if they received therapy via the alternate rescue route. Patients in whom infusion device access could not be obtained had values imputed to the minimum or maximum, however pre-specified. Patients with unsuccessful access to the randomized route were rescued and their data summarized separately (first according to the randomized group, second to the rescued group, and third to the treatment-received group). The ED treatment analysis includes analysis of treatment in the ED only, whether discharged from the ED or hospitalized.

RESULTS

Patient Disposition

A total of 148 patients were randomly assigned to 1 of 2 treatment groups (Figure 1); 73 rHFSC-treated patients and 75 IV-treated patients (ITT population). Of the 75 patients randomized to receive IV therapy, 15 were rescued to rHFSC (rescued population) before fluid infusion because successful IV access was not established; 1 IV-treated patient was withdrawn from the study at parent request after 2 IV attempts. All 73 patients randomized to rHFSC had an SC line, and 59 patients randomized to the IV group had an IV line placed successfully (per-protocol population). Eighty-eight patients received their first hydration fluid by the rHFSC route and 59 by the IV route (treatment-received population).

Characteristics of Study Patients

The patient population (Table II) was similar with the exception of patients in the group aged 1 month to <1 year, which had twice as many patients in the rHFSC group versus the IV group (rHFSC group, 23 [31.5%]; IV group, 12 [16.0%]). Because this was a randomized trial, this randomization difference occurred purely by chance. Mean patient age was 2.3 years (range, 0.2–9.8 years), and the white population (53.4%) and black population (31.8%) were predominant. Most patients were aged <3 years (79.6%) and weighed <20 kg (95.3%), with a similar male:female ratio. Approximately 70% of patients in both groups had moderate dehydration (Gorelick score, 3–6).

Efficacy Results

Total Volume

The primary outcome measure, mean (SD) total volume infused in the ITT population (ED plus inpatient), was 365.0 (324.57) mL or 31.2 (24.17) mL/kg via the rHFSC route (n = 73) delivered over 3.1 hours (mean) versus 455.8 (597.43) mL or 35.8 (52.43) mL/kg delivered via the IV route (n = 75) over 6.6 hours (P = 0.51), which was insufficient to reject the null hypothesis that rHFSC is inferior to IV administration (Table III). The mean duration of infusion difference occurred...
because few patients were hospitalized for continued rehydration with an SC line in place. Thirteen of 73 rHFSC-treated patients and 8 of 59 IV-treated patients were transferred from the ED to the hospital. Of these, 2 of the rHFSC-treated patients continued an SC line, whereas the other 11 rHFSC-treated patients had an IV line placed. Most participating centers did not have protocols or training for the inpatient staff to manage an SC line and subsequently had an IV line placed on admission, explaining this route change. Consequently, more inpatients received fluids intravenously.

Analysis of ED-only volumes in the ITT population reveals that the SC route was shown to be noninferior in the ED with a mean (SD) volume of 334.3 (226.40) mL or 28.7 (16.52) mL/kg (rHFSC, n = 73) and 299.6 (252.33) mL or 22.2 (16.68) mL/kg (IV, n = 75 [P = 0.03]) (Figure 2; Table III). Figure 3 represents fluid received in the ED and inpatient settings in the per-protocol population but removes the 16 patients with failed IV access in the IV group who had “0” entered as the fluid received. The analysis favors IV therapy but is a more appropriate comparison between rHFSC and IV therapy. The volumes in milligram per kilogram are also shown in Table III.

All 15 rHFSC-rescued patients were <3 years old; their response was similar to patients randomized to receive rHFSC therapy. The volumes of fluid received
are similar to the values observed in patients who were randomized to the SC group.

**Other Assessments**

**Infusion-Device Placement**

The number of unsuccessful attempts for infusion-device placement was higher with IV versus rHFSC therapy \((P < 0.01)\). The rate of successful line placement in the IV group was 78.7% (59 of 75) versus 100% (73 of 73) in the rHFSC group \((P < 0.0001)\). All IV failures were in patients < 3 years of age (Figure 4).

Overall, fewer staff members were required for rHFSC administration. Two staff members were required to place the infusion device in 49.3% (36 of 73) of rHFSC-treated patients and 57.6% (34 of 59) of IV-treated patients. One individual alone placed the infusion device in 27.4% (20 of 73) of rHFSC-treated patients and 1.7% (1 of 59) of IV-treated patients. Three or more personnel were required for placement of the infusion device in the remainder of patients.

