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Normal Saline Bolus Use in Pediatric Emergency Departments is Associated with Worse Pain Control in Children with Sickle Cell Anemia and Vaso-occlusive Pain

Marcus A. Carden, MD[1], **David C. Brousseau, MD**[2], **Fahd A. Ahmad, MD**[3], **Jonathan Bennett, MD**[4], **Seema Bhatt, MD**[5], **Amanda Bogie, MD**[6], **Kathleen Brown, MD**[7], **T. Charles Casper, MStat, PhD**[8], **Laura L. Chapman, MD**[9], **Corrie E. Chumpitazi, MD**[10], **Daniel Cohen, MD**[11], **Carlton Dampier, MD**[12,13], **Angela M. Ellison, MD**[14], **Hartmut Grasemann, MD**[15], **Robert W. Hickey, MD**[16], **Lewis L. Hsu, MD**[17], **Sara Leibovich, MD**[18], **Elizabeth Powell, MD**[19], **Rachel Richards**[8], **Syana Sarnaik, MD**[20], **Debra L. Weiner, MD**[21], and **Claudia R. Morris, MD**[12,13] **on behalf of the Sickle Cell Disease Arginine Study Group and the Pediatric Emergency Care Applied Research Network (PECARN)**

[1].Departments of Pediatrics and Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

[2].Medical College of Wisconsin, Milwaukee, WI

[3].Washington University School of Medicine, St. Louis, MO

[4].Alfred I. DuPont Hospital for Children, Wilmington, DE

[5].Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[6].University of Oklahoma Health Sciences Center, Oklahoma City, OK

[7].Children's National Medical Center, Washington, DC

[8].University of Utah, Salt Lake City, UT

[9].Alpert Medical School, Brown University, Providence, RI

[10].Baylor College of Medicine, Houston, TX

[11].Nationwide Children's Hospital, Columbus, OH

[12].Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

[13].Children's Healthcare of Atlanta, Atlanta, GA

Address Correspondence: Claudia R. Morris MD, Associate Professor of Pediatrics and Emergency Medicine, Research Director, Division of Pediatric Emergency Medicine, Emory University School of Medicine, 1760 Haygood Drive NE, W458, Atlanta, GA 30322, Phone: 404-727-5500, claudia.r.morris@emory.edu.

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[14]The Children's Hospital of Philadelphia, Philadelphia, PA

[15]The Hospital for Sick Children, Toronto, ON, Canada

[16]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

[17]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL

[18]UCSF-Benioff Children's Hospital at Oakland, Oakland, CA

[19]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[20]Children's Hospital of Michigan, Detroit, MI

[21]Boston Children's Hospital, Boston, MA

Abstract

Vaso-occlusive pain events (VOE) are the leading cause of emergency department (ED) visits in sickle cell anemia (SCA). This study assessed the variability in use of intravenous fluids (IVFs) and the association of normal saline bolus (NSB) on pain and other clinical outcomes in children with SCA presenting to pediatric emergency departments (PED) with VOE. Four-hundred charts of children age 3–21 years with SCA/VOE receiving parenteral opioids at 20 high-volume PEDs were evaluated in a retrospective study. Data on type and amount of IVFs used were collected. Patients were divided into 2 groups: those who received NSB and those who did not. The association of NSB use on change in pain scores and admission rates was evaluated. Among 400 children studied, 261(65%) received a NSB. Mean age was 13.8±4.9 years; 46% were male; 92% had hemoglobin-SS. IVFs (bolus and/or maintenance) were used in 84% of patients. Eight different types of IVFs were utilized and IVF volume administered varied widely. Mean triage pain scores were similar between groups, but improvement in pain score from presentation-to-ED-disposition was smaller in the NSB group (2.2 vs. 3.0, p=0.03), while admission rates were higher (71% vs. 59%, p=0.01). Use of NSB remained associated with worse final pain scores and worse change in pain scores in our multivariable model. In conclusion, wide variations in practice utilizing IVFs are common. NSB is given to >50% of children with SCA/VOE, but is associated with worse pain control; a controlled prospective trial is needed to determine causality.

