Recombinant Human Hyaluronidase-Enabled Subcutaneous Pediatric Rehydration

WHAT'S KNOWN ON THIS SUBJECT: Rehydration fluids can be given subcutaneously when intravenous access is difficult to obtain. Addition of subcutaneous hyaluronidase accelerates the absorption of subcutaneous fluids by temporarily increasing tissue permeability. rHuPH20 has been proved safe and effective in adults.

WHAT THIS STUDY ADDS: The first pediatric study of rHuPH20-enabled subcutaneous rehydration shows that it is safe, well tolerated, and effective in children with mild/moderate dehydration. The procedure is well accepted by clinicians and parents.

abstract

OBJECTIVES: The Increased Flow Utilizing Subcutaneously-Enabled (INFUSE)-Pediatric Rehydration Study was designed to assess efficacy, safety, and clinical utility of recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous rehydration in children 2 months to 10 years of age.

METHODS: Patients with mild/moderate dehydration requiring parenteral treatment in US emergency departments were eligible for this phase IV, multicenter, single-arm study. They received subcutaneous injection of 1 mL rHuPH20 (150 U), followed by subcutaneous infusion of 20 mL/kg isotonic fluid over the first hour. Subcutaneous rehydration was continued as needed for up to 72 hours. Rehydration was deemed successful if it was attributed by the investigator primarily to subcutaneous fluid infusion and the child was discharged without requiring an alternative method of rehydration.

RESULTS: Efficacy was evaluated in 51 patients (mean age: 1.9 years; mean weight: 11.2 kg). Initial subcutaneous catheter placement was achieved with 1 attempt for 46/51 (90.2%) of patients. Rehydration was successful for 43/51 (84.3%) of patients. Five patients (9.8%) were hospitalized but deemed to be rehydrated primarily through subcutaneous therapy, for a total of 48/51 (94.1%) of patients. No treatment-related systemic adverse events were reported, but 1 serious adverse event occurred (cellulitis at infusion site). Investigators found the procedure easy to perform for 96% of patients (49/51 patients), and 90% of parents (43/48 parents) were satisfied or very satisfied.

CONCLUSIONS: rHuPH20-facilitated subcutaneous hydration seems to be safe and effective for young children with mild/moderate dehydration. Subcutaneous access is achieved easily, and the procedure is well accepted by clinicians and parents. *Pediatrics* 2009;124:e858–e867

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KEY WORDS

rehydration, dehydration, hyaluronidase, pediatric, subcutaneous

ABBREVIATIONS

ORT—oral rehydration therapy
rHuPH20—recombinant human hyaluronidase
ED—emergency department
AE—adverse event

This trial has been registered at www.clinicaltrials.gov (identifier NCT00477152).

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Establishing peripheral intravenous access is challenging,[1] particularly for patients with small or collapsed veins.[2] Although it is recognized that oral rehydration therapy (ORT) is considered first-line treatment for children with mild/moderate dehydration,[3,4] parenteral therapy often is needed for patients who fail to achieve adequate hydration through the oral route or are unable to receive oral rehydration therapy (ORT). In one study, 15% of children admitted to an emergency department (ED) with moderate dehydration were unable to receive ORT,[5] which suggests that, even in institutions adhering to accepted guidelines for first-line management of mild/moderate dehydration, significant numbers of children may require parenteral therapy.

Subcutaneous infusion of fluids is an alternative to intravenous hydration. Reported to be safe and well tolerated[6–9] and to deliver an equivalent fluid volume,[10] compared with intravenous hydration, for adults with mild/moderate dehydration, subcutaneous administration requires no advanced skills to start or to maintain[11,12] and may avoid certain complications of intravenous hydration.[8,13,14] Furthermore, multiple sites are appropriate for subcutaneous access,[15] and lines can be inserted quickly and maintained in relatively insensitive sites,[10,13] which makes it potentially easier, faster, and more economical than intravenous treatment.[10,11,13,15,16]

Subcutaneous fluid and drug absorption can be accelerated by hyaluronidase, a spreading enzyme.[17–21] Hyaluronidase depolymerizes hyaluronan (a viscous component of the interstitial space that inhibits bulk fluid flow), decreasing tissue resistance to subcutaneous fluid administration.[17,22,23]

Animal-derived hyaluronidase has been used for years to facilitate subcutaneous hydration in adults[19,24–29]; however, allergic and rare anaphylactic reactions have limited its use.[30,31] Recombinant human hyaluronidase (rHuPH20) 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.[32] rHuPH20 (Hylenex [Baxter International, Deerfield, IL]) has been approved by the Food and Drug Administration as an subcutaneous fluid administration adjunct for adults and children. rHuPH20 produced no allergic reaction in healthy adults after a single intradermal injection,[32] and the safety and tolerability of rHuPH20-facilitated subcutaneous fluid infusions were demonstrated in adult volunteers and palliative care patients.[17,20]

