A SYSTEMATIC REVIEW OF HYALURONIDASE-ASSISTED SUBCUTANEOUS FLUID ADMINISTRATION IN PEDIATRICS AND GERIATRICS AND ITS POTENTIAL APPLICATION IN LOW RESOURCE SETTINGS

A thesis submitted to the University of Arizona College of Medicine – Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Kelsey Wilhelm
Class of 2017

Mentor: Dawn Barcellona, MD
ABSTRACT

**Title:** A Systematic Review of Hyaluronidase-Assisted Subcutaneous Fluid Administration in Pediatrics and Geriatrics and Its Potential Application in Low Resource Settings.

**Background:**
The role of enzyme-assisted subcutaneous fluid administration (EASFA) in treating mild to moderate dehydration in pediatrics, geriatrics, and palliative care has been studied in developed countries. However, it has historically been underutilized due to widely available health care and alternative treatments, namely peripheral intravenous (IV) fluid administration. Fluid infusions in the subcutaneous tissue have a low risk of infection, are easy to administer, and have wide potential use. The use of EASFA in low resource settings to treat those with difficult IV access or where skilled healthcare workers are not as readily available could prove to be a live saving measure in many situations, including the care of patients in remote areas of the world, mass casualty events, or other disasters.

**Objective:**
Our objective was to determine if EASFA is a valid and appropriate technique to utilize in pediatric and elderly patients, and evaluate if it could be a safe and efficient way to provide fluid resuscitation in low resource settings.

**Study Design:**
For this systematic review MEDLINE and Cochrane Library were searched from January 1950 to December 2015 to recover all available literature relevant to this topic. Studies that met the inclusion criteria were analyzed using Cohen’s D. This was calculated using the mean difference between intervention and control divided by the pooled standard deviation. For dichotomous outcome of the placement success rate the odds ratios were calculated with 95% confidence intervals.

**Results:**
In reviewing 7 articles using Cohen’s D to compare mean differences to determine effect size, we found that catheter placement success rates and infusion rates were similar between EASFA and peripheral intravenous fluid administration. Additionally, it was found that the odds of
correct initial needle placement was 7.19 times higher in EASFA versus intravenous administration.

**Conclusion:**

EASFA is a comparable alternative to intravenous fluid administration when delivering fluids to pediatric and elderly patients with mild to moderate dehydration. While infusion rates and total volume of fluids administered were similar, the high rate of success with placement of the subcutaneous catheter proves it to be more useful in some situations. Venous cannulation is difficult, even for a trained healthcare provider, and the ease of placement of subcutaneous catheters makes training lay people to administer subcutaneous fluids a possibility. Additionally, this type of fluid administration may lead to less psychological trauma to a child from multiple needle sticks, while still achieving a similar outcome of effective volume replacement. Based on the results of this study, further research is needed to evaluate the effectiveness of utilizing EASFA in low resource settings.
# Table of Contents

*Chapter 1 Systematic Review*

- Introduction                                            1
- Methods                                                5
- Results                                                7
- Discussion                                             15
- Conclusions and Implications for further Research       16
- References                                             18

*Chapter 2 Comprehensive Review*

- Introduction, Rationale, Background                     22
- Discussion                                             26
- Summary                                                32
- Future Innovation                                      32
- References                                             34
List of Tables and Figures

Table 1: Included Studies

Figure 1: Infusion Rates

Figure 2: Attempts to Successful Catheter Placement
**Introduction:**

Fluid administration and intravascular access is often necessary when treating a variety of illnesses, most commonly dehydration. However, intravenous (IV) fluid administration necessitates the skills of a trained health professional, and can often times require hospitalization. Enzyme-assisted subcutaneous fluid administration (EASFA), traditionally referred to as hypodermoclysis, is the infusion of fluids into the subcutaneous tissue using a butterfly needle. This technique may be used for the administration of multiple types of fluids such as isotonic fluids for volume replacement, antibiotics and narcotic analgesics.

Subcutaneous fluid administration (SCFA) has a long history of application in both clinical and veterinary medicine, with widespread use throughout the 1940s and 1950s. However, during the 1950s, sporadic reports of serious complications following SCFA appeared in the literature. A later review of these events showed improper use of the technique, such as administration of hypotonic fluids or inappropriate volumes. Administration of inappropriate fluids or rates of infusion lead to osmotic shifts between the vascular and extracellular compartments which may lead to circulatory collapse, shock, and even death. Although SC was successfully administered for years, it fell out of favor with clinicians with the rising popularity and availability of modern disposable intravenous (IV) catheter equipment.

In addition, there was a physiological barrier of the SC interstitial matrix that made diffusion of fluid solutions into the intravascular departments difficult. The extra-adipocyte portion of the SC compartment is a gel-like matrix of collagenous fibrils and glycosaminoglycans. Subcutaneously administered drugs and fluids must traverse this interstitial matrix to enter the vascular or lymphatic system. One glycosaminoglycan is hyaluronan, which contributes to the resistance of fluid movement through the interstitium. Hyaluronidase modifies connective tissue permeability by cleaving protein bonds and allowing easier diffusion of infused substances into the vasculature and lymphatics. Historically the hyaluronidase compounds were derived from animal extracts, specifically from bull testicles, and have been used clinically to facilitate dispersion and absorption of other drugs for over 50 years, largely used in
veterinary medicine. In 2005 the FDA approved human recombinant Hyaluronidase (HRH), as an adjuvant for subcutaneous infusion\textsuperscript{10}. The main advantage of HRH over previous products is the decreased potential for immune response. As a human recombinant agent, HRH poses far less potential allergic reaction as compared to animal-derived Hyaluronidase. The concept of using HRH in actual patients has been demonstrated feasible and effective\textsuperscript{7,10}.

