Original Research

Early Aggressive Hydration Is Associated with Decreased Opioid Use and Readmission in Mild Acute Pancreatitis

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Abstract

Background
Acute pancreatitis (AP) is one of the most common causes of hospital admissions due to gastrointestinal disorders. No pharmacologic agents have been proven to impact the prognosis, and the treatment still remains supportive with intravenous fluids for hydration. Although early hydration has been recommended for the management of mild AP, there is no consensus on the type, rate, and amount of the fluid replacement.

Objective
In this study, we aimed to investigate the outcome of aggressive hydration in patients with AP.

Methods
Retrospective data from patients admitted to 12 hospitals (2015–2017) was used for analysis. Five hundred patients who met the inclusion and exclusion criteria for mild AP were included. The subjects were classified into 3 groups based on the amount of intravenous fluids they received in the first 12 hours of admission: Hydration group A (0-1.5 ml/kg/h), Hydration group B (>1.5–3 ml/kg/h) and Hydration group C (>3 ml/kg/h). Laboratory test results on the second day of admission, length of stay (LOS) and opioid analgesic use on the last day were analyzed using a Chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results
Patients with aggressive hydration (>3 ml/kg/h) had a greater reduction in creatinine (mean difference = -0.05, p = 0.017) compared to those who received standard hydration (0–1.5 ml/kg/h). There was no significant difference in LOS among the three hydration groups. Patients with aggressive hydration were less likely to use opioid analgesics on the last day of hospitalization (23.9% vs. 35.3%, p = 0.044) compared to standard hydration. Patients with hydration were less likely to experience a readmission for any reason within 30 days (Odds ratio (OR) = 1.603, 95% CI, 1.064-2.414, p = 0.024) compared to those who received low hydration.

Conclusions
Our findings showed that less narcotics were required for the patients receiving aggressive hydration in mild AP. On the other hand, early aggressive hydration is not widely implemented in community hospitals, despite beneficial effects.

Keywords
pancreatitis; pancreatitis/theraphy; infusions, intravenous; analgesics, opioid; narcotic use; readmission; treatment outcome

Introduction

Acute pancreatitis (AP) is an inflammatory disorder and one of the most common causes of hospital admissions due to gastrointestinal disorders in the USA and worldwide.[1] Etiology is unknown in about 15% of the patients. Cholelithiasis and chronic alcohol consumption are the main risk factors. A number of drugs are also shown to be associated with AP.[1]

There are many preclinical studies for the treatment of AP. These studies suggest the treatment with anti-secretory agents, protease inhibitors, anti-inflammatory agents and anti-oxidants.[2] Many of these studies have shown therapeutic benefit and improved survival in experimental animal models. However, no pharmacologic agents have been shown to impact the course of AP in humans; and the treatment in patients still remains supportive. Currently, primary clinical management includes early fluid resuscitation, analgesia, and nutritional support.[1,3]

Although early hydration has been the primary recommendation for the management of mild AP, there is no consensus on the type, rate, amount, and duration of the fluid replacement. Some factors such as increased hematocrit, blood urea nitrogen (BUN) and creatinine levels are found to be associated with the development of a more severe course in AP. Thus, these laboratory tests are commonly used to guide fluid resuscitation.[4,5]

Although some evidence demonstrated clinical improvement with aggressive hydration,[6,7] there is an argument whether the change in lab results is due to hemodilution.[8]

In this study, we aimed to investigate the outcome of aggressive hydration in patients with AP through medical records. To our knowledge, this study is the first to evaluate hospital readmission rates in addition to clinical outcomes a patient's outcomes in pancreatitis.

Methods

Study Design

A retrospective cohort study was conducted through the medical records of patients from 12 hospitals in a large healthcare system in North Florida. Records were reviewed from October 1, 2015 to September 30, 2017. The study was approved by the IRB at the University of Central Florida (SBE-18-13791). Informed consent was waived since the data gathered was retrospective and did not contain any patient-identifiers.