Although limited pediatric experience with animal-derived hyaluronidase from the pre–intravenous treatment era indicated 1.6- to 3.3-fold acceleration of subcutaneous fluid absorption in dehydrated infants and children,[33–36] no studies have evaluated rHuPH20-facilitated subcutaneous hydration in children. The Increased Flow-Utilizing, Subcutaneously Enabled, Pediatric Rehydration Study is the first to assess the efficacy, safety, and clinical utility of rHuPH20-facilitated subcutaneous rehydration in children with mild/moderate dehydration.

METHODS

Study Design

In this single-arm, phase IV, multicenter, pilot study, all patients received rHuPH20-facilitated subcutaneous rehydration therapy. The study was conducted in 9 US hospital EDs from August 2007 to June 2008 and was approved by each site's institutional review board.

Inclusion and Exclusion Criteria

Inclusion criteria were age of 2 months to 10 years, weight of <42 kg, presence of 1 to 6 of the symptoms of dehydration shown in Table 1,[37] and need for parenteral fluid therapy. The treating physician determined the need for parenteral therapy on the basis of either failed ORT attempts or a clinical decision that the patient was not a candidate for ORT, as well as worsening dehydration. Patients who had undergone failed attempts at intravenous catheter placement were eligible. Exclusion criteria were severe dehydration, shock, life-threatening conditions, intravenous or substantial oral fluid administration immediately before enrollment, hyponatremia (sodium level of <130 mEq/L), hypernatremia (sodium level of >155 mEq/L), hypokalemia (potassium level of <3.0 mEq/L), hypersensitivity to hyaluronidase or any formulation ingredient, medical conditions precluding subcutaneous injection, or participation in a study of any investigational drug or device within 30 days of study onset.

Screening Procedure

The medical history was recorded, a physical examination was conducted, and the cause of dehydration and the current hydration status were assessed. Uniform instructions and protocol guidance were provided to all investigators at the investigators' meeting, to ensure consistency in diagnostic evaluation. Treatment according to accepted protocol (first-line

TABLE 1 Signs and Symptoms of Dehydration[37]

General condition (lethargy; drowsiness; postural dizziness; limp, cold, cyanotic extremities; muscle cramps; coma)
Radial pulse weak, thready, feeble, or impalpable
Deep or rapid respiration
Diminished skin elasticity (pinch retracts slowly or very slowly)
Eyes sunken or very sunken
Absence of tears
Mucous membranes dry or very dry
Urine output reduced or no urine passed for many hours
Heart rate of >150 beats per min
Capillary refill time at fingertip of >2 s

therapy with ORT, including antiemetic treatment as indicated) was attempted before enrollment. Mild dehydration was defined as 1 or 2 of the symptoms described by Gorelick et al[37] (Table 1) and moderate dehydration as 3 to 6. The number of previous failed intravenous insertion attempts also was recorded.

Rehydration Protocol

A 24-gauge angiocatheter or needle was inserted into the mid-anterior thigh or interscapular area (Fig 1). One dose of rHuPH20 (1 mL, 150 U) was injected subcutaneously through the angiocatheter/needle, followed by continuous, pump-facilitated, subcutaneous infusion of 20 mL/kg isotonic fluid over 1 hour; infusion was continued, with or without electrolytes, up to 72 hours as needed.

The volume of fluid infused was recorded at 30 minutes, 1 hour, 2 hours, and 4 hours and then every 4 hours until the end of hydration. If infusion site swelling or another unacceptable reaction occurred, then the flow rate was decreased, flow was interrupted, or the infusion was moved to another site. The rHuPH20 injections were repeated every 24 hours if continued subcutaneous hydration was needed, to a maximum of 3 injections. Clinicians could use the initial catheter or a new catheter in another site after each 24-hour period. Dehydration symptoms were assessed at the end of subcutaneous hydration.

