

Richard A. Brodsky, MD
Combined EM Journal Club
EVMS (EM) & CHKD (Peds Fellowship)
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- P – In pediatric patients with significant dehydration who are resistant/incapable of hydration via PO route
- I – Can rehydration via the subcutaneous route
- C – Compared to IV infusion
- O – Have similar or improved efficacy, safety, and tolerance of the hydration process

Clinical scenario:

JT is an 18 month old male child whose mother reports significant diarrhea and vomiting for the last 5 days. The episodes started shortly after restarting daycare where a teacher reports several other children have a similar illness. Initially, JT only vomited a few times a day and was still able to tolerate PO. For the last 2 days he has vomited with every attempt at feeding Pedialyte but still manages to have 7-10 diarrhea diapers a day. The mother is unsure of how much JT is urinating because the diapers are always wet. Today she notes that he is significantly less active and does not even want to try to drink. She thinks he is breathing more rapidly and says his skin is very dry.

T – 37.6, HR – 150, BP – 95/60, RR – 30, SaO₂ 100% on RA
Gen: Significantly decreased activity level, but arouses to stimulation.
HEENT: Dry, cracked lips and mucous membranes. Sunken eyes. TM normal B/L.
CV: RRR, no m/r/g. Cap refill 3-4 seconds.

The patient was given ondansetron at appropriate dosing and PO trial is attempted unsuccessfully. The patient refuses all attempts at PO. You instruct your nurses to attempt to place an IV for a bolus of fluids. They come back to you after an hour saying: “We cannot get an IV, the patient's veins are too collapsed.” The family is insisting that the patient has been “stuck too much” and they do not want further IV attempts.

Is Subcutaneous Hydration a safe and efficacious treatment for this patient?

What is Hylanex? (Hyaluronidase)

“Hyaluronidase is a spreading or diffusing enzyme that increases the permeability of connective tissue through the hydrolysis of hyaluronan (hyaluronic acid), a polysaccharide found in the intercellular matrix of connective tissue. Hyaluronan acts as a barrier to drug and fluid dispersion. Hyaluronidase hydrolyzes hyaluronan by splitting the glucosaminidic bond between C₁ of an N-acetylglucosamine moiety and C₄ of a glucuronic acid moiety. The hydrolysis of hyaluronan temporarily decreases the viscosity of the intercellular matrix and promotes diffusion of injected fluids or of localized transudates or exudates.¹

Hyaluronidase increases dispersion in the interstitial matrix provided local pressure is adequate to furnish the necessary mechanical impulse. Such impulse is normally initiated by injected solutions. The rate of diffusion is proportionate to the amount of enzyme. The extent of diffusion is proportionate to the volume of solution.¹ At 24 hours, the restoration of the hyaluronan barrier is incomplete and inversely related to the dosage of the enzyme. At 48 hours, the barrier is completely restored.¹

¹*hylanex* recombinant (hyaluronidase human injection) [Prescribing Information]. Deerfield, IL: Baxter Healthcare Corporation.”

Summary: Hyaluronic acid exists in our skin as part of a matrix that gives it density and acts as a diffusion barrier. This medicine temporarily dissolves that substance to allow for the infusion of fluid and medicine into the Sub Q tissues without difficulty.

Article	Patient Group	Study Type	Key Results	Conclusions	Weakness
Kuensting LL. <i>Treatment of intravenous infiltration in a neonate.</i> Journal of Pediatric Health Care. 24(3):184-8, 2010 May-Jun.	A single 4 day old infant admitted to PICU and had extravasation of IV fluids with significant swelling and possible need for Plastic Surgery involvement	Case Report	1 ml of recombinant hyaluronidase was placed Sub-Q in the area. Within 5 minutes, the swelling had reduced significantly and within 24 hours resolved.	No firm conclusion can be drawn other than proof of concept. The author does an excellent job of discussing current research and direction of use of recombinant hylauronidase.	Case report (n=1)