**Gorelick Scores and Weight**

Objective measures of dehydration were comparable. Mean (SD) reduction from baseline dehydration score at the end of infusion (ITT population) was 2.6 (1.26) in the rHFSC group \((n = 73)\) and 2.2 (1.64) in the IV group \((n = 75)\) \((P = 0.07)\) (Table III). Mean percent increase in weight from baseline to end of infusion in the ITT population was 2.9% (15.17%) in the rHFSC group \((n = 68)\) and 3.8% (15.17%) in the IV group \((n = 67)\) \((P = 0.62)\). No difference between treatment groups was seen in time from start of fluid infusion to first urine output in the ED (2.3 hours with rHFSC rehydration vs 2.9 hours with IV rehydration).

**Subjective Assessment of Hydration Success**

Successful hydration, defined according to the HCPs’ subjective assessment of the randomized route of hydration therapy (ITT population), was 93.2% (68 of 73) and 76.0% (57 of 75) in the rHFSC and IV groups, respectively \((P = 0.07)\). All 15 rHFSC-rescued

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Table II. Demographic and baseline clinical characteristics in the intention-to-treat population.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>rHFSC (n = 73)</th>
<th>IV (n = 75)</th>
<th>Total (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>2.1 (1.72)</td>
<td>2.4 (2.07)</td>
<td>2.3 (1.91)</td>
</tr>
<tr>
<td>Age group, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo to &lt;1 y</td>
<td>23 (31.5)</td>
<td>12 (16)</td>
<td>35 (23.6)</td>
</tr>
<tr>
<td>≥1 y to &lt;2 y</td>
<td>20 (27.4)</td>
<td>28 (37.3)</td>
<td>48 (32.4)</td>
</tr>
<tr>
<td>≥2 y to &lt;3 y</td>
<td>17 (23.3)</td>
<td>18 (24.0)</td>
<td>35 (23.6)</td>
</tr>
<tr>
<td>≥3 y</td>
<td>13 (17.8)</td>
<td>17 (22.7)</td>
<td>30 (20.3)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (46.6)</td>
<td>39 (52.0)</td>
<td>73 (49.3)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (53.4)</td>
<td>36 (48.0)</td>
<td>75 (50.7)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>25 (34.2)</td>
<td>22 (29.3)</td>
<td>47 (31.8)</td>
</tr>
<tr>
<td>White</td>
<td>39 (53.4)</td>
<td>40 (53.3)</td>
<td>79 (53.4)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (12.3)</td>
<td>13 (17.3)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Mean (SD) baseline body weight, kg</td>
<td>11.8 (4.14)</td>
<td>12.9 (4.68)</td>
<td>12.4 (4.44)</td>
</tr>
<tr>
<td>Gorelick dehydration score, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (1–2)</td>
<td>20 (27.4)</td>
<td>23 (30.7)</td>
<td>43 (29.1)</td>
</tr>
<tr>
<td>Moderate (3–6)</td>
<td>53 (72.6)</td>
<td>52 (69.3)</td>
<td>105 (70.9)</td>
</tr>
</tbody>
</table>

rHFSC = recombinant human hyaluronidase-facilitated subcutaneous; IV = intravenous.

*There were no significant differences except for the 1-month to < 1-year group.
Table III. Primary (volume) and secondary efficacy outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>rHFSC</th>
<th>IV</th>
<th>P or 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized (ITT) Population (n = 73)</td>
<td>Patients Switched From IV to rHFSC (n = 15)*</td>
<td>Post hoc Treatment-Received Population Analyses (n = 88)†</td>
</tr>
<tr>
<td>Mean (SD) volume infused in the ED plus inpatient hospital stay, mL</td>
<td>365.0 (324.57)</td>
<td>388.3 (281.13)</td>
<td>369.0 (316.19)</td>
</tr>
<tr>
<td>Mean (SD) volume infused in the ED plus inpatient hospital stay in mL/kg§</td>
<td>31.2 (24.17)</td>
<td>38.6 (25.96)</td>
<td>32.4 (24.47)</td>
</tr>
<tr>
<td>Mean (SD) volume infused during ED stay, mL</td>
<td>334.3 (226.40)</td>
<td>315.3 (150.38)</td>
<td>331.0 (214.73)</td>
</tr>
<tr>
<td>Mean (SD) volume infused during ED stay, mL/kg§</td>
<td>28.7 (16.52)</td>
<td>31.5 (14.79)</td>
<td>29.1 (13.33)</td>
</tr>
<tr>
<td>Mean (SD) Gorelick dehydration score at end of infusion</td>
<td>0.6 (0.83)</td>
<td>0.3 (0.62)</td>
<td>0.6 (0.80)</td>
</tr>
<tr>
<td>Mean (SD) Gorelick dehydration score change from baseline at end of infusion</td>
<td>−2.6 (1.26)</td>
<td>−3.1 (1.22)</td>
<td>−2.7 (1.26)</td>
</tr>
</tbody>
</table>