Vital signs were recorded at baseline (before rHuPH20 injection) and at 1, 2, 3, 4, 12, and 24 hours after each rHuPH20 dose. Body weight was recorded at baseline, 2 and 4 hours after each rHuPH20 dose, and at ED discharge. If patients did not demonstrate adequate improvement with rHuPH20-facilitated subcutaneous rehydration, then they could be offered alternative therapy (ie, renewed attempts at ORT

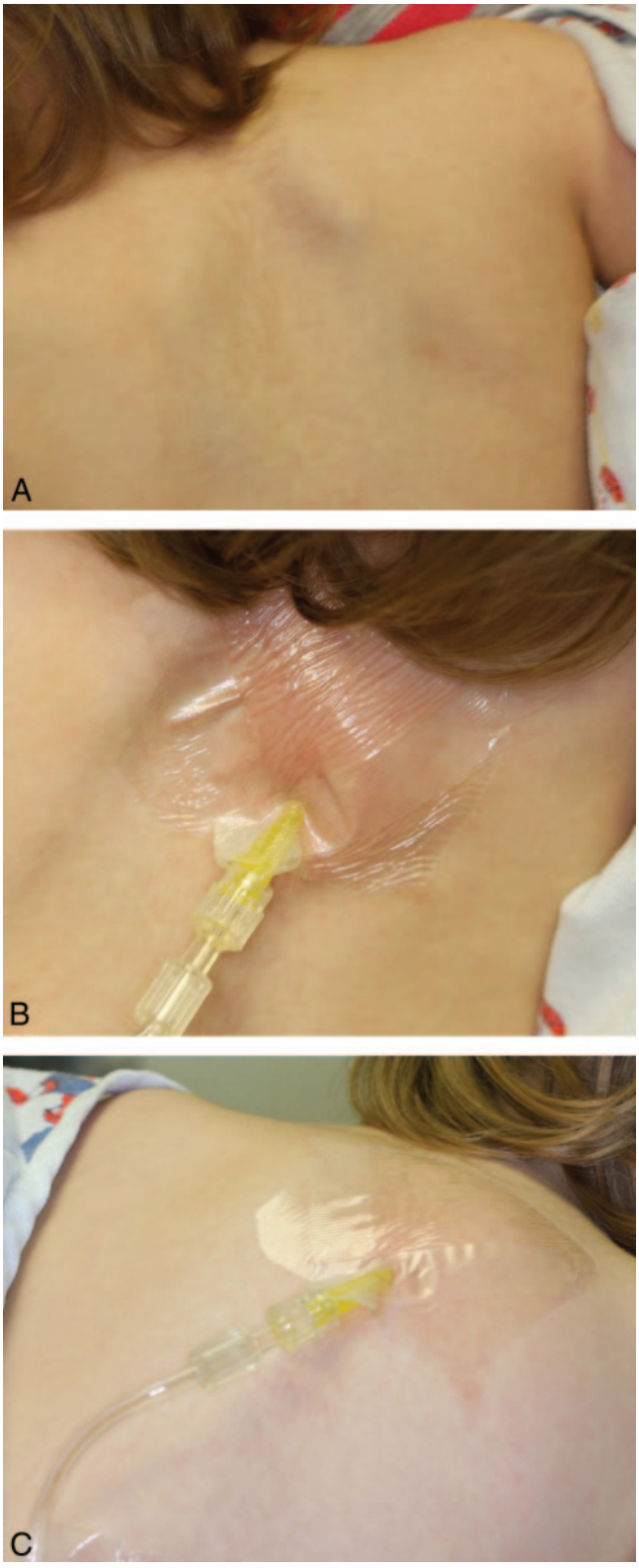

FIGURE 1
Representative interscapular infusion site before infusion (A), 4 minutes after initiation of infusion (B), and 44 minutes after initiation of infusion (C).

or nasogastric, intravenous, or intraosseous infusion). Safety and tolerability were assessed at regular intervals until ED discharge and by telephone on days 3 and 7 after ED discharge. The total study duration was 10 days.

Infusion sites were assessed for pain, tenderness, erythema, pruritus, swelling, ecchymosis, and rash before rHuPH20 injection, after rHuPH20 injection, immediately before initiation of the infusion, 1, 2, 3, 4, and 24 hours after initiation of subcutaneous hydration, and at the end of hydration. Measurements were repeated at these time points after each additional rHuPH20 dose. The severity of infusion site tenderness and pruritus was scored on a 4-point scale of 0 (none), 1 (minimal), 2 (some), or 3 (a lot). For infusion site swelling, erythema, ecchymosis, and papular rash, the largest diameter for each clinical sign was scored as 0 (none), 1 (<2.5 cm), 2 (2.5 to < 5 cm), or 3 (≥5 cm).

Infusion site pain was self-rated by children 3 to 10 years of age, with the FACES Pain Rating Scale.[38] Investigators used the Objective Pain Rating Scale for children <3 years of age.[39] Systemic adverse events (AEs) were described on the basis of their severity and probable relationship to rHuPH20 or fluids. Digital photographs of the infusion site were taken before, during, and/or after fluid administration, at the investigator's discretion.

