Subcutaneous Hydration in Children Using Recombinant Human Hyaluronidase: Safety and Ease of Use

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Introduction

- Dehydrated children often need emergency parenteral fluids and electrolytes, but starting their intravenous (IV) lines can be challenging and time-consuming, especially if they are agitated or have difficult venous access (DVA) due to small, delicate, or collapsed veins
- Multiple IV insertion attempts are painful and upsetting to children, and distressing to parents and clinicians. They also delay treatment and may raise the risk of complications
- rHuPH20 150 U/mL (***hylenex***; Baxter International Inc., Deerfield, IL) is FDA-approved for use with SC hydration in both children and adults
- When injected SC, rHuPH20 enzymatically depolymerizes hyaluronan, temporarily increasing connective tissue permeability and enhancing the dispersion and absorption of SC fluids[1,2]
- Tissue permeability returns to baseline within 24 to 48 hours as hyaluronan is regenerated[1,2]
- In healthy adults, co-administration of rHuPH20 increases mean SC fluid flow rate fourfold over SC fluids alone, with good safety and tolerability[3]
- In palliative care patients, rHuPH20 permits flow rates of up to 500 mL/hr, without difficulty or significant adverse events (AEs), even after successive days of use[4]
- Administration of SC fluids is straightforward and does not require advanced nursing skills; lines can be inserted quickly and maintained in relatively insensitive areas of the body, with no need to immobilize a limb
- The SC technique may be particularly useful in infants and children because they are already anxious and fearful when they arrive at the Emergency Department (ED)

Study Objective

- The objective of this study was to explore the utility, safety, and effectiveness of an alternate route of fluid administration in children: subcutaneous (SC) hydration enhanced with the enzymatic spreading agent recombinant human hyaluronidase (rHuPH20)

Methods

- The Increased Flow Utilizing Subcutaneously Enabled (INFUSE) Pediatric Rehydration Study was a multicenter, Phase IV, single-arm study conducted in the EDs of 9 United States hospitals from August 2007 to June 2008

SUBJECTS

- Main inclusion criteria
  - Age: 2 months to 10 years and weight: <42 kg
  - Diagnosis of mild or moderate dehydration in the ED based on the presence of 1 to 6 signs and symptoms (Table 1)
  - Need for parenteral fluids because oral rehydration therapy (ORT) was either not appropriate or had failed, and/or attempts to place an IV line had failed

Table 1. Signs and Symptoms of Dehydration

1.	General condition (lethargy; drowsiness; postural dizziness; cold, cyanotic extremities; muscle cramps; coma)
2.	Weak radial pulse
3.	Deep or rapid respiration
4.	Diminished skin elasticity
5.	Sunken eyes
6.	Absence of tears
7.	Dry mucous membranes
8.	Little or no urine output
9.	Heart rate >150 bpm
10.	Capillary refill time at fingertip >2 sec

Adapted from Gorelick 1997.[5]

- Main exclusion criteria
  - Severe dehydration, shock, or other life-threatening situation
  - IV or substantial oral fluids received immediately prior to enrollment
  - Known hyponatremia (serum sodium <130 mEq/L) or hypernatremia (serum sodium >155 mEq/L)
  - Known hypokalemia (serum potassium <3.0 mEq/L)
  - Known hypersensitivity to hyaluronidase or a condition precluding SC injection

METHODS

- rHuPH20 and subsequent fluids (lactated Ringer's or normal saline solution) were delivered through a 24-gauge angiocatheter placed SC into the anterior thigh or upper mid-back (interscapular area)
  - 1 mL rHuPH20 (150 U) was injected SC by push, followed by continuous pump-assisted SC infusion of 20 mL/kg of isotonic fluid over the first hour
  - Pump-assisted SC hydration was then continued as needed for up to 72 hours after initial infusion, until patient was discharged to home or alternative treatment was started
  - If therapy was continued longer than 1 day, rHuPH20 injections were repeated every 24 hours up to a maximum of 3 injections
  - If the injection site swelled or any other reaction occurred that the investigator deemed unacceptable, the infusion flow rate could be decreased or infusion site moved
- Hydration was deemed successful if:
  - The investigator attributed it primarily to rHuPH20-augmented SC fluid infusion and
  - The patient was discharged to home without needing alternative rehydration therapy (IV catheter, nasogastric tube, intraosseous infusion, or renewed attempt at ORT)
- Safety and tolerability were assessed at regular intervals throughout the rehydration period until ED discharge and by telephone on Days 3 and 7 after discharge
- Infusion site tenderness, pruritus, rash, swelling, erythema, and ecchymosis were graded on scales ranging from 0 to 3
  - Immediately before first dose of rHuPH20
  - Immediately after rHuPH20 injection but prior to fluid infusion
  - At 1 h, 2 h, 3 h, 4 h, and 24 h
  - At end of hydration treatment
- Infusion site pain was graded at the same time points using a self-rated scale ranging from 0 to 5 for children ≥3 years of age,[6] and an investigator-rated scale ranging from 0 to 10 for children <3 years of age[7]
- Assessments were repeated after each subsequent dose of rHuPH20, if administered
- Ease of use and parent/investigator satisfaction with the SC procedure were assessed at the end of treatment
- Descriptive statistics were provided for all data; no hypothesis testing was done