<p>Thomas JR, et al. <i>Assessing the Role of Human Recombinant Hyaluronidase in Gravity-Driven Subcutaneous Hydration: The INFUSE-LR Study.</i> Journal of Palliative Medicine. 2007; 10(6).</p>	<p>n = 54 healthy volunteers split into 2 stages - Stage 1 (n=5) for pilot data - Stage 2 had 3 cohorts for dosing of recombinant hyaluronidase</p>	<p>Randomized, Double Blind, Placebo Controlled,</p>	<p>Significantly increased flow rates in all cohorts compared with placebo. 383ml/hr +/- 119 vs 82ml/hr +/- 30 in 150U cohort Reduction in pain scores with SQ (p<0.002) No clinically significant adverse event occurrences between placebo and SQ groups.</p>	<p>In adults, Hylenex increases permeability of SQ infusions to allow a less painful and relatively safe method of LR delivery. This may not be exclusive to LR</p>	<p>Healthy volunteers Non-pediatric population Studied LR , which is not what would be given in peds dehydration</p>
<p>Remington R, Hultman,T <i>Hypodermoclysis to Treat Dehydration: A Review of the Evidence.</i> JAGS, 2007; 55. pg 2051-2055</p>	<p>Elderly patients (mean ages ranging 71-85) requiring hydration via parenteral/sub Q route 4 studies: residents of long-term care facilities. 2 studies: acute geriatric units, 1 was in a hospice.</p>	<p>Review article comprised of: two randomized, controlled trials, and six cohort studies</p>	<p>See Attached</p>	<p>In the elderly population, HDC is appeared to be safe alternative that is equally efficacious when compared with IV therapy.</p>	<p>-Significant Variation between the study settings and populations. (acute, chronic, and terminally ill patients) -Several reports were of “non-inferiority” results. -Some conclusions were low powered -Most were not blinded</p>

<p>Allen. et. al. <i>Recombinant Human Hyaluronidase-Enabled Subcutaneous Pediatric Rehydration.</i> Pediatrics 2009;124:e858-e867</p>	<p>n = 51 2 mo – 10yrs <42 kg</p> <p>1-6 symptoms of dehydration (Severe dehydration and shock excluded)</p> <p>Clinical failure of PO or decision that parenteral necessary</p>	<p>Phase IV, Multicenter - 9 hospitals/ INFUSE [INcreased Flow Utilizing Subcutaneously Enabled pediatric rehydration] study research group, Single arm, non-RCT</p>	<p>48/51 patients determined to be successfully hydrated by clinician/investigator</p> <p>4 reported infusion site pain.</p> <p>0 adverse events attributed to the use of hyaluronidase (though, some related to sub Q injection)</p> <p>Ease of catheter placement noted.</p>	<p>Initial Pilot study demonstrates that Hylenex was safe and in this age population. However, non randomized control trial, superiority or inferiority to IVF cannot be determined.</p>	<p>Not controlled / single arm study. Investigator Bias Small number of patients ORT therapy not monitored Subjective assessment criteria by investigators. Industry sponsored.</p>
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<p><i>(Abstract)</i> Hahn B, Mace SE, Maher G, Harb G. <i>Recombinant Human Hyaluronidase-Facilitated Subcutaneous vs Intravenous Hydration Therapy in Infants and Children.</i> Annals of Emergency Medicine, September 2009, 54(3)</p>	<p>1 mo - <3yrs n = 41 (to date) Mild to moderate dehydration</p>	<p>(Abstract) Ongoing, Phase 4, randomized controlled, prospective clinical trial</p>	<p>1° - mean total volume infused at a single site, was 329.4 mL for SC vs 560.2 mL for IV. The mean total volumes, adjusted for duration of infusion, were 466mL for SC and 429 mL for IV. 2° – Initial data shows trends toward ease of management, time to urination and % of patients rehydrated.</p>	<p>Preliminary results reveal that rHuPH20-facilitated SC infusions were safe and resulted in a higher percentage of patients who were successfully hydrated compared with IV. Duration-adjusted mean volume of fluids infused was comparable for both routes of administration. Non-inferiority study currently. Needs more power.</p>	<p>Very small study, not enough power yet for definitive conclusions Ongoing No data is significant as of yet.</p>

CONCLUSION:

Limited studies, most data were in elderly and hospice patients demonstrated evidence of efficacy and low complication rates. Subcutaneous rehydration may be a feasible alternative in pediatric patients when IV therapy is unavailable and oral rehydration has failed. Trends in certain studies show that it appears to be safe and effective in adults, but this cannot be extrapolated to children yet. The INFUSE (Increased Flow Utilizing Subcutaneous Enabled) pediatric rehydration and INFUSE II studies show promising leads, but larger clinical trials are required before conclusions can be drawn.