After subcutaneous infusion, parents/guardians were asked whether they considered their child's procedure successful; whether they or their child had previously received intravenous fluids and, if so, how subcutaneous infusion compared with intravenous infusion; whether they would opt for this procedure if they or their child needed rehydration in the future; and their level of satisfaction with the procedure. Investigators recorded whether they found the procedure easy to perform; how they rated the efficacy and difficulty of the procedure, compared with intravenous infusion; and whether there were unacceptable side effects.

Outcome Measures

Efficacy Criteria

The primary efficacy end point was the proportion of patients with successful rehydration. Rehydration was considered successful if it was attributed by the investigator primarily to rHuPH20-facilitated subcutaneous infusion and the child was discharged from the hospital from the ED, without requiring alternative rehydration therapy. Secondary efficacy end points included the change in the number of dehydration symptoms from baseline to the end of subcutaneous hydration; fluid volume infused; infusion flow rate during the first hour and total infusion time; time from the start of infusion to the first urine output; change in body weight from baseline to ED discharge; time from the start of infusion to ED discharge to home or the hospital; need for and nature of alternative hydration therapy; incidence of readmission or retreatment for dehydration during the 7-day follow-up period; and parent and investigator satisfaction.

Ease of Use Criteria

Ease of rHuPH20-facilitated subcutaneous hydration use was assessed as the time from initial catheter placement to the start of subcutaneous infusion; the number of attempts needed to achieve subcutaneous catheterization; and the number of, and reasons for, infusion site changes or recatheterizations, flow rate changes, and interruptions.

Safety and Tolerability Criteria

Safety and tolerability were evaluated in terms of infusion site pain and reactions and AEs.

Sample Size Determination

A 50-patient sample size was chosen to allow an estimate of the true proportion of children with successful hydration, within ±7% (95% confidence interval). This sample size was deemed adequate for a single-arm, pilot study.

Statistical Analyses

All study outcome measures were summarized by using descriptive statistics (number, mean, median, SD, minimum, and maximum). Categorical data were summarized with frequency tabulations.

RESULTS

Demographic and Baseline Characteristics

Of the 52 patients enrolled, 51 received rHuPH20-facilitated subcutaneous hydration. One was not treated because the parent withdrew consent before the start of the procedure. Demographic and baseline characteristics are listed in Table 2.

Efficacy

In total, 48 (94.1%) of 51 patients were deemed clinically rehydrated primarily through subcutaneous therapy (Fig 2). Of those, 43 (84.3%) of 51 patients were rehydrated through subcutaneous therapy in the ED (successful treatment, according to the protocol definition); for 5 patients (9.8%), hydration was completed during hospitalizations and was deemed by the investigators to have been primarily through the subcutaneous route. Only 3 patients (5.9%) were not rehydrated through the subcutaneous route. Three children required subcutaneous hydration for >24 hours and received a second dose of rHuPH20. On day 1, the average fluid volume infused was 417.9 mL. In the first hour, the median flow rate was 18.9 mL/kg per hour (Table 3). Figure 3 shows the distribution of day 1 results.

TABLE 2 Demographic and Baseline Characteristics ($N = 51$)

Age, y	
Mean ± SD	1.9 ± 1.9
Range	0.3–9.8
Age of <3 y, *n* (%)	43 (84)
Gender, *n* (%)	
Male	29 (57)
Female	22 (43)
Weight, kg	
Mean ± SD	11.2 ± 5.4
Range	5.1–31.4
No. of signs and symptoms of dehydration, *n* (%)[a]	
1	2 (4)
2	9 (18)
3	15 (29)
4	13 (25)
5	11 (22)
6	1 (2)
Mean ± SD	3.5 ± 1.2
Race, *n* (%)	
White	31 (61)
Black	9 (18)
Other	7 (14)
Asian	3 (6)
American Indian or Alaskan Native	1 (2)
Ethnicity, *n* (%)	
Not Hispanic	42 (82)
Hispanic	9 (18)
Diagnosis underlying dehydration, *n* (%)	
Gastroenteritis	36 (71)
Other	15 (29)
ORT history, *n* (%)	
Not candidate for ORT	5 (9.8)
Failed ORT	34 (66.7)
Antiemetic (ondansetron) treatment history, *n* (%)	15 (29.4)
Initial rehydration fluid, *n* (%)	
Lactated Ringer solution	33 (65)
Normal saline solution	18 (35)
Initial infusion site, *n* (%)	
Thigh	15 (29)
Interscapular area	36 (71)

[a] ORT indicates oral rehydration therapy. Mild dehydration (1 or 2 symptoms): $n = 11$ (22%); moderate dehydration (3 to 6 symptoms): $n = 40$ (78%).