In brief, the steps to placing a subcutaneous infusion involve inserting an appropriate gauge angiocatheter between the shoulder blades, inject 150 U recombinant human Hyaluronidase (HRH) SC through the catheter (same dose for all patients); repeat dose once every 24 h during infusion, as needed. Connect T-connector to angiocatheter and start fluid infusion. Fluid can be delivered subcutaneously by gravity at a rate of 1 mL per minute at one site; thus, about 1.5 L can be delivered at one site and 3 L at two separate sites over 24 hours\textsuperscript{9}. However, some investigators have found that infusion rates in the 400 mL/hr range are easily attainable (and painless)\textsuperscript{10}. In comparison, standard, large bore (eg, 14- to 16-gauge) peripheral IV catheters using an infusion pump, typically allow delivery of 1 L of crystalloid in 10 to 15 min. It should be noted that the true goal of fluid administration should be to achieve proper rehydration or fluid replacement in the patient. Monitoring for clinical signs and symptoms of rehydration is necessary.

Today, EASFA has been described in the literature as a safe and effective alternative to intravenous fluid administration\textsuperscript{2-6}. There are multiple advantages of EASFA over IV hydration discussed in the literature, including reduced or similar complication rates, decreased cost, greater patient comfort, and less nursing time needed to start and maintain the infusion. This technique can also be used in the emergency department because it is less invasive and generally less painful than IV, while still permitting the administration of appropriate volumes of rehydration fluids. EASFA appears to be most appropriate in patients who present with mild-to-moderate dehydration and have failed attempts at oral rehydration\textsuperscript{7}. It remains largely unclear from the literature why EASFA is used so infrequently in the United States. It is possible that many medical providers do not know about the technique and that much of the population...
has access to a trained healthcare provider that is comfortable placing IV lines.

Currently EASFA is used in patients with mild to moderate dehydration that are unable to take fluids orally and in which placing an IV line is difficult or unsuitable. Previously, alternatives to IV fluid administration, especially in underdeveloped countries were limited to oral rehydration or intragastric, subcutaneous, peritoneal, and rectal infusion. Oral rehydration is not an adequate method in some cases and is impractical if nausea, vomiting, infection, or cognitive impairment were also present.

In many rural communities or other low resource settings it can be difficult to administer fluids for many reasons. Lack of trained personnel and lack of access to healthcare leave many underdeveloped countries and communities with few options for the treating the sick or injured. EASFA offers an alternative that could be used in these areas due to its ease of placement and efficacy. There are many challenges and limitations of IV infusion including requiring a trained healthcare provider, difficulty in obtaining venous access and the risk of systemic infection. There are limited alternative options and even those have risks and difficulties associated with placement and delivery. All other alternatives besides oral rehydration are more invasive and require a skilled professional. Currently, the literature describes the use of EASFA primarily in geriatric and palliative/chronic care patients, with a few recently published randomized clinical trials involving its role pediatric medicine.

ROLE IN PEDIATRICS

Fluid administration is indicated in the adult and pediatric populations for a variety of reasons, but dehydration is among the most common and serious conditions. The traditional intravenous method requires a skilled professional to administer, especially with children or the elderly. In one prospective study consisting of a non-randomized sample of 249 total IV placements by registered nurses, only 53% placed successful Peripheral intravenous (PIV) cannulation on the first attempt, 67% within two attempts, and 91% within four attempts. Similar rates exist even with ultrasound guided IV placement. In another study analyzing
ultrasound-guided peripheral intravenous success rates, thirty-five operators recorded 180 encounters; 100 (56%) were successful on the first skin puncture, and 152 (84%) were eventually successful\(^\text{13}\). Not only is there evidence that IV placement is difficult, but also that many unsuccessful attempts a placement can be detrimental. Multiple needle sticks increase patient anxiety, pain, and suffering especially in children\(^\text{14}\).

Difficult intravenous access (DVA) is defined as a clinical condition in which numerous attempts and/or special interventions are anticipated or required to achieve and maintain peripheral venous access\(^\text{14}\). Clinical studies have shown that 51% of children and 83% of toddlers experience high levels of distress during routine venipuncture, and 36% of young children experience significant pain\(^\text{14,15}\). Not surprisingly, children in hospitals find IV sticks painful and 74% report that intravenous lines are the source of their worst pain\(^\text{16}\). The long-term consequences of poorly managed DVA include increased anticipatory and procedure-related distress during subsequent encounters\(^\text{16}\). In the right setting, the use of EASFA could reduce the trauma of multiple needle sticks with its ease of placement and is relatively painless. A study on RHR Subcutaneous fluid delivery found that the first attempt at needle insertion succeeded in 98% of subjects; the median time for first catheter placement was less than 1 minute\(^\text{17}\). A review of the literature by Eldridge looked at difficulties in obtaining IV access in the pediatric population and alternative methods for fluid replacement\(^\text{18}\). He found that subcutaneous rehydration was a promising alternative to IV when IV placement was difficult or impractical\(^\text{18}\). He encourages physicians not to blindly choose IV administration and take into account that it is invasive, painful, and sometimes traumatic for the children and families\(^\text{18}\).

**ROLE IN ELDERLY AND PALLIATIVE CARE**

On the other end of the spectrum, fluid administration is commonly needed in the elderly and those in palliative care. Dehydration is a serious acute condition that is associated with significant morbidity and mortality. The geriatric population is particularly susceptible to dehydration because of a decrease in thirst with age, and diminished kidney function leading to fluid electrolyte imbalances\(^\text{13}\). They may also be on multiple medications for numerous chronic
illnesses that also contribute to improper fluid maintenance. The efficacy and benefits of EASFA in this population has been well-studied. A randomized control study concluded that subcutaneous rehydration in elderly hospitalized patients with mild-moderate dehydration is not inferior to intravenous infusion, and it may have additional benefits. Patients receiving palliative care can be managed with SC fluid infusions and medication dosing with this method without having the risk of line infections.