Outcomes and Data Elements

The primary outcome was all-cause, 30-day readmission, which was defined as a repeat hospitalization within 30 days of discharge. The secondary outcomes included opioid analgesic use on the last day at the hospital as well as the length of stay (LOS) in the hospital. Demographic and clinical data collected for all patients included gender, age and laboratory tests.

Study Cohort

Patients included in this study were at least 18 years of age and identified as having AP using ICD 10 (The International Classification of Diseases, Tenth Revision) code (K85, K85.1, K85.10, K85.2, K85.20, K85.3, K85.8, K85.80 and K85.90). Patients with systemic inflammatory response syndrome (SIRS), sepsis, heart failure, ascites, pulmonary edema, edema, gastrointestinal bleeding, pregnancy, hypotension (systolic blood pressure <90 mmHg), respiratory insufficiency (oxygen saturation <90% on room air), renal insufficiency (Cr >2 mg/dl at admission) and hyponatremia (sodium <135 meg/l) were excluded. A total of 500 patients were included in the analysis. The patients were classified into three groups based on the amount of hydration they received in the first 12 hours of vitals check: Hydration group A (0–1.5 ml/kg/h), Hydration group B (>1.5–3 ml/kg/h) and Hydration group C (>3 ml/kg/h), or into 2 groups, high hydration (0–1.5 ml/kg/h) and low hydration (>1.5 ml/kg/h).

Statistical Analysis

Demographic and laboratory tests on the first day of admission were summarized using percentages for categorical variables and mean (SD) for continuous variables. Laboratory test changes on the second day from the first day were assessed individually using a general linear model (GLM) with adjusting for age, sex and the test value on the first day. Similarly LOS was evaluated using GLM with adjusting only for age and sex. Opioid analgesic use on the last day and readmission within 30 days among

intravenous hydration groups were analyzed using multivariate logistic regression model adjusting for age and sex. A p-value of less than 0.05 was considered as statistically significant. All data analyses were conducted using IBM SPSS Statistics 24.

Results

Demographic and laboratory tests on the first day of admission by intravenous hydration groups are summarized on **Table 1**. Patients with aggressive hydration (>3 ml/kg/h) had a greater reduction in creatinine (mean difference = -0.06, p = 0.006), calcium (mean difference = -0.15, p = 0.011) and albumin (mean difference = -0.10, p = 0.010) compared to those who received low hydration (0–1.5 ml/kg/h). They also had a greater reduction in calcium (mean difference = -0.18, p = 0.006) compared to those who received medium hydration (>1.5-3 ml/kg/h). (**Table 2**) There was no significant difference in LOS among three hydration groups, p >0.05. (**Table 3**)

Patients with aggressive hydration (>3 ml/kg/h) were less likely to use opioid analgesics on the last day of hospitalization (Odds ratio (OR) = 1.916, 95% CI, 1.078–3.406, p = 0.027) compared to those who received low hydration (0–1.5 ml/kg/h). (**Table 4**)

Patients with greater hydration (>1.5 ml/kg/h) were less likely to experience a-within-30-days -readmission for any reason (OR = 1.603, 95% CI, 1.064–2.414, p = 0.024) compared to those who received lower hydration (0–1.5 ml/kg/h). (**Tables 5 and 6**)

Discussion

AP is a frequent cause of hospitalization, but treatment options are limited. All patients with pancreatitis should have its cause determined by features of the history, results of laboratory tests, and findings on transabdominal ultrasound.[5] Aggressive and goal-directed therapy for intravenous fluid resuscitation are recommended in the management of AP.[4]

Table 1. Demographic and laboratory tests on the first day of admission by intravenous hydration groups.