Results

SUBJECTS

- 52 patients were enrolled, of whom 51 received treatment and were evaluated for effectiveness (the remaining patient was not treated because the parent withdrew consent prior to initiation of therapy). Demographics and baseline characteristics are summarized in Table 2
- The initial infusion site was the thigh for 15 children and the midline interscapular area for 36 children

Table 2. Demographics and Baseline Characteristics (N=51)

Characteristic	Value
Age (yr)	
Mean ± SD	1.9 ± 1.9
Range	0.3–9.8
Number (%) of children under 3 years	43 (84%)
Gender, n (%)	
Male	29 (57%)
Female	22 (43%)
Weight (kg)	
Mean ± SD	11.2 ± 5.4
Range	5.1–31.4
Number of signs/symptoms of dehydration, n (%)	
1	2 (4%)
2 (Mild)	9 (18%)
3	15 (29%)
4 (Moderate)	13 (25%)
5 (Moderate)	11 (22%)
6 (Moderate)	1 (2%)
Mean ± SD	3.5 ± 1.2
Race, n (%)	
White	31 (61%)
Black or African American	9 (18%)
Other	7 (14%)
Asian	3 (6%)
American Indian or Alaska Native	1 (2%)
Ethnicity, n (%)	
Not Hispanic or Latino	42 (82%)
Hispanic or Latino	9 (18%)
Diagnosis Underlying Dehydration, n (%)	
Gastroenteritis	36 (71%)
Other	15 (29%)

Abbreviation: SD=standard deviation.

EFFECTIVENESS

- 43/51 (84.3%) children were successfully rehydrated via SC therapy
- An additional 5 patients (9.8%) were admitted to the hospital for continued support, and were later deemed to be clinically rehydrated (4 of them continued to receive SC therapy as inpatients). In total, 48/51 (94.1%) patients were rehydrated primarily by SC therapy
- 3 patients (5.9%) were not rehydrated SC: 1 discontinued treatment after 9 min due to infusion site pain, 1 discontinued due to parental withdrawal of consent, and 1 was switched to IV fluids and admitted to the hospital
- On Day 1 of therapy, the patients received an average of 417.9 mL of fluid (range, 20–1360 mL) over a median infusion period of 2.6 hours (range, 0.2–24.0 hr). The median flow rate in the first hour of treatment was 18.9 mL/kg/hr (range, 5.0–26.1 mL/kg/hr)
- No child was readmitted for retreatment of dehydration during the 7-day follow-up period

SAFETY AND TOLERABILITY

Local Reactions

- After catheter placement but prior to rHuPH20 injection on Day 1, no patient had infusion site tenderness, erythema, pruritus, swelling, ecchymosis or rash, but 4 patients had infusion site pain
- Tables 3 and 4 summarize the incidence and severity of infusion site reactions and pain on Day 1, immediately after rHuPH20 injection but prior to the start of fluid infusion, and the maximum scores after the start of infusion
- All patients had typical infusion site reactions, but no patient needed a site change
- No patient experienced pruritus at the infusion site
- Pain was reported in 40/46 (87.0%) patients immediately after rHuPH20 injection and prior to the start of fluid infusion, with scores ranging from the lowest to the highest end of the scales
- 15/46 (32.6%) patients experienced pain during fluid infusion on Day 1, with the maximum scores being in the low to mid-range

Table 3. Number of Patients with Infusion Site Reactions on Day 1

	Score Recorded After rHuPH20 Injection but Prior to Fluid Infusion				Maximum Score Recorded After Start of Fluid Infusion			
	0	1	2	3	0	1	2	3
Number of Patients (N=51)								
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

Tenderness and pruritus were scored as: 0=none, 1=minimal, 2=some, and 3=a lot.
For 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, and 3=≥5 cm.

Table 4. Number of Patients with Infusion Site Pain on Day 1

Score Recorded After rHuPH20 Injection but Prior to Fluid Infusion							Maximum Score Recorded After Start of Fluid Infusion						
Objective Pain Rating Scale (children <3 yrs)													
0	1-2	3-4	5-6	7-8	9-10		0	1-2	3-4	5-6	7-8	9-10	
Number of Patients (n=40)													
4	6	9	10	7	4		28	7	4	1	0	0	
FACES Pain Rating Scale (children 3–10 yrs)													
0	1	2	3	4	5		0	1	2	3	4	5	
Number of Patients (n=6)													
2	3	0	1	0	0		3	1	1	1	0	0	

Five patients were excluded from the analysis because the wrong pain scale was used (the FACES Scale for 3 patients who were <3 years old and the Objective Pain Rating Scale for 2 patients who were 3–10 years old). Objective Pain Rating Scale: 0 (best), 1, and 2 (worst) in face, legs, activity, cry, and consolability → sum score range [0, 10].
FACES Pain Scale: 0=no hurt, 1=hurts little bit, 2=hurts little more, 3=hurts even more, 4=hurts whole lot, and 5=hurts worst.