RATIONALE

Establishing access to the vascular compartment is a priority in a critically ill patient and in a number of more common illnesses. The importance of rehydration in children and adults who are dehydrated due to illness or disease is well documented and practiced worldwide.

In some circumstances, accessing the intravascular space can be difficult even for a trained professional. Difficult venous access could be caused by a number of different conditions including diabetes, obesity, chronic illness, IV drug abuse, dehydration, burns, trauma, and vasculopathy. The healthcare provider must choose the appropriate alternative technique based on the patient’s situation.

Our objective was to determine if Enzyme-Assisted Subcutaneous Fluid Administration (EASFA) is a valid and appropriate technique to utilize in pediatric and elderly patients that is a safe and efficient way to provide fluid resuscitation in low resource settings, mass casualty events, or disasters scenarios.

METHODS:

Criteria for the consideration of studies for this review:

**Inclusion criteria for selected studies included the following:**

1. Evaluation of infusion rates and volume infused OR
2. Assessment of successful placement of catheter AND
3. Pediatric or elderly population

**Types of studies:** All relevant RCTs, prospective and retrospective trials, and observational studies that compared EASFA to IV. We excluded reviews or meta analyses from this study.
**Types of participants:** Study had to include dehydrated but otherwise healthy children under the age of 18, a geriatric population of at least 65, or those persons receiving palliation or long term care.

**Types of interventions:** Interventions were limited to EASFA and IV infusions.

**Types of outcome measurements:** Outcome measurements that were evaluated included infusion rate and number of attempts to successful catheter placement.

**Search methods for identification of studies:**

**MEDLINE search criteria:**

**Search 1:**

{("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND "hypodermoclysis"[MeSH Terms] OR "hypodermoclysis"[All Fields] OR ("subcutaneous"[All Fields] AND "fluid"[All Fields] AND "administration"[All Fields]) OR "subcutaneous fluid administration"[All Fields]) OR ("humans"[MeSH Terms] OR "hypodermoclysis"[All Fields]) AND ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND "humans"[MeSH Terms] AND English[lang])

**Search 2:** (includes only literature published in the last 10 years)

{("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND ("subcutaneous fluid administration"[All Fields]) OR ("hypodermoclysis"[MeSH Terms] OR "hypodermoclysis"[All Fields]) AND (("2004/01/01"[PDAT] : "2014/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Additional studies were identified as references used in previous reviews and meta analyses about EASFA and IV fluid administration. These reviews were identified under the original search criteria listed above.

**Data Collection and Analysis:**
Selections of studies: Studies were evaluated for pertinence by their title and abstract, and those that were irrelevant were excluded. The full article was reviewed and analyzed in those studies deemed relevant. Studies involving the infusion of pharmacotherapies other than standard crystalloid fluids were excluded.

Data extraction and management: Data was extracted from the studies and compared using a data management chart. The collected data was reviewed by more than one editor to reduce the possibility of errors. Only data concerning the above measured outcomes was reported.

Assessment of risk of bias in included studies
Medical research study quality was assessed using the JADAD score/Oxford quality scoring system.

Measures of intervention effect
The data were analyzed with the use of Stata version 14 (College Station, Texas). Cohen’s D was calculated using the mean difference between intervention and control divided by the pooled standard deviation. For dichotomous outcome of the placement success rate, we calculated odds ratios with 95% confidence intervals.

Assessment of reporting biases
Eggers test was used to ascertain small study bias. P values > 0.05 indicated that there were no biases between each study.

RESULTS:
Included studies:
Our search identified 7 studies that fit our predetermined inclusion criteria. A summary of the characteristics of the included studies are briefly are summarized below in Table 1.
Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spandorfer</td>
<td>RTC</td>
<td>148 pediatric patients</td>
</tr>
<tr>
<td>Kuensting</td>
<td>Retrospective</td>
<td>39 pediatric patients</td>
</tr>
<tr>
<td>Allen</td>
<td>Phase IV, single arm study</td>
<td>51 pediatric patients</td>
</tr>
<tr>
<td>O’Keeffe</td>
<td>Observational Study</td>
<td>180 geriatric patients</td>
</tr>
<tr>
<td>Slesak</td>
<td>Prospective randomized open clinical trial</td>
<td>96 geriatric patients</td>
</tr>
<tr>
<td>Dasgupta</td>
<td>Prospective observational study</td>
<td>55 geriatric patients</td>
</tr>
<tr>
<td>Noriega</td>
<td>Prospective RCT</td>
<td>67 geriatric patients</td>
</tr>
</tbody>
</table>
Further details of the included studies are described below in brief abstract form.

**Spandorfer**

“The authors performed a randomized clinical trial compared recombinant human Hyaluronidase-facilitated SC (rHFSC) rehydration with standard IV rehydration for use in dehydrated children in the emergency department. 148 patients 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 (226.40) mL in the rHFSC group versus 299.6 (252.33) mL in the IV group (P = 0.03). Dehydration scores and weight changes post-infusion 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. Although rHFSC was inferior to IV hydration for the primary outcome measure, rHFSC was noninferior in the ED phase of hydration. The study also found additional benefits of rHFSC included time and success of line placement, ease of use, and satisfaction. The study concluded that EASFA should be considered a reasonable treatment option for children who have mild to moderate dehydration, especially those with difficult IV access.”