Variable	Hydration (0-1.5 ml/kg/hr) Total	n (%) or mean±SE	Hydration (>1.5-3 ml/kg/hr) Total	n (%) or mean±SE	Hydration (>3 ml/kg/hr) Total	n (%) or mean±SE
Gender	252		161		87	
Female		124 (49.2)		80 (49.7)		49 (56.3)
Male		128 (50.8)		81 (50.3)		38 (43.7)
Age (years)	252	53.2 ±1.03	161	52.9 ±1.47	87	50.7 ±1.93
Creatinine	216	0.96 ±0.02	145	0.96 ±0.02	78	0.93 ±0.03
BUN	157	14.2 ±0.50	106	14.3 ±0.69	63	14.1 ±0.78
Calcium	160	8.82 ±0.05	107	8.92 ±0.05	64	8.78 ±0.07
ALT	145	144.8 ±15.50	102	131.8 ±20.19	58	105.7 ±18.58
AST	145	139.7 ±14.92	102	124.4 ±19.59	58	125.6 ±27.97
ALB	149	3.57 ±0.04	109	3.62 ±0.04	60	3.65 ±0.06
WBC	172	10.5 ±0.37	114	10.3 ±0.37	72	9.9 ±0.47
HCT	220	41.31 ±0.38	152	40.66 ±0.37	85	41.88 ±0.53
HGB	220	13.92 ±0.14	152	13.73 ±0.14	85	14.20 ±0.20
BILT	216	1.22 ±0.10	151	1.14 ±0.12	83	0.93 ±0.14

Abbreviations: BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HCT: hematocrit; HGB: hemoglobin; T-BIL: total bilirubin

Table 2. Comparison of lab values among intravenous hydration groups at 24 hours.

Outcome (2nd day change from 1st day)	A. Hydration (0-1.5 ml/kg/hr) N mean±SE	B. Hydration (>1.5-3 ml/kg/hr) N mean±SE	C. Hydration (>3 ml/kg/hr) N mean±SE	Mean difference C-A mean±SE P-value	Mean difference C-B mean±SE P-value
Cr	182 -0.09± 0.01	121 -0.13±0.01	72 -0.15±0.02	-0.06±0.02 0.006	-0.02±0.02 0.302
BUN	157 -2.14±0.29	106 -2.50±0.36	63 -3.08±0.46	-0.93±0.55 0.090	-0.58±0.59 0.324
Calcium	160 -0.58±0.03	107 -0.56±0.04	64 -0.74±0.05	-0.15±0.06 0.011	-0.18±0.06 0.006
ALT	145 -7.3±6.2	102 -22.9±7.4	58 -23.7±9.8	-16.4±11.6 0.160	-0.7±12.3 0.952
AST	145 -34.3±7.6	102 -51.3±9.0	58 -33.7±12.0	0.58±14.2 0.968	17.6±15.0 0.241
ALB	149 -0.53±0.02	109 -0.57±0.02	60 -0.63±0.03	-0.10±0.04 0.010	-0.06±0.04 0.116
WBC	172 -1.14±0.22	114 -1.50±0.27	72 -0.97±0.34	0.17±0.41 0.672	0.53±0.44 0.221
HCT	173 -3.46± 0.22	114 -3.68±0.27	72 -3.54±0.34	-0.09±0.40 0.832	0.13±0.46 0.760
HGB	173 -1.26±0.07	114 -1.39±0.09	72 -1.37±0.11	-0.12±0.13 0.380	0.02±0.14 0.907
BILT	145 0.01±0.07	103 -0.06±0.08	58 0.04±0.10	0.03±0.12 0.820	0.10±0.13 0.459

Abbreviations: BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HCT: hematocrit; HGB: hemoglobin; T-BIL: total bilirubin

Table 3. Length of stay (LOS) comparisons among intravenous hydration groups.