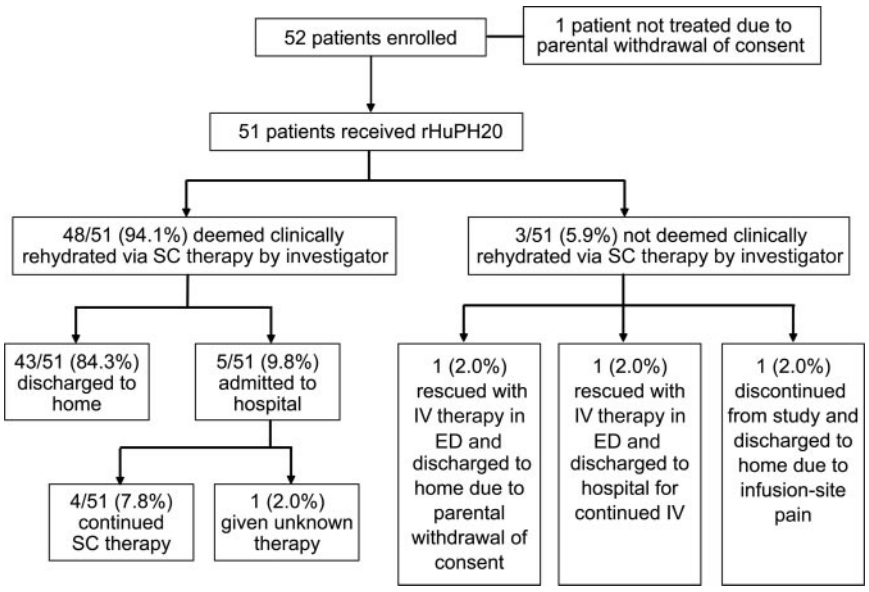

FIGURE 2
Patient disposition. ED, emergency department; IV, intravenous; SC, subcutaneous.

TABLE 3 End Points of Subcutaneous Infusions

	1 h	Day 1	Day 2	Total Day 1 + Day 2
Fluid volume received, mL				
N	51	51	3	3
Mean ± SD	182.9 ± 91.2	417.9 ± 295.0	540.3 ± 338.1	1736.7 ± 560.9
Median	184.0	362.0	578.0	1938.0
Range	20.0–568.0	20.0–1360.0	185.0–858.0	1103.0–2169.2
Duration of subcutaneous hydration, h				
N		49	3	3
Mean ± SD		4.9 ± 6.1	13.9 ± 8.2	36.4 ± 10.1
Median		2.6	14.4	38.4
Range		0.2–24.0	5.5–21.9	25.5–45.3
Fluid volume received per body weight, mL/kg				
N	51	51	3	3
Mean ± SD	16.7 ± 4.7	40.4 ± 29.8	54.8 ± 29.7	181.3 ± 36.7
Median	19.0	32.1	58.4	195.8
Range	1.4–25.6	1.4–137.4	23.4–82.5	139.6–208.6
Flow rate, mL/kg per h				
N	49	49	3	3
Mean ± SD	17.4 ± 3.9	12.8 ± 5.2	4.0 ± 0.2	5.1 ± 0.4
Median	18.9	12.9	4.1	5.1
Range	5.0–26.1	5.0–22.4	3.8–4.3	4.6–5.5

The baseline number of dehydration symptoms was 3.5 ± 1.2, which decreased to 0.5 ± 0.9 at the end of hydration. Of the 11 patients who had 1 or 2 symptoms at baseline, 10 (91%) had no symptoms at the end of treatment. Of the 40 patients who had 3 to 6 symptoms at baseline, 34 (85%) had no or 1 symptom at the end of treatment.

The mean percentage body weight change from the start of infusion to ED discharge was +2.4 ± 5.0% (range: −3.5% to 30.8%). The median time from the start of infusion to the first urine output was 1.7 hours, and the median time to ED discharge to home or hospital was 3.4 hours (median time to discharge to home: 3.3 hours). No patient was readmitted for retreatment of dehydration during the 7-day follow-up period.