**Kuensting**

“The authors performed a study with a retrospective descriptive design for review of medical records for 36 children from November 2008 to May 2010 who had received SC fluids only or received SC fluids after 2 or more failed IV attempts. Results: The IV/SC group had significantly longer time to infusion (M = 97.33 minutes) than did the SC group (M = 20.95 minutes; P < .001). The IV/SC group included the number of needlesticks for the intravenous attempts plus the needle stick needed for the subcutaneous infusion. A significant difference was found
between the 2 groups (mean IV = 4.87; mean SC = 1; Z = .000; P < .001). Discussion: In a child who is not seriously ill, SC infusions appear to facilitate the initiation of parenteral rehydration. SC infusions minimized the number of needlesticks a child endured. More study is needed to determine if SC fluids enhance success of subsequent venous cannulation.”

Allen⁶

“This trial was a phase IV, multicenter, single-arm study of patients with mild/moderate dehydration requiring parenteral treatment in US emergency departments. They received subcutaneous injection of 1 mL rHuPH20 (Hyaluronidase 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. 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. The authors concluded that EASFA seems to be safe and effective for young children with mild/moderate dehydration and that subcutaneous access is achieved easily, and the procedure is well accepted by clinicians and parents.”

O’keefe²⁴

“The authors performed a randomized control trial of 60 elderly patients (mean age of 80) with cognitive impairment who required parenteral fluids for at least 48 hours. Results showed there was no significant difference in the mean volume of fluid prescribed over 48 hours in the two groups (SC 3.3L vs. 3.6L IV) or in the proportion of prescribed fluids actually administered (SC 0.82 vs. 0.76 IV). The authors believe these results suggest that EASFA is the treatment of choice in nonurgent situations for the confused patients who require parental fluids.”

Slesak²⁵

“The authors performed a prospective, randomized, open clinical trial set in hospital geriatric wards during a period of 20 months. 96 patients with a mean age +/- standard deviation of 85.3 +/- 6.7 with signs of mild to moderate dehydration needing parenteral fluids. Geriatric patients were randomly allocated to receive SC or IV infusions of half-normal saline-glucose solutions as long as clinically necessary. Forty-eight patients were randomized into each group. Median
duration of fluid administration was 6 days (SC and IV, P 0.33). Median volume was 750 mL/day (SC) and 1,000 mL/day (IV, P .002). In 13 patients, the therapy had to be changed from SC to IV (SC/IV sub-group): 11 times because of the exigency of an IV drug application and twice because of poor resorption. In 17 patients, there was a change from IV to SC (IV/SC sub-group), mainly because of impossibility of further peripheral IV punctures (8 times) and permanent removal of the IV cannula (5 times). The clinical and laboratory changes during therapy were similar in both trial arms. Authors concluded that rehydration by hypodermoclysis is equally well accepted by geriatric patients as the IV therapy and offers a similarly easy feasibility. Additionally, in confused patients and in those in whom IV punctures are difficult to achieve, it represents the far superior method. Both techniques are comparably safe and effective.”

Dasgupta23

“The authors completed a prospective observational study of 55 residents of a long-term care facility treated with fluid therapy during a 5-week period. The mean age of the entire cohort was 83.7 years (standard deviation (SD) = 10.5) (range 52-100 years); 40 (73%) were female and 37 (67%) had dementia. Main outcomes included efficacy of hydration and adverse effects that were obtained from detailed chart review, interviews with healthcare providers, and investigator observations. Patients started on hypodermoclysis received 2/3D5-1/3NS or normal saline as the infusion solution, at rates varying between 5-75 mL/hour (only one patient received rates as low as 5 mL/hour, whereas the remainder received at least 35mL/hour). The mean duration of hypodermoclysis fluid therapy was 11.4 (SD = 9.8) days. The authors concluded that EASFA is an effective procedure for providing fluids for both chronic maintenance needs and acute situations associated with mild to moderate dehydration in a long-term care setting. Hypodermoclysis appears safer and can avoid transfers to hospital for rehydration.”

Noriega16

“The authors performed a prospective, randomized and controlled interventional trial of patients 65 years and older admitted to an Acute Geriatric Unit with mild to moderate
dehydration and oral intolerance, evaluating the non-inferiority of subcutaneous fluid therapy versus the intravenous route. Sixty seven patients completed the study (34 SC, age 86.4±8.5 years, 41% women, vs. 33 IV, 84.3±6.6, 54.5% women). The intervention consisted of the administration of up to 1.5 L/day/route for 72 hours subcutaneous vs. intravenous. The amount of fluid administered per day by route was 1.320 ml±400 SC vs. 1.480 ml±340 IV, P=.092. Fewer catheter extraction episodes were observed in the SC group. The authors concluded that the efficacy of subcutaneous rehydration in elderly hospitalized patients with mild-moderate dehydration is not inferior to that obtained intravenously, and may even have additional advantages.”

**Excluded studies:**
The majority of studies were excluded for ineligible study design such as review articles. Other studies that were excluded included non-human studies involving EASFA and studies that utilized oral rehydration in combination with IV or EASFA.

**Infusion Rate** In 6 included studies the infusion rate was used as a measure of efficacy of rehydration in a clinical setting. This rate should provide evidence that fluids were being safely administered in a reasonable amount of time in their respective setting (i.e. ED or long term care facility) in the presence of mild to moderate dehydration. Pump settings for EASFA in Allen were set to 20mL/kg, which is consistent with evidence-based guidelines for bolus fluid administration in dehydrated pediatric patients. If present, adverse effects were reported in these studies.

**Placement Success** First time success and number of attempts to success is an important measure that not only shows the ease of placement for clinicians, but can also be correlated with patient/caregiver satisfaction. As previously mentioned, children and the elderly can both be very difficult populations for IV placements.
Figure 1. Infusion rate
Figure 2. Attempts to Successful Catheter Placement
Figure 1 shows the results of our analysis on rate of infusion of subcutaneous fluid administration in comparison to IV. This figure shows that 4 of the 6 papers that were included exhibited higher rates of infusion within the IV group versus the EASFA group. However, the overall pooled Cohen’s D measure of 0.31 indicates that the this effect size was not statistically significant and considered small. This difference was not clinically significant. The P value that was calculated only evaluated the heterogeneity of the data that used. In the studies that showed an IV infusion rate faster than subcutaneous, the average rate was only 7.3 cc/hr faster in IV. No study showed a difference of more than 25 cc/hr faster in the IV group. In fact, the Spandorfer trial showed an infusion rate 42.6 cc/hr faster in the SC group.