Outcome	A. Hydration (0-1.5 ml/kg/hr) N mean±SE	B. Hydration (>1.5-3 ml/kg/hr) N mean±SE	C. Hydration (>3 ml/kg/hr) N mean±SE	Mean difference C-A mean±SE P-value	Mean difference C-B mean±SE P-value
Length of stay (days)	252 3.80±0.18	161 3.61±0.23	87 4.03±0.31	0.23±0.36 0.520	0.42±0.38 0.276

Table 4. Opioid analgesic use on the last day by three intravenous hydration groups.

Effect	Opioid analgesic use	Odds ratio	95% CI	P-value
Hydration (ml/kg/hr)				
0≤Hydration≤1.5	34.5% (87/252)	1.916	1.078-3.406	0.027
1.5<Hydration≤3	28.0% (45/161)	1.368	0.737-2.540	0.320
Hydration>3 (Ref.)	23.0% (20/87)	1		

Table 5. Readmission within 30 days for any reason by three intravenous hydration groups.

Effect	30-day readmission	Odds ratio	95% CI	P-value
Hydration (ml/kg/hr)				
0≤Hydration≤1.5	29.8% (75/252)	1.718	0.952-3.100	0.072
1.5<Hydration≤3	21.7% (35/161)	1.112	0.584-2.118	0.746
Hydration>3 (Ref.)	20.7% (18/87)	1		

Table 6. Readmission within 30 days for any reason by two intravenous hydration groups.

Effect	30-day readmission	Odds ratio	95% CI	P-value
Hydration (ml/kg/hr)				
0≤Hydration≤1.5	9.8% (75/252)	1.603	1.064-2.414	0.024
Hydration>1.5 (Ref.)	21.4% (53/248)	1		

Even though there are several studies reporting the beneficial effect of aggressive fluid treatment in AP, to our knowledge this is the first study to evaluate hospital readmission rates in addition to clinical outcomes during a patient's hospital stay.[6,7]

In our study, we found that only 17 percent of the patients with mild AP received aggressive hydration in 12 community hospitals. The low number of patients exposed to aggressive hydration may be attributed to the low awareness in the community hospitals or physicians avoiding to load high volume fluids.

We also found that there was a significant reduction in the lab test values of the aggressive hydration group, which may be due to hemodilution in the first 24 hours. Nevertheless, a close correlation between mortality and blood glucose, urea, partial pressure of oxygen, white blood cell count, hemoglobin, total bilirubin and cholesterol was shown in patients with AP, and these lab results serve as prognostic markers for predicting mortality.[9,10] Similar to our outcome findings, in a clinical trial, it was shown that aggressive resuscitation initiated within 4 hours of pancreatitis diagnosis hastened clinical improvement by reducing hemoconcentration and persistent SIRS development.[6] The proportion of patients with clinical improvement, as well as rate of improvement within 36 hours, was higher in the aggressive resuscitation group compared to the standard resuscitation group.

There are other studies which report that early fluid replacement reduced morbidity and mortality.[7,11] Moreover, inadequate hydration and subsequent persistent hemoconcentration are associated with development of necrotizing pancreatitis in studies.[12] Our in hospital mortality rate was not different among groups. This lack of difference may be because we only included mild cases. On the other hand, the time course of the aggressive fluid resuscitation is as important as the amount of the fluid given. Early fluid therapy is the cornerstone of treatment and is universally recommended. However, there is a lack of consensus regarding the type, rate, amount and end points of fluid replacement.[13] One could question whether decreased lab values, such as hematocrit, BUN and creatinine, or indicators of volume influenced by the rate of fluid resuscitation and fluid sequestration are adequate indicators of clinical improvement.[8] Furthermore, in another randomized controlled clinical trial, where the average age was higher, almost ¼ of the patients developed symptoms due to fluid overload in the first 24 hours.[14] One should note that their patients were older than those in the Buxbaum study (mean age 63 vs 45). The average age for our patients were similar in the 3 groups: 53, 53 and 51, respectively from low to high hydration group.