Safety and Tolerability

Infusion Site Pain and Reactions

After catheter insertion but before rHuPH20 injection on day 1, no patient had infusion site tenderness, erythema, pruritus, swelling, ecchymosis, or rash; however, 4 had infusion site pain. Tables 4 and 5 sum-

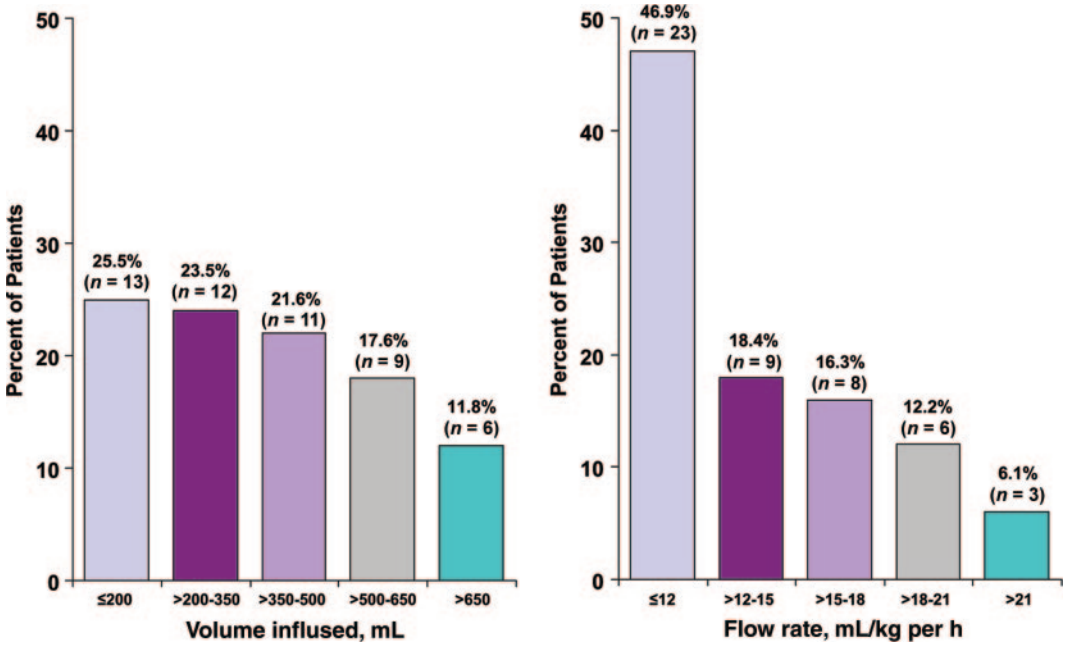

FIGURE 3
Frequency distributions of subcutaneously administered fluid volume (left) and flow rate (right) on day 1 of treatment.

TABLE 4 Numbers of Patients With Infusion Site Reactions on Day 1 ($N = 51$)

	n							
	Score Recorded After rHuPH20 Injection But Before Fluid Infusion				Maximal Score Recorded After Start of Fluid Infusion			
	0	1	2	3	0	1	2	3
Swelling	17	22	8	4	0	12	10	29
Erythema	19	23	5	4	16	24	10	1
Tenderness	29	10	11	1	34	14	3	0
Ecchymosis	50	1	0	0	49	2	0	0
Rash	49	2	0	0	50	1	0	0
Pruritus	51	0	0	0	51	0	0	0

Scores were as follows: tenderness and pruritus: 0 = none, 1 = minimal, 2 = some, 3 = a lot; swelling, erythema, ecchymosis, and papular rash (largest diameter): 0 = none, 1 = <2.5 cm, 2 = 2.5 to <5 cm, 3 = ≥5 cm.

marize day 1 infusion site reactions and pain.

Systemic AEs

Systemic AEs occurred in 9 patients. For 2 patients (1 with mild vomiting and 1 with mild otitis media), the AEs occurred before their discharge to home. For the remaining 7 patients, AEs reported on day 3 or day 7 were mild vomiting ($n = 1$); mild pyrexia and bronchopneumonia ($n = 1$); mild pyrexia and mild generalized rash ($n = 1$); mild abdominal distention ($n = 1$); mild nasopharyngitis ($n = 1$); moderate influenza and moderate ear infection ($n = 1$); mild antibiotic sensitivity (facial edema and hives); and cellulitis ($n = 1$). No systemic AEs were deemed to be related to rHuPH20 or infusion fluid.

Cellulitis, a serious AE, occurred in a 3-year-old girl with a history of Angelman syndrome and recurrent sinopulmonary infections. Her dehydration was treated with subcutaneous administration of rHuPH20 and fluids in the upper back for 45.3 hours. At discharge, the subcutaneous site appeared normal; however, 20 hours af-

TABLE 5 Numbers of Patients With Infusion Site Pain on Day 1

	n																					
	Objective Pain Rating Scale (Children <3 y of Age) ($N = 40$)												FACES Pain Rating Scale (Children 3–10 y of Age) ($N = 6$)											
	Score Recorded After rHuPH20 Injection But Before Fluid Infusion						Maximal Score Recorded After Start of Fluid Infusion						Score Recorded After rHuPH20 Injection But Before Fluid Infusion						Maximal Score Recorded After Start of Fluid Infusion					
	0	1–2	3–4	5–6	7–8	9–10	0	1–2	3–4	5–6	7–8	9–10	0	1	2	3	4	5	0	1	2	3	4	5
	4	6	9	10	7	4	28	7	4	1	0	0	2	3	0	1	0	0	3	1	1	1	0	0