Figure 2 shows the analytic results of the 4 articles identified to analyze successful catheter placement in the IV and the SC groups. All of the articles show an increased likelihood of a successful catheter placement using the SC method. Therefore, the overall pooled odds ratio shows a 7.19 times higher likelihood of successful placement within the SC group compared to the IV group. This data seems corroborate our clinical assumption that placing a subcutaneous catheter is achieved with far more success than IV catheter placement.

**DISCUSSION:**

It is likely that IV fluid administration will remain the primary route of fluid resuscitation in many developed countries and communities with trained health professionals. However, evidence shows EASFA has useful applications in palliative geriatric, pediatric medicine and a viable alternative for other populations with difficult venous access. As EASFA has been shown to have the same efficacy as oral and IV rehydration, there are some unique advantages it has over IV infusion in particular. These advantages include a simple insertion, less distressing for the patient, a more comfortable overall experience, less staff supervision and less need for hospitalization. Furthermore, there is a decreased risk of thrombophlebitis and septicemia and has the advantage of being easily started and stopped.
CONTRAINDICATIONS AND ADVERSE EVENT REPORTS IN EASFA

Since the advancement and creation of the human recombinant form of the enzyme, reactions to the enzyme have decreased dramatically, however the possibility of local reactions still exists and do rarely happen\(^\text{10}\). It is important to watch closely for any adverse reactions and ensure that dosage, volume, and rate infusion is appropriate for each individual to avoid rapid osmotic shifts.

There are few contraindications for the use of EASFA. For instance, is should not be used where large amounts of fluid need to be administered rapidly, instances of shock, major electrolyte imbalances, and severe dehydration when resources are available for alternatives of fluid resuscitation\(^\text{9}\). In addition, the literature states that this procedure is contraindicated in patients who may be at higher risk for pulmonary congestion or edema such as those with congestive heart failure. Contraindications also exist in patients with clotting and bleeding disorders due to possible bleeding at the injection site.

CONCLUSION AND IMPLICATIONS FOR FURTHER RESEARCH:

In conclusion, EASFA is a comparable alternative to intravenous fluids in regards to infusion rates in both pediatric and elderly patients with mild to moderate dehydration. The higher rate of successful catheter placement in subcutaneous tissue may prove useful in select populations and low resource settings.

APPLICATION IN LOW RESOURCE SETTINGS

The use of EASFA in low resources settings could bring much needed care to those who are dehydrated, ill, or in a hospice setting away from a hospital or care center. In a study called EASI Access I, the investigators observed that the placement of the EASI access lines required minimal training and very limited medical knowledge. The ease of placement associated with EASFA lends to the ability to train community members to place subcutaneous lines when needed\(^\text{10}\). Without cost being a barrier, fluids could be administered before the effects of
dehydration could lead to further harm or death. Subcutaneous lines are also being studied for their potential use in disaster medicine and other prehospital care scenarios. Every year, hundreds of thousands of children and adults die due to dehydration for illnesses such as diarrhea. Prompt fluid administration is key to saving these lives. The application of this procedure could be revolutionary, especially in low resource settings where there is a lack of trained healthcare personnel to administer intravenous fluid. The ease of placement makes it easy to train lay community members to place lines when medical care is not readily available or in emergency settings. For instance, in disaster scenarios or epidemics when the number of patients overwhelms the medical system, fluid administration with the aforementioned techniques could be administered by lay persons with equal efficacy, likely leading to decreased morbidity and mortality. Therefore, we suggest further studies to determine the effectiveness of EASFA in these situations.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest in relation to this research.

RESOURCES/FACILITIES
University of Arizona College of Medicine-Phoenix
University of Arizona College of Medicine-Phoenix Health Science Library
REFERENCES


Chapter 2


A Thesis submitted to the University of Arizona College of Medicine -- Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Medical Student:
Name: Kelsey Wilhelm
Class of 2017
Student Email: kelseywilhelm@email.arizona.edu
Other Student Contact: (402)-690-5344

Mentor:
Name: Dawn Barcellona, M.D.
Mentor Email: dbarcellona@email.arizona.edu
Mentor Phone: (480) 209-4419

Project Performance Site:
University of Arizona College of Medicine- Phoenix
Phoenix, Arizona
I. ABSTRACT

This comprehensive review explores enzyme-assisted subcutaneous fluid administration (EASFA), also known as Hyaluronidase-facilitated subcutaneous infusion (HRH-SCI), and it’s role in pediatric and geriatric medicine. Fluid administration and intravascular access is often necessary when treating a variety of common illnesses. However, intravenous (IV) fluid administration necessitates the skills of a trained health professional and often times also require hospitalization. EASFA offers some unique benefits to the traditional IV, including quick and easy placement that does not require advanced skills. It is especially helpful in patients who have poor venous access such as geriatric, pediatric, and hypovolemic populations. It is a safe alternative and as an added benefit, it does not predispose the patient to intravascular related infections. This paper will discuss the technique used to administer subcutaneous fluids, the indications and contraindications for its use, and rationale for the use of EASFA in the pediatric and geriatric population. Finally, the potential use EASFA in low resource settings will be described. A MEDLINE and Cochrane Library search was performed from January 1950 to December 2014 to recover all available literature on this topic.