Keywords

NHLBI guidelines; normal saline bolus; pediatric emergency department; Pediatric Emergency Care Applied Research Network (PECARN); sickle cell anemia; vaso-occlusive painful episodes

INTRODUCTION

Pain is the hallmark of sickle cell disease and vaso-occlusive pain episodes (VOEs) are the most common complication of this hemoglobinopathy.[1] VOEs are also, by far, the primary reason patients with SCD seek emergency department (ED) care.[2] Treatment of VOE commonly includes analgesics and intravenous fluids (IVFs).[3–5] However, evidence for utilizing IVF in euvolemic patients or guiding the clinicians' choice for IVFs is lacking [3–5], has changed little over the last decade, [6–8] and was not adequately addressed by recent National Heart, Lung, and Blood Institute (NHLBI) guidelines on SCD management.[3]

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The historical use of saline for intravenous resuscitation dates to early 19th-century Britain during the cholera epidemic.[9] An international standard of practice, normal saline continues to be the most commonly used IVF for resuscitation in the ED globally, with over 200 million liters of normal saline used per year in the United States alone.[10] However, recent evaluation suggests normal saline boluses (NSB) may be associated with increased mortality in patients demonstrating impaired perfusion and living in resource-limited settings, as demonstrated in the Fluid Expansion as Supportive Therapy (FEAST) study.[11] While the number of patients with SCD was not reported in the FEAST trial, many patients had significantly decreased hemoglobin values similar to those often observed in patents with sickle cell disease presenting to the ED with acute illness but without significant fluid deficits, which could make these results relevant in such settings.[12] Further, recent reports showed NSB also led to worse clinical outcomes compared to the administration of a Lactated Ringer's bolus in both critically ill and non-critically ill adult patients presenting to a single ED in the United States, as reported in the Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial and the Isotonic Solutions and Major Adverse Renal Events Trial (SMART).[13,14]

Use of NSB during the treatment of sickle cell disease-related VOE in the ED is common.[15,16] However, some practitioners discourage its use due to concerns that patients with kidney dysfunction, a common finding in sickle cell disease, may not effectively excrete its high sodium, hyperosmolar load. In large volumes, normal saline can lead to hyperchloremic metabolic acidosis.[4,5,10,17] Importantly, adverse kidney events were recently reported with the use of NSB in the SALT-ED and SMART trials.[13,14] Other providers advocate administering hypotonic IVFs during VOE.[4,5] Reducing plasma osmolality with these particular IVFs may improve the rheological behavior of sickle red blood cells (sRBCs) by improving their hydration, which could improve deformability and allow sRBCs to escape the capillary bed before deoxygenation can cause Hb-S polymerization and vaso-occlusion.[18–20] We recently showed that increased extracellular fluid tonicity and sodium levels can negatively impact sRBC deformability and adhesion in *in vitro* models.[21]

Given the growing controversy surrounding ED use of IVF boluses, we recently investigated the use of IVF to treat VOE in pediatric patients with sickle cell anemia (SCA) presenting to the three EDs at Children's Healthcare of Atlanta, where guidelines discourage the use of NSB in euvolemic patients with uncomplicated, moderate-severe VOE. In that single-site study, we found significant variation in physician use of IVFs for SCA-related VOE. We also found that the use of NSB was associated with worse pain control.[16] Here we investigate the use of NSB on a larger scale.

METHODS

Study Design, Setting, Population, and Measurements:

This is a retrospective cohort study of IVF use by physicians practicing in a pediatric emergency department setting and predictors of pain outcomes among pediatric patients with SCA presenting to the ED with uncomplicated, moderate-severe VOE requiring parenteral opioids. The primary objective was to evaluate the impact of NSB on pain scores and ED disposition (hospital admission vs. discharge). Inclusion criteria identified patients

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with SCA (genotypes HbSS and HbSβ0-thalassemia), aged 3–21 years old, who required parenteral opioids (including intravenous or intranasal) for VOE. Patients diagnosed with acute chest syndrome in the ED were excluded.