rHFSC = recombinant human hyaluronidase-facilitated subcutaneous; IV = intravenous; ITT = intention to treat; ED = emergency department.

*One patient withdrew before receiving fluids.
†The treatment-received group was combined post hoc to show the combined results of the patients who actually received rHFSC and IV therapy (rescue treatment group plus the per-protocol group).
‡Data pertain to IV.
§Three rHFSC randomized, 1 rHFSC rescued, and 2 IV patients had known volumes but missing data on weight (n = 70 rHFSC; n = 57, IV; and n = 14, rescued).

n = 58 patients.
patients were considered by the HCP to be successfully hydrated by using the rescue route.

**Infusion Rates**

Mean (SD) flow rate observed in the ITT population (ED plus hospital) was 15.4 (5.62) mL/kg/h in the rHFSC group (n = 70) and 12.3 (9.50) mL/kg/h in the IV group (n = 73) (difference, 2.9; 95% CI, 0.3 to 5.5). In the ED alone, mean flow rate was 15.6 (5.33) mL/kg/h in the rHFSC group and 13.3 (9.50) mL/kg/h in the IV group (difference 2.2; 95% CI, −0.2 to 4.7). Mean flow rates in the per-protocol population were similar to values in the ITT population.

**Treatment Times**

Less time was required for rehydrating the rHFSC group. Median total treatment time (first catheterization attempt to end of infusion) via the randomized route in the ITT population was shorter (1.3 hours) for rHFSC compared with IV hydration (2.3 hours) (P < 0.0001) and was the same in the ED plus inpatient and ED only. Median time from first catheterization attempt to start of fluid infusion in the ITT population was shorter (3.5 minutes [rHFSC, n = 73] vs 11.8 minutes [IV, n = 75]; P < 0.001).

**HCP and Parent/Caregiver Assessments**

In the ITT population, HCPs rated fluid administration as easy to perform in 94.5% (69 of 73) of the rHFSC group versus 65.3% (49 of 75) of the IV group (P < 0.001), and rHFSC administration less difficult than IV administration (78.1% [57 of 73]). Parents/caregivers were satisfied or very satisfied with fluid administration in 94.5% (69 of 73) of rHFSC-treated patients and 73.3% (55 of 75) of IV-treated patients.

**Safety Profile**

**Serious Adverse Events**

SAEs were reported in 8 patients (rHFSC, 3; IV, 5). One SAE fatality was an episode of cardiopulmonary arrest in a 2-month-old black male (4.5 kg) from Gambia. He was admitted to the ED with a 2-week history of diarrhea that had been treated with amoxicillin and metronidazole, with the last dose 72 hours before enrollment into the trial. The patient was dehydrated on evaluation in the ED and enrolled. He received rHFSC followed by 90 mL of normal saline over the first hour and an additional 50 mL of 5% dextrose in 0.2% sodium chloride SC over the next 2 hours (140 mL delivered, SC total). Due to his ongoing fluid loss with continued vomiting and diarrhea, the patient was hospitalized, and IV therapy initiated. The patient improved over the next 2 days but was unable to tolerate

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**Figure 2.** Total volume delivered in the emergency department (ED) was similar between recombinant human hyaluronidase-facilitated subcutaneous (rHFSC) and intravenous (IV) routes of administration.