II. INTRODUCTION, RATIONALE, BACKGROUND

INTRODUCTION

EASFA is the infusion of fluids into the subcutaneous tissue using a butterfly needle. This technique may be used for the administration of multiple types of fluids such as isotonic fluids for volume replacement, antibiotics and narcotic analgesics. This technique was traditionally known as Hypodermoclysis. EASFA has been described in the literature as a safe and effective alternative to intravenous fluid administration. There are multiple advantages of EASFA over IV hydration discussed in the literature, including reduced or similar complication rates, decreased cost, greater patient comfort, and less nursing time needed to start and maintain the infusion. This technique can also be used in the emergency department because it is less
invasive and generally less painful than IV, while still permitting the administration of appropriate volumes of rehydration fluids. EASFA appears to be most appropriate in patients who present with mild-to-moderate dehydration and have failed attempts at oral rehydration. It remains largely unclear from the literature why EASFA is used so infrequently in the United States. It is possible that many medical providers do not know about the technique, and that much of the population has access to a trained healthcare provider that is proficient in placing IV lines.

RATIONALE
Establishing access to the vascular compartment is a priority in a critically ill patient and in a number of more common illnesses. The importance of rehydration in children and adults who are dehydrated due to illness or disease is well documented and practiced worldwide. Currently EASFA is used in patients with mild to moderate dehydration that are unable to take fluids orally and in which placing an IV line is difficult or unsuitable. Previously, alternatives to IV fluid administration, especially in underdeveloped countries were limited to oral rehydration, subcutaneous, peritoneal, and rectal infusion. Oral rehydration is not an adequate method in some cases and is impractical if nausea, vomiting, infection, or cognitive impairment were also present.

In some circumstances, accessing the intravascular space can be difficult even for a trained professional. Difficult venous access (DVA) could be caused by a number of different conditions including diabetes, obesity, chronic illness, IV drug abuse, dehydration, burns, trauma, and vasculopathy. The healthcare provider must choose the appropriate alternative technique based on the patient’s situation. The current options for fluid delivery are listed below.

Routes for fluid delivery, ordered from least to most invasive:
- Oral
- Subcutaneous (SC)
- Intravenous
Naso/orogastric (NG)
Peripherally inserted central catheter
Intraosseous (IO)
Central Venous Cannulation
Central Venous Cutdown

In many rural communities or other low resource settings it can be difficult to administer fluids for many reasons. Lack of trained personnel and lack of access to healthcare leave many underdeveloped countries and communities with few options for the treating the sick or injured. EASFA offers an alternative that could be used in these areas due to its ease of placement and efficacy. There are many challenges and limitations of IV infusion including requiring a trained healthcare provider, difficulty in obtaining venous access and the risk of systemic infection. There are limited alternative options and those mentioned previously all have risks and difficulties associated with placement. All other alternatives besides oral rehydration are more invasive and require a skilled professional. Currently, the literature describes the use of EASFA primarily in geriatric and palliative/chronic care patients, with a few recently published randomized clinical trials involving its role pediatric medicine.

BACKGROUND
THE HISTORY OF THE TECHNIQUE AND DISCUSSION OF HYALURONIDASE ENZYME FACILITATION
Subcutaneous fluid administration has a long history of application in both clinical and veterinary medicine, with widespread use throughout the 1940s and 1950s. However, during the 1950s, sporadic reports of serious complications following EASFA appeared in the literature. A later review of these events showed improper use of the technique, such as administration of hypotonic fluids or inappropriate volumes. Administration of inappropriate fluids or rates of infusion lead to osmotic shifts between the vascular and extracellular compartments which may lead to circulatory collapse, shock, and even death. Although EASFA was successfully administered for years, it fell out of favor with clinicians with the rising popularity and availability of modern disposable intravenous (IV) catheter equipment.
In addition, there was a physiological barrier of the SC interstitial matrix that made diffusion of fluid solutions into the intravascular departments difficult\textsuperscript{10}. The extra-adipocyte portion of the SC compartment is a gel-like matrix of collagenous fibrils and glycosaminoglycans. Subcutaneously administered drugs and fluids must traverse this interstitial matrix to enter the vascular or lymphatic system. One glycosaminoglycans is hyaluronan, which contributes to the resistance of fluid movement through the interstitium. Hyaluronidase modifies connective tissue permeability by cleaving protein bonds and allowing easier diffusion of infused substances into the vasculature and lymphatics\textsuperscript{10}. Historically the hyaluronidase compounds were derived from animal extracts, specifically from bull testicles, and have been used clinically to facilitate dispersion and absorption of other drugs for over 50 years, largely used in veterinary medicine. In 2005 the FDA approved human recombinant hyaluronidase (HRH), as an adjuvant for subcutaneous infusion\textsuperscript{10}. The main advantage of HRH over previous products is the decreased potential for immune response. As a human recombinant agent, HRH poses far less potential allergic reaction as compared to animal-derived hyaluronidase. The concept of using HRH in actual patients has been demonstrated feasible and effective\textsuperscript{7,10}.

III. THE ADMINISTRATION OF EASFA

THE ADMINISTRATION SITE
In ambulatory patients, sites include the abdomen, upper chest, above the breast, over an intercostal space and the scapular area. In those who are confined to bed, preferred sites are the thighs, the abdomen and the outer aspect of the upper arm\textsuperscript{9}.

THE VOLUME AND RATE
Fluid can be delivered subcutaneously by gravity at a rate of 1 mL per minute at one site; thus, about 1.5 L can be delivered at one site and 3 L at two separate sites over 24 hours\textsuperscript{9}. However, some investigators have found that infusion rates in the 400 mL/hr range are easily attainable, and painless \textsuperscript{10}. In comparison, standard, large bore (eg, 14- to 16-gauge) peripheral IV catheters using an infusion pump, typically allow delivery of 1 L of crystalloid in 10 to 15 min. It should be noted that the true goal of fluid administration should be to achieve proper
rehydration or fluid replacement in the patient. Monitoring for clinical signs and symptoms of
rehydration is necessary.