Twenty consecutive charts per site were evaluated from 20 high-volume pediatric EDs (N=400), including 14 Pediatric Emergency Care Applied Research Network (PECARN) sites, across the United States and Canada. Age, SCD genotype, and parenteral opioid use were confirmed at time of chart review. Demographics and clinical data (including weight, triage vital signs, time to first parenteral opioid, total oral and/or parenteral opioid or other analgesic use, IVF administration including bolus use (defined as ≥5 ml/Kg IVF given rapidly over 30–60 minutes) were extracted from the chart. IVF maintenance fluid use (defined as fluids provided as ml per hour), total IV fluid amount, pain scores, and admission outcome data were also collected from the ED visit. Numerical pain assessment scores were obtained as anchored verbal pain scales or FACES Pain Scale with a 0–10 range (0=no pain, 10=worst pain). First ED encounter is defined as ED time of arrival or ED time of triage, whichever came first. Web-based training was provided by the Data Coordinating Center, University of Utah, to all participating site investigators and research coordinators extracting data for chart review.

The study was approved by institution review boards at all participating sites with a waiver of informed consent.

Statistical Analysis:

Results are presented as mean and standard deviation, percentage of participants with characteristic, regression coefficient with 95% confidence interval (CI) or odds ratios with 95% CI, as appropriate. The Chi-square test was used to compare categorical variables. The Kruskal-Wallis test was used to compare continuous variables. Univariable linear and logistic regression were used to evaluate relationships between the dependent variables of final pain score, change in pain score, and admission with the following clinical variables where appropriate: time to first parenteral opioid [including intranasal fentanyl (INF)], total amount of parenteral opioid, use of INF, use of any IVF, use of IVF bolus, use of maintenance IVF, total IVF given, first pain score, final pain score, change in pain score from triage to disposition, amount of saline given, use of oral opioid, time of ED presentation (AM, PM, overnight), gender, age, and site. Multivariable regression was performed using variables known or suspected to contribute to both admission and pain scores. The variables INF received in the ED, age, oral opioid in the ED, IV fluid bolus in the ED and total amount of parenteral opioids were used in each of the multivariable regression models. In all calculations, missing values for any variable were not included, $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics:

Characteristics of the patients recruited are listed in Table 1. All patients had HbSS or HbSβ^0-thalassemia, which are considered the more severe genotypes of SCD. The mean age

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of the 400 children in this cohort was 13.8±4.9 years; 46% were male, and 66% (N=263) received an IVF bolus. Of those that received any IVF bolus, 99.2% (N=261) received a NSB; 1 patient received a ½ normal saline bolus and 1 patient received a Lactated Ringer's solution bolus. The rate of IVF bolus utilization varied significantly across the 20 sites from 15–100%, with 11 sites delivering an IVF bolus to ≥80% of all children with SCD evaluated (Supplemental Table 1). Maintenance IVF was given to 43.5% of children in the ED. On average, patients received a total of 18.2±9.5 mL/kg of IV fluid during their ED stay.

The majority of patients were not febrile, tachycardic, or hypoxic at time of triage. Fever was reported at home or during the ED stay in 18.5% of patients.

Mean time to IV placement was within one hour after ED arrival. IV opioids were given to 91.3% of patients while 18.8% received INF. Sixty-six percent of all patients received IV ketorolac for their pain. The mean triage pain score was 8/10 at ED presentation and dropped to 5.5 at ED discharge, with an average drop in pain of 2.4 points on a 10-point scale. Mean length of ED stay was 5.1 hours, and 67% of patients were eventually admitted to the inpatient service for VOE.

Patients who received a normal saline bolus vs. no bolus

The use of IVF was common in this cohort with a bolus and/or maintenance fluid given to 84% of patients. There was significant variation in fluid-type used, with eight different kinds of IVF ordered by pediatric ED-based physicians (Table 2). The amounts of IVF given to patients also varied widely (7.6±6.0 vs. 20.3±8.6 mL/kg, $p<0.001$; No Bolus vs. Bolus group respectively).

Clinical characteristics of patients who received a NSB versus no bolus are also summarized in Table 1. Age, sex, weight, and type of SCA were similar between the two groups. At triage, vital signs of temperature, blood pressure, respiratory rate, and oxygen saturation were similar between the two groups, while heart rate (in beats per minute) was modestly different (94.9±17.3 vs. 99.1±18.8, $p=0.05$), although still in the normal range, on average <100. While more patients in the NSB group reported a fever at home or had a fever documented in the ED, the time to IV placement (in minutes) was higher in the Bolus group compared to the No Bolus group.

The use of INF was higher in the No Bolus group, while the use of IV opioids was higher in the bolus group. However, in total (i.e. including INF and IV opioids), the use of parenteral opioids in morphine equivalents (mg/kg) was similar between the two groups.