**Figure 3.** Total volume delivered in emergency department (ED) was similar between non-rescued recombinant human hyaluronidase-facilitated subcutaneous (rHFSC) and intravenous (IV) therapy.
oral fluids. Examination of the SC site did not reveal any erythema or edema. The IV therapy was discontinued, and oral fluids were tolerated; however, the patient developed a fever of 38.9°C related to the finding of a urinary tract infection positive for *Klebsiella pneumoniae*. Five days later, he was discharged. One day after discharge (day 8 after rHFSC fluid administration), the patient experienced a fatal cardiopulmonary arrest. An autopsy performed determined the cause of death was acute bronchopneumonia and complicating interstitial (viral-type) pneumonia. The reporting investigator considered the episode of fatal cardiopulmonary arrest to be unrelated to rHFSC fluid administration.

Other SAEs in the rHFSC group included a case of viral gastroenteritis and a case of pneumonia. SAEs in the IV group included single cases of pyrexia, rotavirus infection, ongoing dehydration, Kawasaki’s disease, and viral syndrome. No SAEs were considered related to study treatment.

**Treatment-Related Events**

At least 1 treatment-related event (TRE) was experienced by 100% (73 of 73) of rHFSC-treated patients and 90.7% (68 of 75) of IV-treated patients (*P* = 0.01) (Figure 5). Most TRES were considered mild to moderate in severity. Although the proportion of patients with TRES in the rHFSC group (100%) was numerically higher than that in the IV group (90.7%), this was primarily due to a higher incidence of infusion-site reactions that are expected with the SC route of fluid administration (specifically, erythema, swelling, and pain). Greater numbers of patients in the rHFSC group reported infusion-site erythema (rHFSC, 74.0%; IV, 25.3%), swelling (rHFSC, 80.8%; IV, 21.3%), and edema (rHFSC, 6.8%; IV, 1.3%) than in the IV group. All infusion-site events were mild to moderate in severity, except for 1 case of severe infusion-site pain in the rHFSC group. All infusion-site events resolved spontaneously with no additional treatment.

**Pain Assessments**

Pain was assessed after catheter placement and at the end of infusion. The most frequently experienced treatment-emergent AE for both groups was infusion-site pain. Reports of infusion-site pain were similar in frequency between the 2 treatment groups (mild: rHFSC, 61.6%; IV, 66.7%; moderate: rHFSC, 15.1%; IV, 12.0%). The data on FLACC scores (patients aged <3 years) are provided in Figures 6A and 6B at the time of needle stick and at the end of infusion. The results were similar between FLACC and FACES scales.

**Return Visit to ED and Subsequent Admission**

Nine of 73 (12.3%) rHFSC-treated patients, 9 of 59 (15.3%) IV-treated patients, and 1 of 15 (6.7%) patients in the rHFSC rescued group returned to the ED.
after initial discharge. Two of 9 patients in the rHFSC group and 2 of 9 in the IV group were hospitalized for continued retreatment of dehydration. No patient in the rHFSC rescued group was readmitted for retreatment of dehydration.

**DISCUSSION**

The primary outcome measure, mean total volume of fluid administered at a single infusion site from the start to the cessation of fluid administration (ED plus inpatient hospital stay), showed that more fluid was administered intravenously than subcutaneously and therefore failed to meet our primary objective. The investigators did not anticipate the need to train inpatient staff and develop hospital protocols to have inpatients continue the rHFSC route of hydration if they were admitted to the hospital. However, this trial also shows that rHFSC infusion provides an effective and reasonably well tolerated alternate route for rehydration in mild to moderately dehydrated children in the ED (secondary outcomes). These results are consistent with a previous pediatric study.13 As a result, it is the opinion of the authors that the secondary outcomes reflect the comparison between IV and SC routes of hydration that would be of greatest interest to the clinician.

During the study, the FDA removed the restriction on the label that limited the amount of fluid that could be administered subcutaneously in infants and children <3 years old. Because the labeling change was approved without the need for additional clinical study data, the study design was modified to include children up to 10 years of age so the study results could better represent the pediatric population in whom SC rehydration is most likely to be used.