- Figure 1 shows an infusion site before and during fluid administration
- Infusion site reactions prompted flow rate reductions and/or flow interruptions in 6 patients. One of these 6 patients withdrew from the study due to infusion site pain (as noted above)

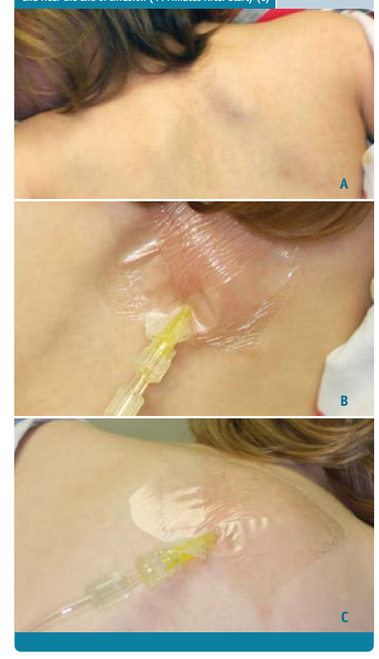
Systemic Adverse Events

- Systemic AEs occurred in 9 patients: they included mild vomiting (n=2), mild otitis media (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 (manifested as facial edema and hives), and cellulitis (n=1)
- None were considered to be related to rHuPH20 or infusion fluid

Serious Adverse Event

- A 3-year-old girl presented with febrile illness and a history of Angelman's syndrome and recurrent sinopulmonary infections
- Her dehydration was treated with SC rHuPH20 150 U and SC fluids in the upper back for 45.3 hours
- At discharge, the SC site appeared normal with no irritation but 20 hours after the catheter had been removed, the patient developed cellulitis at the infusion site and was readmitted to the hospital
- Treatment with antibiotics was successful, and the patient was discharged 8 days after admission (cellulitis resolved within 4 days)
- Event was considered unrelated to rHuPH20 or infusion fluid, but may have been related to SC needle placement procedure

Figure 1. Representative Interscapular Infusion Site Before Infusion (A), 4 Minutes After Starting Infusion (B), and Near the End of Infusion (44 Minutes After Start) (C)

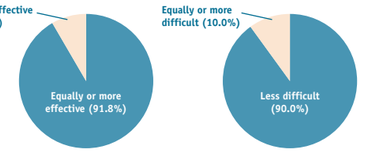


Ease of Use

- The median time from initial catheter placement to the start of SC fluid infusion was 2 min (range 0–15 min)
- Fluid infusion began within 5 minutes of insertion for 88.2% (45/51) of the patients
- SC access was achieved and the catheter was secured in place with 1 attempt in 44 patients (86.2%), 2 attempts in 6 patients (11.8%), and 3 attempts in 1 patient (2.0%)
  - In some of the cases requiring multiple attempts, the catheter was successfully inserted on the first try but was then dislodged or pulled out
- Multiple IV insertion failures occurred in the 10 children who underwent attempted IV hydration prior to study enrollment
- Investigators rated the procedure as easy to perform in 49/51 (96.1%) cases and reported unacceptable side effects in 4/51 (7.8%) cases
- Compared to prior experience with IV therapy, investigators rated SC therapy as equally or more effective in 45/49 (91.8%) cases, and as less effective in 4/49 (8.2%) cases (Figure 2)
- Investigators found SC therapy less difficult than IV therapy in 45/50 (90.0%) cases, and equally or more difficult than IV therapy in 5/50 (10.0%) cases (Figure 2)

Figure 2. Investigator Ratings of Effectiveness and Ease of Use of SC Therapy

Compared to investigators' prior experience with IV therapy, SC therapy was:



Parent Satisfaction

- In 43/48 (89.6%) cases, parents were satisfied or very satisfied with SC hydration
- Parents were dissatisfied in 4/48 (8.3%) cases, and very dissatisfied in 1 (2.0%) case
- 45/48 (93.8%) parents felt the procedure was successful
- If they or their child ever needed rehydration therapy in the future, 42/48 (87.5%) said they would opt for SC hydration again
- 34 parents said they or their child had previously had IV fluids and answered a question comparing the two routes. Of these, 31 (91.2%) said the SC hydration experience was the same or better

Conclusions

- rHuPH20-augmented SC hydration with isotonic fluids appears to be safe and effective in appropriately selected children with mild or moderate dehydration
- Fluid volumes can be administered in a clinically relevant timeframe
- SC access can usually be achieved on the first attempt
- The procedure is rated as easy to perform and well accepted by parents and physicians

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