Table 3 summarizes clinical outcomes of patients who received a NSB compared to those who did not receive a bolus. Although mean triage pain scores were similar between the groups (8 vs. 8), improvement in pain score from presentation-to-ED-disposition was smaller in the NSB group compared to patients who did not receive a bolus. Patients who received a NSB also spent more time (in hours) in the ED.

Admission rate was significantly higher in children who received a NSB compared to those not treated with a bolus (71% vs. 59%, $p=0.01$; Table 3). Univariable logistic regression analysis revealed that patients who received a NSB had 1.8 times the odds of being admitted

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to the hospital for continued VOE treatment [95% CI: 1.1 – 2.7; p=0.01], than those who did not receive a NSB. However, use of NSB was not associated with admission in the multivariable analysis model (OR [95% CI], 1.5 [0.9–2.4]; p=0.11).

Variables associated with pain scores at time of ED disposition

Variables associated with worse final pain scores recorded prior to ED disposition (to home or to the inpatient ward) in univariable linear regression analysis included age, whether a patient received a NSB, first pain score, total amount of parenteral morphine equivalents per hour (mg/kg/hr), and geographical site, while decreased time from first ED encounter to first parenteral opioid dose was associated with improved final pain scores (Supplemental Table 2).

In our multivariable model, only age (p=0.0001), total morphine equivalents of parenteral opioids in mg/kg/hr (p=0.05), and use of NSB (p=0.002) remained independently associated with worse final pain scores at ED disposition (Supplemental Table 2).

Variables associated with change in pain scores from triage to ED disposition

NSB was also associated with a smaller change in pain scores in patients from triage to ED disposition (Table 4), based on univariable regression (mean estimate [95% CI]: −0.80 (−1.45, −0.15), p=0.02). Patients who received a NSB had pain scores that dropped less from first pain score to final pain score than those who did not receive NSB. Patients admitted from the ED to the inpatient unit for VOE also had a worse change in pain scores. On multivariable analysis, only age (mean estimate [95% CI]: −0.06 [−0.13, 0.001], p=0.05), and the receipt of a NSB (−0.94 [−1.62, −0.26], p=0.007) remained independently associated with a smaller change in pain scores. Receipt of oral opioids and total parenteral opioids given in the ED (mg/kg and mg/kg/hr) did not make a difference in change in pain scores in our patient cohort on multivariable analysis.

DISCUSSION

The main goal of our study was to investigate the impact of NSB on pain outcomes in pediatric patients with SCD and VOE presenting to the ED. The use of IVF in the treatment of SCD-related acute pain in the ED is in equipoise and the recent NHLBI guidelines lack firm guidance for how providers should administer IVF, if at all, in this clinical scenario.[7] Emphasis regarding IV hydration in the published guidelines focuses on the hypovolemic patient, [3,15] however clinical practice appears to have extended this to the majority of patients. Specifically, the NHLBI guidelines state “in euvolemic adults and children with SCD and VOE who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration”. [3,15] However, in the largest, multi-institutional and international cohort of pediatric patients with SCA to investigate this topic to date, this study demonstrates that NSB is commonly used in the treatment of euvolemic pediatric patients with uncomplicated, moderate-severe VOE despite a paucity of evidence to support its use. Further, there was a significant negative association between NSB use and pain outcomes in this group of patients, confirming our recent single institution experience.[15]

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While pain physiology in SCD is very complex,[22] numerical pain assessment scores, i.e. anchored verbal pain scales with ranges typically 0–10 (0=no pain, 10=worst pain), are commonly used to monitor pain and guide ED disposition decisions regarding admission vs. discharge during treatment of VOE episodes.[23,24] As pain is the most frequent complaint leading to an ED visit in sickle cell disease, and the lack of relief of pain in the ED is associated with inpatient admission, this study suggests that routine use of NSB in euvolemic patients is not indicated. We found no evidence of benefit from the use of NSB and potentially some evidence of harm.