We also analyzed opioid analgesic use on the last day of hospitalization. Opioid analgesics remain mainstay treatment for the pain related to AP despite the risks for addiction and other adverse effects.[15] Although opioid use in therapeutic procedures like endoscopic retrograde cholangiopancreatograph (ERCP), minimally-invasive necrosectomy and decompressive laparotomy have been widely studied, a clear consensus has not yet been reached about their clinical effectiveness and safety.[3] Treatment with analgesics for abdominal pain in AP probably does not modify the course of disease or mortality. However, the treatment of pain as a symptom improves comfort and patient-reported outcomes.[15] In agreement with this argument, the pain scores and clinical outcome were improved with aggressive hydration in a clinical trial.[6] The decreased need for opioids in our study could be due to decreased pain as mentioned above. Another possible mechanism is the improved perfusion. Fluid resuscitation

increases pancreatic and splanchnic blood flow and maintains hemodynamic balance as well as decreasing manifestations of systemic inflammatory response.[16]

In our study, all-cause 30-day readmission rates were also significantly lower in the aggressive hydration group, even though there was no significant difference among the groups in terms of length of stay in the hospital.

About 1 in 7 patients had a 30-day readmission according to a national database and about half of these readmissions were related to AP. The risk of early unplanned readmission was significantly lower in patients who underwent cholecystectomy. However, the cases that originated from alcohol and idiopathic etiology remained at high risk for early readmission.[17] Whitlock et al. (2011) have developed a scoring system to determine a risk for early readmission in AP, which includes symptoms at discharge, presence of pancreatic necrosis, and the ability to tolerate diet.[18] Our study showed an association of early aggressive hydration with reduced 30-days readmission. Patients who received an early aggressive hydration needed less pain medication during their hospital stay, and they were less likely to readmit. We can speculate that this result was due to clinical improvement. Such improvement was observed in other studies with aggressive hydration.[6,7]

Our study has several strengths. We have 500 patients from 12 community hospitals, which allows us to see the broad practice in Florida. Selection and participation biases are minimized given that the sample is taken from a broad range of patient demographics and hospital characteristics.

Our study has several strengths. We have 500 patients from 12 community hospitals, which allows us to see the broad practice in Florida. Selection and participation biases are minimized given that the sample is taken from a broad range of patient demographics and hospital characteristics.

The major risk of aggressive hydration is readmission due to volume overload and its side effects, but we have validated our outcomes by calculating readmission rate. We have also excluded the patients with hyponatremia, elevated creatinine, and hypotension on admission, which mandate aggressive hydration to remove bias.

Our study has some limitations. Due to the retrospective nature, the ability to remove confounders is limited compared to a randomized, controlled clinical study. Another major limitation was the exclusion of patients with severe AP, SIRS, and other major comorbidities. We used ICD-10 codes to include and exclude patients rather than laboratory values and imaging studies, which always raise an issue of under- and over-reporting AP.

Conclusion

Although early aggressive hydration has been shown to be beneficial in mild AP, our results show that it is not widely followed in community hospitals. Our findings showed that fewer narcotics were required for those patients receiving aggressive hydration.

Abbreviations

AP	Acute pancreatitis
BUN	Blood urea nitrogen
GLM	General linear model
HCA	Hospital Corporation of America
ICD 10	The International Classification of Diseases, Tenth Revision
LOS	Length of stay
SD	Standard Deviation
SIRS	Systemic inflammatory response syndrome

Author Contributions

Shreyans Doshi: study concept and design, drafting manuscript
Hong Liang: acquisition of data; analysis and interpretation of data
Hale Toklu: study concept and design, acquisition of data, drafting of the manuscript
Selina Fritze: acquisition of data
Sue-Wei Luu: critical revision of the manuscript, study supervision

Conflicts of Interest

The authors declare they have no conflicts of interest.

Dr. Luu is an employee of North Florida Regional Medical Center, a hospital affiliated with the journal's publisher.

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