Five patients are excluded from the analysis because the wrong pain scale was used (the FACES scale for 3 patients who were <3 years of age or the Objective Pain Rating Scale for 2 patients who were 3–10 years of age). The Objective Pain Rating Scale is as follows: 0 (none), 1, or 2 (worst) in face, legs, activity, cry, and consolability; score sums range from 0 to 10. The FACES Pain Scale is as follows: 0 = no hurt, 1 = hurts a little bit, 2 = hurts a little more, 3 = hurts even more, 4 = hurts a whole lot, 5 = hurts worst.

ter catheter removal, the subject developed infusion site cellulitis, was admitted, and was given intravenous antibiotic therapy. The cellulitis resolved within 4 days, but the patient remained hospitalized for another 4 days with suspected pneumonia. The cellulitis was not considered related to rHuPH20 or infusion fluid but possibly was related to the subcutaneous needle placement procedure.

Ease of Use

The median time from initial catheter placement to initiation of subcutaneous fluid infusion was 2 minutes (range: 0–15 minutes). Fluid infusion began within 5 minutes after insertion for 88% of patients (45 of 51 patients). Initial subcutaneous access was achieved and the catheter secured with 1 attempt for 46 patients (90.2%) and with 2 attempts for 5 patients (9.8%). For 2 of the patients who required 2 attempts, access was achieved on the first attempt but a second insertion was needed because the child pulled the catheter out or moved excessively before the catheter was secured. Ten children underwent failed intravenous insertion attempts before enrollment (1–4 attempts for 6 children and 5–9 attempts for 4 children).

No subcutaneous infusion site was changed during rehydration. Infusion site reactions required flow rate reductions and/or interruptions for 6 patients, 1 of whom withdrew because of infusion site pain (as noted above). Table 6 summarizes flow rate changes.

Investigators rated the procedure as easy to perform in 49 (96%) of 51 cases. Side effects were considered unacceptable in 4 (8%) of 51 cases, but all were mild and resolved. Compared with previous experience with intravenous hydration, investigators rated the subcutaneous procedure as equally or more effective in 45 (92%) of 49 cases and as less effective in 4 (8%) of 49 cases. They found subcutaneous therapy less difficult than intravenous therapy in 45 (90%) of 50 cases and equally or more difficult in 5 (10%) of 50 cases.

TABLE 6 Adjustments in Infusion Flow Rate

	n (%)	
	Adjustment in First Hour ($N = 51$)	Adjustment at Any Time in Day 1 ($N = 51$)
Patients with ≥1 flow rate increase	12 (23.5)	18 (35.3)
Administrative reasons[a]	8 (15.7)	9 (17.6)
Maintenance	0 (0.0)	2 (3.9)
Other	9 (17.6)	12 (23.5)
Pump beeping	1 (2.0)	1 (2.0)
Patients with ≥1 flow rate decrease	18 (35.3)	30 (58.8)
Administrative reasons[a]	3 (5.9)	5 (9.8)
Catheter kinking	1 (2.0)	1 (2.0)
Maintenance	8 (15.7)	17 (33.0)
Other	1 (2.0)	4 (7.8)
Pump beeping	2 (3.9)	2 (3.9)
Infusion site symptoms	3 (5.9)	5 (9.8)
Patients with ≥1 flow rate interruption	8 (15.7)	12 (23.5)
Catheter kinking	1 (2.0)	1 (2.0)
Other	1 (2.0)	2 (3.9)
Pump beeping	3 (5.9)	3 (5.9)
Infusion site observation	1 (2.0)	3 (5.9)
Infusion site symptoms	2 (3.9)	3 (5.9)

Patients might have had >1 adjustment within a category; therefore, the number of patients listed can exceed the total number of patients in that category. Proportions were calculated by using the total number of patients as the denominator.
[a] In nearly all cases, administrative reasons referred to waiting for the physician's reassessment or adjusting the flow rate toward the 20 mL/kg target.

In 43 (90%) of 48 cases, parents were satisfied or very satisfied with the procedure; parents were dissatisfied in 4 cases and very dissatisfied in 1 case. Ninety-four percent (45 of 48 parents) thought the procedure was successful. Forty-two (88%) of 48 parents said that they would choose subcutaneous therapy if they or their child required rehydration therapy in the future. Thirty-four parents said that they or their child had received intravenous fluids previously, and they responded to a question comparing the 2 routes; of those parents, 31 (91%) said that subcutaneous hydration was the same as or better than intravenous hydration.