Recent randomized trials in non-critically ill adults suggests the use of balanced crystalloid solutions, such as Lactated Ringer's solution, leads to less adverse kidney events than NSB in the ED.[13] This is important in SCA, where kidney disease is common.[17] We recently showed that the use of high-sodium, high-chloride IVF can stiffen sickle red cells and negatively impact their deformability in capillary-sized channels, which may be important in elucidating the impact of IVF administration on end-organ function in SCD-related pathology.[25] Further, we have shown that increased extracellular fluid tonicity found in higher sodium IVF such as that found in normal saline can negatively impact the flow of sickle red cells under hypoxic conditions in capillary-sized microchannels and also increases adhesion to human endothelium and laminin under post-capillary venular flow conditions, where vaso-occlusion is thought to take place.[21] Fluid overload in sickle cell disease, which can result from NSB, also puts patients at risk for developing acute chest syndrome.[26] This information, along with evidence that large volumes of saline are associated with hyperchloremic metabolic acidosis,[27,28] suggests that more physiologic, balanced salt solutions may be better resuscitation fluids for patients with SCA and VOE in the ED. However, consideration for a more restrictive fluid approach may be warranted under euvolemic circumstances that avoids NSB.

Balanced salt solutions, such as Lactated Ringer's solution and Plasma-lyte, are recommended in various hospitalized patients instead of normal saline due to the excess sodium and chloride found in normal saline compared to these IVFs,[10] although they too can have adverse side effects if given in large amounts. Also, some of these resuscitation fluids are hypotonic compared to extracellular fluid, which could be particularly beneficial in sickle cell disease and VOE, as hypotonicity can reduce the risk of hemoglobin-S polymerization under hypoxic conditions, thereby theoretically reducing the risk of sickle red cell occlusion in the microvasculature.[20,21,29] However, excessive use of hypotonic fluids in sickle cell disease or other patients may lead to hyponatremia, so practitioners should exercise caution if they decide to utilize these fluids in this population.[30]

Like other intravenous pharmacotherapies, IVF should be administered with attention and care to the underlying disorder being treated, with consideration given to the type, rate, and volume given to the patient. Further, toxicities of various IVF can be patient and population-specific. This study demonstrates that IVF use in SCA requires further inquiry. More research is critically needed to determine the appropriate type of IVF, if any, best administered in the ED to patients with sickle cell disease and VOE, as well as the ideal rate and volume given.

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Limitations

Being retrospective, our analysis cannot prove causality between the variables tested due to possible confounders. Further, as there were multiple sites involved, institutional algorithms and treatment protocols were site-specific and not harmonized, although all site investigators were aware of the 2014 NHLBI guidelines for the treatment of VOE in SCD. In addition, the absence of a gold standard definition for dehydration is a significant limitation of this study. While we attempted to control for hydration status and severity of patient illness in our comparisons of the Bolus vs. No Bolus group by comparing vital signs and presenting pain scores, this does not substitute for provider interactions and evaluation of the patient. Heart rate is not a reliable indicator of hypovolemia, and it is possible that patients treated with a NS bolus were more dehydrated. However the practice of delivering a NS bolus appears routine at a majority of ED sites studied, where over 80% of children received an IVF bolus. Additionally, a potential confounder was the presence of fever in the ED or reported at home that may have influenced the clinician to order an IVF bolus. However, the time to IV placement (in minutes) was actually higher in the Bolus group vs. No Bolus group suggesting these patients did not appear sicker during triage to mandate more rapid care.

We also found a univariable association of NSB, IV maintenance fluid use, and any IVF use (yes vs. no) with admission, which may be reflective of a clinician's decision to start IV fluids once a hospital admission decision is made, rather than an adverse outcome of IVF use. Information on the timing of IVF orders placed during the course of the ED stay was not collected, so temporality cannot be determined. Interestingly, unlike its association with admission, maintenance fluid use and any IVF use (yes vs. no) was not associated with change in pain score, nor was total amount of IV fluid given (mg/kg), suggesting a unique contribution of NSB to sickle-pain severity that warrants further consideration. Use of a NSB independently remained significantly associated with higher pain scores at ED disposition and worse improvement in pain score from triage to disposition in multivariable regression analysis, while the significant univariable associate of NSB with admission was lost in the multivariable regression model.

Finally, we did not control for ED volume and acuity, and these may impact outcomes studied, particularly if they resulted in a delay in care.