Fig 1. Pinch Skin at Appropriate site  

Figure 2. Correctly placed EASI Line

THE PROCEDURE
The steps to placing a subcutaneous infusion are as follows:

Properly prepare the desired area and pinch the skin to separate the SC space from the
underlying muscle. Insert an appropriate gauge 1-in angiocatheter at a 30- to 45-degree angle,
between the shoulder blades (as an example). Insert angiocatheter all the way to hub, and
inject 150 U recombinant human Hyaluronidase (HRH) SC through the catheter (same dose for
all patients); repeat dose once every 24 h during infusion, as needed. Connect T-connector to
angiocatheter and start fluid infusion. Prop up catheter with gauze padding and secure sterile
occlusive dressing.

IV. DISCUSSION
CONTRAINDICATIONS AND ADVERSE EVENT REPORTS OF EASFA
Since the advancement and creation of the human recombinant form of the enzyme, reactions
to the enzyme have decreased dramatically. However the possibility of local reactions still exist
and do rarely happen. It is important to watch closely for any adverse reactions and ensure
that dosage, volume, and rate infusion is appropriate for each individual to avoid rapid osmotic
shifts.

There are few contraindications for the use of EASFA. For instance, it should not be used where large amounts of fluid need to be administered rapidly, instances of shock, major electrolyte imbalances, and severe dehydration when resources are available for alternatives of fluid resuscitation. In addition, the literature states that this procedure is contraindicated in patients who may be at higher risk for pulmonary congestion or edema such as those with congestive heart failure. Contraindications also exist in patients with clotting and bleeding disorders due to possible bleeding at the injection site.

ROLE IN PEDIATRICS

Fluid administration is indicated in the adult and pediatric populations for a variety of reasons, but dehydration is among the most common and serious conditions. The traditional intravenous method requires a skilled professional to administer, especially with children or the elderly. In one prospective study consisting of a non-randomized sample of 249 total IV placements by registered nurses, only 53% placed successful Peripheral intravenous (PIV) cannulation on the first attempt, 67% within two attempts, and 91% within four attempts. Similar rates exist even with ultrasound guided IV placement. In another study analyzing ultrasound-guided peripheral intravenous success rates, thirty-five operators recorded 180 encounters; 100 (56%) were successful on the first skin puncture, and 152 (84%) were eventually successful. Not only is there evidence that IV placement is difficult, but also that many unsuccessful attempts a placement can be detrimental. Multiple needle sticks increase patient anxiety, pain, and suffering especially in children.

Difficult intravenous access (DVA) is defined as clinical condition in which numerous attempts and/or special interventions are anticipated or required to achieve and maintain peripheral venous access. Clinical studies have shown that 51% of children and 83% of toddlers experience high levels of distress during routine venipuncture, and 36% of young children experience significant pain. Not surprisingly, children in hospitals find IV sticks painful and 74% report that intravenous lines are the source of their worst pain. The long-term consequences of poorly managed DVA include increased anticipatory and procedure-
related distress during subsequent encounters\textsuperscript{16}. In the right setting, the use of EASFA could reduce the trauma of multiple needle sticks with its ease of placement and is relatively painless. A study on RHR Subcutaneous fluid delivery found that the first attempt at needle insertion succeeded in 98\% of subjects; the median time for first catheter placement was less than one minute\textsuperscript{17}. A review of the literature by Eldridge looked at difficulties in obtaining IV access in the pediatric population and alternative methods for fluid replacement\textsuperscript{18}. He found that subcutaneous rehydration was a promising alternative to IV when IV placement was difficult or impractical\textsuperscript{18}. He encourages physicians not to blindly choose IV administration and take into account that it is invasive, painful, and sometimes traumatic for the children and families\textsuperscript{18}.

A recent randomized clinical trial by Spandorfer et al. compared recombinant human hyaluronidase-facilitated SC (rHFSC) rehydration with standard IV rehydration for use in dehydrated children in the emergency department and the results are below\textsuperscript{19}.

“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 (226.40) mL in the rHFSC group versus 299.6 (252.33) 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.”

Although rHFSC was inferior to IV hydration for the primary outcome measure, rHFSC was noninferior in the ED phase of hydration\textsuperscript{19}. The study also found additional benefits of rHFSC included time and success of line placement, ease of use, and satisfaction\textsuperscript{19}. The study
concluded that EASFA should be considered a reasonable treatment option for children who have mild to moderate dehydration, especially those with difficult IV access.19

An additional study by Allen et al. studied patients with mild/moderate dehydration requiring parenteral treatment in US emergency departments in a phase IV, multicenter, single-arm study.6 The study is summarized below.

“The patients received subcutaneous injection of 1 mL rHuPH20 (Hyaluronidase 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. 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. The authors were able to conclude that EASFA seems to be safe and effective for young children with mild to moderate dehydration. Subcutaneous access is achieved easily, and the procedure is well accepted by clinicians and parents.”

This studied provided excellent data in regards to ease of placement and satisfaction scores.

ROLE IN ELDERLY AND PALLIATIVE CARE
On the other end of the spectrum, fluid administration is commonly needed in the elderly and those in palliative care. Dehydration is a serious acute condition that is associated with significant morbidity and mortality. The geriatric population is particularly susceptible to dehydration because of a decrease in thirst with age, and diminished kidney function leading to fluid electrolyte imbalances.13 They may also be on multiple medications for numerous chronic
illnesses that also contribute to improper fluid maintenance. The efficacy and benefits of EASFA in this population has been well-studied. A randomized control study concluded that subcutaneous rehydration in elderly hospitalized patients with mild-moderate dehydration is not inferior to intravenous infusion, and it may have additional benefits. Patients receiving palliative care can be managed with SC fluid infusions and medication dosing with this method without having the risk of line infections.