DISCUSSION

In this pilot study, rHuPH20-facilitated subcutaneous fluid administration treated dehydrated infants and children safely and effectively. Clinical response was usually prompt; the median time from the start of infusion to the first urine output was 1.7 hours, and the median time to ED discharge to home was 3.3 hours. The median flow rate in the first hour was 18.9 mL/kg per hour, which is comparable to recommendations of the American Academy of Pediatrics, the World Health Organization, and the Centers for Disease Control and Prevention (20 mL/kg in the first hour) for parenteral fluid administration for management of dehydration in children.[4,40,41] Although the study protocol stipulated 20 mL/kg in the first hour, some investigators preferred to start the infusion more slowly, with gradual increases over the first few minutes.

All children experienced infusion site reactions, but these reactions did not require site changes. Flow rate reductions and/or interruptions were attributed to infusion site reactions for 6 patients. The severity of infusion site pain varied widely, but most scores de-

creased to low to mid-range values during fluid infusion. Although nearly all patients experienced pain immediately after rHuPH20 injection, two thirds (31 of 46 patients) were free of pain during fluid infusion. Systemic AEs occurred in 9 patients but were not attributed to fluid therapy or rHuPH20. Most investigators found the subcutaneous procedure easy to perform, with subcutaneous access being established in 1 attempt in most cases.

Literature supports the use of subcutaneous fluid administration for the management of mild/moderate dehydration,[15,19,29,42] with some studies noting severe dehydration as a contraindication to this route of administration.[42,43] This pilot study is the only recent trial evaluating subcutaneous fluid administration in children and, consistent with current usage in adults, patients presenting with more-severe dehydration were excluded.

Our outcomes are similar to those reported previously for intravenous therapy and ORT. In a study comparing intravenous therapy and ORT for 73 moderately dehydrated children, 8 weeks to 3 years of age, who were treated in the ED,[5] mean fluid volumes administered within 4 hours were similar for intravenous therapy (40.0 mL/kg) and ORT (36.3 mL/kg), as well as for subcutaneous therapy in our study (38.4 mL/kg). The rates of urine production within 4 hours also were similar (86% for intravenous therapy, 88% for ORT, and 85% for subcutaneous therapy). One half of the patients treated with intravenous therapy and one third of the patients treated with ORT were admitted to the hospital, compared with 12% in our study. In the present study, 88% of parents said that they would choose subcutaneous hydration again for their children or themselves; in the previous study, only 61% of parents of children who received ORT and 51% of parents of children who received intravenous therapy said that they would choose that modality again for their children.[5]

The rate of AEs associated with subcutaneous fluid administration has not been compared with that for intravenous therapy in this study or other clinical trials with pediatric populations; however, the safety of subcutaneous fluid administration, compared with that of intravenous therapy, in adults suggests that the complication rate in this study is lower than that expected with intravenous therapy. For example, in one study with adults in long-term care,[8] fewer total complications per day were reported with subcutaneous therapy (0.07 $\pm$ 0.16 complications per day) than with intravenous therapy (0.21 $\pm$ 0.25 complications per day; $P = .04$) and, among those, there were fewer local reactions around the catheter site (swelling, redness, or obstruction) with subcutaneous therapy (0.05 $\pm$ 0.10 reactions per day) than with intravenous therapy (0.2 $\pm$ 0.25 reactions per day; $P = .02$). Similarly, in this study, although mild/moderate local AEs were commonly reported, only 1 (0.2%) of 51 patients experienced a systemic complication (cellulitis) attributed to the subcutaneous infusion.

STUDY LIMITATIONS

This pilot study was designed to explore the safety and efficacy of rHuPH20-facilitated fluid administration in children. Efficacy and safety conclusions drawn from this study are limited by the small number of patients and the lack of a control arm. A larger sample size and comparison of rHuPH20-facilitated subcutaneous fluid administration with other routes of ED treatment for children with mild/moderate dehydration in ongoing studies should enable further determination of the usefulness of this method for this indication.

The volume of oral fluid intake during rHuPH20-facilitated subcutaneous hydration was not monitored during this study. In future studies, ORT volumes administered during subcutaneous hydration should be recorded, as objective measures of the extent to which successful hydration is attributable to rHuPH20-facilitated subcutaneous fluid administration.

CONCLUSIONS

In this study, rHuPH20-facilitated subcutaneous infusion of isotonic fluid seemed to be safe and effective for infants and children with mild/moderate dehydration. Subcutaneous access was obtained easily and dehydration was corrected rapidly in most cases. The procedure was well accepted by parents and clinicians.

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