Conclusions

Wide variations in practice utilizing IVFs are common among physicians in pediatric EDs across the United States and Canada when it comes to treating children with SCD and VOE. In this retrospective cohort study, a NSB is given to approximately two-thirds of children presenting to a pediatric ED with sickle-related pain and was associated with worse pain control compared to children not given a NSB. As the use of NSB has recently been associated with negative clinical outcomes in non-SCD patients, the results from this large retrospective study provide a rationale to question this ED-based practice in euvolemic patients.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Claudia R. Morris, MD, is the inventor or co-inventor of several UCSF-Benioff Children's Hospital Oakland patents/patent-pending applications that include nutritional supplements, and biomarkers of cardiovascular disease related to arginine bioavailability, is an inventor of an Emory University School of Medicine patent application for a nutritional supplement, is a consultant for Pfizer, and has received research support from MAST Therapeutics, the United States Food and Drug Administration, and the National Institutes of Health. Carlton Dampier MD has received research support from Pfizer.

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Table 1:

Comparison of patient characteristics based on whether the patient received a Normal Saline Bolus versus No Bolus in the Emergency Department

Variable	Total (N=400)	Fluid Type*		P-value**
		No Bolus (N = 137)	NS Bolus# (N = 261)	
Sex - Male	185 (46%)	65 (47%)	119 (46%)	0.73[1]
Age (years)	13.8 (4.9)	13.8 (4.9)	13.8 (4.9)	0.90[2]
Patient Weight (kg)	47.4 (21.3)	46.5 (19.7)	47.9 (22.1)	0.65[2]
Type of Sickle cell anemia				0.05[1]
HbSS	367 (92%)	121 (88%)	245 (94%)	
HbS Beta-Zero Thalassemia	33 (8%)	16 (12%)	16 (6%)	
Vital Signs (from triage)				
Temperature (^{0}C)	37.0 (0.6)	37.0 (0.5)	37.1 (0.6)	0.21[2]
Heart Rate (beats/minute)	97.7 (18.3)	94.9 (17.3)	99.1 (18.8)	0.05[2]
Systolic Blood Pressure (mmHg)	118.4 (13.1)	117.8 (12.7)	118.8 (13.3)	0.43[2]
Diastolic Blood Pressure (mmHg)	68.3 (10.8)	68.4 (11.2)	68.3 (10.5)	0.90[2]
Mean Arterial Pressure (mmHg)	85.0 (10.2)	84.8 (10.6)	85.1 (9.9)	0.58[2]
Oxygen saturation (%)	97.6 (2.6)	97.7 (2.7)	97.6 (2.6)	0.31[2]
Fever at home or in the ED	74 (18.5%)	18 (13%)	56 (22%)	0.04
First pain score recorded	8.0 (2.2)	8.0 (2.1)	8.0 (2.1)	0.71[2]
Minutes from first ED encounter to IV placement	56.7 (41.3)	51.8 (40.1)	59.2 (41.7)	0.05[2]
IVF bolus received in the ED	263 (66%)	-	-	-
IV opioids received in the ED	365 (91%)	115 (84%)	249 (95%)	<.001[1]
Intranasal Fentanyl received in the ED	75 (18.8%)	43 (31%)	32 (12%)	<.001[1]
Total parenteral morphine equivalents given in ED (mg/kg)	0.2 (0.2)	0.3 (0.3)	0.2 (0.2)	0.72[2]
Total parenteral morphine equivalents given in ED (mg/kg/hr)	0.1 (0.6)	0.1 (0.09)	0.1 (0.04)	0.14[2]
Oral opioids received in the ED	98 (24.5%)	48 (35.0%)	50 (19.2%)	<.001[1]

[1]Chi-squared test.

[2]Kruskal-Wallis test.

[3.]Missing disposition data on 3 patients from Bolus group.

[#]Of 400 patients, N=263 were given an IVF bolus. N=1 received ½ NS bolus and N=1 received LR bolus, which were not included in the Bolus vs. No Bolus data analysis for the table.