A confounder exists in this study that helps to explain the difference in the total volumes administered between the 2 treatment groups. This confounder is mean infusion duration (rHFSC, 3.1 hours; IV, 6.6 hours). Only 2 patients were hospitalized for continued rehydration therapy with an SC line. SC therapy is a new treatment technique, and there were no hospital protocols for SC line use for inpatients, which resulted in IV line placement, and these patients were considered treatment failures. Analysis of volumes delivered in the ED alone supports this explanation. It is important to note that mean volume infused in the ED with rHFSC was shown to be noninferior to IV rehydration. Similarly, the mean infusion flow rate achieved with rHFSC was comparable to IV infusion in the ED.

Both rHFSC and IV routes yielded similar improvements in objective clinical parameters, including improvement in Gorelick dehydration scores, weight gain, and time from fluid administration to first urine output. HCPs reported patients were rehydrated by assigned route more frequently with rHFSC therapy than with IV therapy. The lower rate in the IV group

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**Figure 5.** Adverse events (AEs) and common infusion-site events. rHFSC = recombinant human hyaluronidase-facilitated subcutaneous; IV = intravenous. *Any general disorder or infusion-site event; †Erythema and swelling at infusion site.
The inability to establish IV access in 21.3% (16 of 75) of patients. All patients for whom an IV infusion device could not be placed had successful rescue with an rHFSC infusion.

The ability to obtain infusion device access favored rHFSC rehydration. Significantly more placement attempts were required for IV versus rHFSC therapy; there was a ~20% IV placement failure rate for patients randomized to IV therapy. All IV access failures occurred in children <3 years old, an observation previously described. No rHFSC access failures occurred in this population. No patient randomized to rHFSC rehydration requested to have the SC line removed and rehydration continued through an IV line.

Both methods of fluid delivery were reasonably well tolerated, with mild to moderate infusion-site pain related to needle insertion being similarly reported between groups and resolving postinsertion.

A post hoc analysis was performed on the treatment-received population. The original statistical analysis plan did not account for this, and there were 15 patients who were rescued with rHFSC. The results of the post hoc analysis did not change any of the conclusions.

Clinicians who are not familiar with SC hydration often ask if the treatment is painful or if the family will accept this treatment modality. This study demonstrated that pain is comparable to IV therapy and that families and patients are willing to receive rHFSC hydration as a treatment for dehydration. However, as this study also shows, it is important to develop rHFSC rehydration protocols, as well as nursing policies and procedures, before instituting this treatment modality to ensure optimal success.

Some limitations to this study deserve discussion. At the time the protocol was devised, the FDA limited total SC fluid volume augmented with recombinant human hyaluronidase in a single infusion to 200 mL in infants and children <3 years old. Therefore, the primary end point was selected to assess total volume of fluid delivered; however, the end point lost the clinical importance it once held. Another limitation was that most centers did not have protocols allowing use of an SC line in the inpatient setting, which limited data on rHFSC compared with IV therapy and caused an imbalance in the amount of fluid received by the rHFSC route in the hospital. These findings suggest that training and guidelines are needed for successful implementation of rHFSC fluid administration in the inpatient setting. Finally, it is important to note that the results of this study are applicable only to appropriately selected children who have mild to moderate dehydration.

CONCLUSIONS

This study demonstrated that in patients who required parenteral therapy for mild to moderate dehydration, both IV and rHFSC fluid administration were effective and well-tolerated methods of rehydration in the ED setting. Although combined total volume of fluid delivered in an ED and inpatient hospital setting was insufficient with rHFSC
administration to reject inferiority compared with IV administration, assessment of the ED-only portion did reveal noninferiority. SC hydration using rHFSC represents an appropriate treatment for rehydration of children who have mild to moderate dehydration. Based on the results of this trial, rHFSC rehydration is a reasonable alternative to IV fluid replacement in these select patients who have mild to moderate dehydration in the ED. It is less invasive and is clinically effective in the ED. rHFSC was easy to perform and required less staff time than IV hydration. rHFSC hydration may be particularly useful for patients with difficult IV access. Additional research in SC hydration should be performed to validate the secondary objectives that were shown in this study. Furthermore, SC rehydration should be considered for inclusion in future dehydration treatment algorithms along with ORT and IV treatment options.

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CONFLICTS OF INTEREST

Drs. Friend, Harb, and Lebel were employed by Baxter Healthcare during the course of this study and publication development. All study investigators received research funds from Baxter Healthcare. Additionally, Drs. Spandorfer, Mace, and Allen served on the Baxter Healthcare speakers’ bureau discussing subcutaneous rehydration in children.

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