Slesak et. al. completed a prospective, randomized, open clinical trial set in hospital geriatric wards during a period of 20 months. This trial is summarized below.

“96 patients with a mean age +/- standard deviation of 85.3 +/- 6.7 with signs of mild to moderate dehydration needing parenteral fluids. Geriatric patients were randomly allocated to receive SC or IV infusions of half-normal saline-glucose solutions as long as clinically necessary. Forty-eight patients were randomized into each group. Median duration of fluid administration was 6 days (SC and IV, P 0.33). Median volume was 750 mL/day (SC) and 1,000 mL/day (IV, P .002). In 13 patients, the therapy had to be changed from SC to IV (SC/IV sub-group): 11 times because of the exigency of an IV drug application and twice because of poor resorption. In 17 patients, there was a change from IV to SC (IV/SC sub-group), mainly because of impossibility of further peripheral IV punctures (8 times) and permanent removal of the IV cannula (5 times). The patients of the IV/SC subgroup scored their discomfort significantly worse (median 5.5 vs all other groups median 2, P .017). This corresponded with the scoring of feasibility by the nurses (IV/SC: median 4.25 vs all other groups median 2, P .009) and by the doctors (IV/SC: median 4 vs all other groups: median 2, P .001). Both methods of rehydration caused only few systemic adverse reactions. Some patients experienced local side effects (SC, n =29 vs IV, n =24; P 0.41), mainly to a mild extent (SC, n =25 vs IV, n =24; P 1.0). Major local side effects (large edema, phlebitis, cellulitis, erythema and strong pain) occurred in nine SC and eight IV (P 1.0) patients. Authors concluded that rehydration by hypodermoclysis is equally well accepted by geriatric patients as the IV therapy and offers a similarly easy feasibility. Additionally, in confused patients and in those in whom IV punctures are difficult to achieve, it represents the far superior method. Both
techniques are comparably safe and effective\textsuperscript{25}. It is important to note the data in regards to discomfort scoring as clinicians attempt to reduce pain in both children and palliative patients as much as possible.”

COST
In a study comparing the cost of rehydration therapies (oral, subcutaneous, and IV) for dehydration secondary to acute gastroenteritis in the US showed that EASFA was less costly that IV rehydration therapy\textsuperscript{22}. It is important to note that although most patients with dehydration can be effectively treated in an outpatient setting, hospitalization is frequently warranted. This study found that with estimated annual inpatient costs for dehydration therapy exceeded $1 billion USD in the US in 1999 for elderly patients alone\textsuperscript{22}. Another study evaluated the cost-effectiveness of recombinant human hyaluronidase-facilitated subcutaneous (rHFSC) fluid administration compared to intravenous (IV) fluid administration in children with mild to moderate dehydration in the emergency department\textsuperscript{26}. This clinical trial also showed that rHFSC fluid administration demonstrated greater treatment effectiveness and cost-effectiveness than traditional IV fluid administration in the ED\textsuperscript{26}. The author believed the primary reasons for the results included ease of obtaining parenteral access via rHFSC in young patients (especially those under 3) where IV access is difficult, and a shorter ED stay with rHFSC fluid administration\textsuperscript{25}.

APPLICATION IN LOW RESOURCE SETTINGS
The use of EASFA in low resources settings could bring much needed care to those who are dehydrated, ill, or in a hospice setting away from hospital or care center. In a study called EASI Access I, the investigators observed that the placement of the EASFA access lines required minimal training and very limited medical knowledge. The ease of placement associated with EASFA lends to the ability to train community members to place subcutaneous lines when needed\textsuperscript{10}. Without cost being a barrier, fluids could be administered before the effects of dehydration could lead to further harm or death.
Every year, thousands of children and adults die due to dehydration for illnesses such as diarrhea. Prompt fluid administration is key to saving these lives. The application of this procedure could be revolutionary, especially in low resource settings where there is a lack of trained healthcare personnel to administer intravenous fluid. The ease of placement makes it easy to train lay community members to place lines when medical care is not readily available or in emergency settings. For instance, in disaster scenarios or Cholera epidemics when the number of patients overwhelms the medical system, fluid administration with the aforementioned techniques could be administered by lay persons with equal efficacy, likely leading to decreased morbidity and mortality.

V. SUMMARY
It is likely that IV fluid administration will remain the primary route of fluid resuscitation in many developed countries and communities with trained health professionals. However, evidence shows EASFA has useful applications in palliative geriatric, pediatric medicine and a viable alternative for other populations with difficult venous access. As EASFA has been shown to have the same efficacy as oral and IV rehydration, there are some unique advantages it has over IV infusion in particular. These advantages include a simple insertion, less distressing for the patient, a more comfortable overall experience, less staff supervision and less need for hospitalization. Furthermore, there is a decreased risk of thrombophlebitis and septicemia and has the advantage of being easily started and stopped. In light of this review of the literature, the authors of this paper have concluded that there needs to be a systematic review of the literature done on subcutaneous fluid administrations in the pediatric population.

VI. FUTURE INNOVATION
The application of this procedure could be revolutionary, especially in low resource settings where there is a lack of trained health personnel to administer intravenous fluid. Every year, hundreds of thousands of children and adults die each year due to dehydration for illnesses such as diarrhea. Prompt fluid administration is key to saving these lives. Using this technique, the person administering the fluids does not need to find a vein, which has been proven to be
very difficult on a dehydrated pediatric or elderly patient. The ease of placement makes it easy to train lay community members to place lines when medical care is not available or in emergency settings. Therefore we suggest further studies to determine the effectiveness of EASFA in these situations.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest in relation to this research

RESOURCES/FACILITIES
University of Arizona College of Medicine-Phoenix
University of Arizona College of Medicine-Phoenix Health Science Library
REFERENCES