[*]All values are given in N (%) or Mean (SD) unless otherwise specified

[**]All comparisons are between the Bolus and No Bolus groups

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Table 2:

Variations of IV fluids used in the ED amongst the Bolus and No Bolus groups

	Fluid Type*		
	No Bolus (N = 137)	**Bolus** ** **(N = 263)**	**P-value**
Total bolus amount given in the ED (ml/Kg)[1]			
<=12.5 ml/kg	- (-)	55 (20.9%)	
12.5–17.5 ml/kg	- (-)	60 (22.8%)	
17.5–22.5 ml/kg	- (-)	127 (48.3%)	
>22.5 ml/kg	- (-)	21 (8.0%)	
Maintenance Fluid Received			0.049[2]
NS	13 (9.5%)	14 (5.3%)	
1/2 NS	1 (0.7%)	1 (0.4%)	
D5NS	11 (8.0%)	29 (11.0%)	
D5 1/2 NS	33 (24.1%)	51 (19.4%)	
D5 1/4 NS	11 (8.0%)	2 (0.8%)	
D5NS + KCL 20 Meq	1 (0.7%)	1 (0.4%)	
D5+1/2NS + KCL 20 Meq	1 (0.7%)	2 (0.8%)	
More Than One	1 (0.7%)	2 (0.8%)	
None	65 (47.4%)	161 (61.2%)	
Total IV fluid amount per kg (ml/kg)	7.6 (5.99)	20.3 (8.60)	<.001[3]
Total IV fluid amount per kg (ml/kg/hr)	1.6 (1.29)	4.4 (2.26)	<.001[3]

[1] Bolus fluids used included NS (N=261), ½ NS (N=1), and Lactated Ringers (N=1).

[2] Chi-squared test of no association.

[3] Kruskal-Wallis test.

* All values are given in N (%) or Mean (SD) unless otherwise specified.

** Bolus is defined as IVF ≥ 5ml/Kg given rapidly over set time of 30–60 minutes.

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Table 3:

Clinical Outcomes in patients who received a Normal Saline Bolus versus No Normal Saline Bolus given in the Emergency Department

Variable	Total (N=400)	Fluid Type*		P-value**
		No Bolus (N = 137)	NS Bolus# (N = 261)	
Final pain score recorded	5.5 (3.3)	5.0 (3.3)	5.8 (3.2)	0.01[1]
Difference in pain score from presentation to discharge	2.4 (3.2)	3.0 (3.3)	2.2 (3.0)	0.03[1]
Patient was admitted to Hospital: Yes	268 (67%)	81 (59%)	185 (71%)[2]	0.01[3]
Total time spent in ED (first encounter to departure, hours)	5.1 (2.3)	4.8 (2.3)	5.2 (2.2)	0.01[1]

1. Kruskal-Wallis test.

2. Missing disposition data on 3 patients from Bolus group.

3. Chi squared test

Of 400 patients, N=263 were given an IVF bolus. N=1 received ½ NS bolus and N=1 received Lactated Ringers (LR) bolus, which were not included in the Bolus vs. No Bolus data analysis for the table.

* All values are given in N (%) or Mean (SD) unless otherwise specified

** All comparisons are between the Bolus and No Bolus groups

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Table 4:

Regression Analysis showing factors associated with change in pain scores from triage to ED disposition

Linear Regression Estimates - Change in Pain Score		
Variables Being Tested	**P-Value**	**Estimate (95% CI)**
UNIVARIABLE ANALYSIS		
Normal saline bolus received in ED	0.02	−0.80 (−1.45, −0.15)
Maintenance fluids received	0.71	0.12 (−0.51, 0.75)
Total IV fluid amount (ml/kg)	0.09	−0.03 (−0.07, 0.01)
Any IV fluids received in ED	0.47	−0.31 (−1.16, 0.54)
First pain score recorded	<.0001	0.42 (0.28, 0.56)
Time from first ED encounter to first parenteral opioid dose (per 10 min)	0.41	0.02 (−0.03, 0.07)
Disposition: Admitted	<.0001	−2.31 (−2.94, −1.68)
Intranasal fentanyl received in ED	0.44	−0.31 (−1.11, 0.49)
Total amount of parenteral morphine equivalents (kg/hr)	0.32	−0.03 (−0.08, 0.03)
Gender, Female vs Male	0.24	−0.37 (−1.00, 0.26)
Age	0.06	−0.06 (−0.13, 0.001)
Oral opioids received in ED	0.61	0.19 (−0.54, 0.92)
Site Number & Change in Pain Score	<.0001	
MULTIVARIABLE ANALYSIS		
Normal saline bolus received in ED	0.007	−0.94 (−1.62, −0.26)
Age	0.05	−0.06 (−0.13, 0.001)