Efficacy of aggressive hydration with normal saline versus lactated Ringer’s solution for the prevention of post-ERCP pancreatitis in high-risk patients: a randomized controlled trial

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ABSTRACT
Background and study aims Post-ERCP pancreatitis (PEP) is a common adverse event in high-risk patients. Current intervention known to reduce the incidence and severity of PEP include pancreatic duct stent placement, nonsteroidal anti-inflammatory drugs per rectum, and intravenous (IV) fluids. We compared aggressive normal saline (NS) vs aggressive lactated Ringer’s (LR) infusion for the prevention of PEP in high-risk patients undergoing ERCP.

Patients and methods Patients were randomized to receive either an aggressive infusion of NS or LR. The infusion was started at a rate of 3 mL/kg/hr and continued throughout the ERCP procedure. A 20 mL/kg bolus was given at the end of the procedure, then continued at a rate of 3 mL/kg/hr.

Results A total of 136 patients were included in our analysis. The incidence of PEP was 4% (3/72 patients) in the LR group versus 11% (7/64 patients) in the NS group resulting in a relative risk (RR) of 0.38 (95% confidence interval [CI] 0.10 to 1.42; \( P = 0.19 \)). The relative risk reduction (RRR) was 0.62 (95% CI –0.41 to 0.90) along with an absolute risk reduction (ARR) of 0.07 (95% CI –0.025 to 0.17) and an number needed to treat of 15 (95% CI –41 to 6).

Conclusions To our knowledge, this is the first study comparing aggressive IV NS to aggressive IV LR in high-risk patients. The incidence of PEP was lower in the group receiving an aggressive LR infusion (4%) compared to NS infusion (11%). However, the difference was not statistically significant likely due to poor accrual thereby impacting the power of the study.

Introduction
Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used procedure to evaluate and/or treat biliopancreatic disorders. Some adverse events (AEs) that can occur during or after ERCP include: perforation, bleeding, cholecystitis, and pancreatitis. In some patients, post-ERCP pancreatitis (PEP) can become severe enough to necessitate Intensive Care Unit (ICU) monitoring or even result in death. The estimated incidence of PEP is approximately 8.8% in average-risk patients to...
14.1% in high-risk patients [1]. Factors which place patients at a high risk of PEP include both patient-related factors and procedure-related factors. Patient-related factors include: suspected sphincter of Oddi dysfunction, female gender, previous pancreatitis, previous PEP, younger age, non-dilated extrahepatic bile ducts, absence of chronic pancreatitis, and normal serum bilirubin. Procedure-related factors include duration and number of cannulation attempts, pancreatic duct (PD) guidewire passages >1, PD contrast injection, precut sphincterotomy, pancreatic sphincterotomy, biliary balloon dilatation, intraductal ultrasound, and failure to clear bile duct stones [2–5].

There has been significant headway in reducing the incidence and severity of PEP with multiple interventions, which includes PD stent placement, nonsteroidal anti-inflammatory drugs (NSAIDs) per rectum, and aggressive peri-procedure intravenous fluids [5–10]. Both the American College of Gastroenterology and American Society for Gastrointestinal Endoscopy endorse the use of these items to reduce the risk of severe PEP in high-risk patients [9, 10]. In addition, the European Society of Gastrointestinal Endoscopy have recently updated their guidelines in 2020 in which they recommend aggressive hydration with Lactated Ringer’s solution (LR) in patients with contraindication to NSAIDs, provided that they are not at risk of fluid overload and that a prophylactic PD stent is not placed [2].

A current topic of interest is understanding the optimal type and rate of peri-procedural intravenous hydration to prevent PEP. There are multiple studies and meta-analyses indicating that aggressive peri-procedural hydration, specifically LR, may significantly lower the incidence of PEP [11, 12]. In the majority of these studies, aggressive IV hydration with LR is compared to either standard IV hydration with LR or normal saline (NS). Talukdar et. al found that a higher mean volume of IV fluid (IVF) (752±783 mL vs 1012±725, P=0.036) and use of LR (OR, 0.56; 95% confidence intervals (CI) 0.31–0.99) was associated with a lower risk of PEP in a secondary analysis of an international multicenter PEP prevention trial in high-risk patients [13].

To date, there have only been two studies which evaluated the efficacy of aggressive NS when compared to aggressive LR for PEP prevention. In the first study, there were four patient groups, of which only two of the patient groups received both rectal indomethacin and 1L of either NS or LR within 30 minutes of their ERCP. Thirteen percent of the NS group and 6% of the LR group experienced PEP, which was not statistically significant and the number of patients in each arm was low [14]. A subsequent prospective randomized controlled trial (RCT) evaluated aggressive LR hydration vs aggressive NS hydration vs standard LR hydration. While there was a statistical difference in lowering PEP between the aggressive and standard groups, there was no difference in the PEP rates between the aggressive LR and aggressive NS groups. In addition, this study examined both average and high-risk patients who underwent ERCP [15].

To our knowledge, there has not been a study with a head-to-head comparison of PEP occurrence with aggressive NS infusion vs aggressive LR infusion for specifically high-risk patients whom all received rectal indomethacin. We performed the first RCT to compare aggressive NS infusion vs aggressive LR infusion for the prevention of PEP in high-risk patients all receiving rectal indomethacin and undergoing ERCP. A part of this manuscript was published as an abstract in the journal of Gastrointestinal Endoscopy [16].

**Methods**

**Study design**

A randomized, blinded, controlled trial was performed at a single tertiary care center (Tampa General Hospital) in the United States from June 2017 to June 2019. This study was in compliance with the Declaration of Helsinki and approved by our institution’s investigational review board (approved 7/2017). This trial was registered online at clinicaltrials.gov (NCT03215862) before enrollment of any patients. A data and safety monitoring board provided oversight.

**Patients**

All consecutive adult (>18 years of age) patients scheduled to undergo ERCP were screened for exclusion criteria. These criteria were: age less than 18, age greater than or equal to 75, inability to provide informed consent, pregnancy, acute pancreatitis, chronic pancreatitis, any contraindication to aggressive IVF hydration [evidence of clinical volume overload (peripheral or pulmonary edema)], respiratory compromise (oxygen saturation <90% on room air), chronic kidney disease (creatinine clearance <40 mL/min), systolic congestive heart failure (ejection fraction <45%), cirrhosis, severe electrolyte disturbance with sodium <130 mEq/L or >150 mEq/L, cholangitis, and/or a true NSAID allergy.

Patients who did not meet the exclusion criteria were consented for the study. Patients were eligible to be randomized to either NS or LR group if they met one major or two minor validated patient or procedural risk factors for developing PEP. Major criteria include: sphincter of Oddi dysfunction, personal history of PEP, total bilirubin less than 1.0, more than eight cannulation attempts or more than 10 minutes, precut sphincterotomy, endoscopic papillary balloon dilation of an intact sphincter, pancreatic sphincterotomy, and ampullectomy. Similarly, possession of two or more of the following minor criteria: female sex, age under 50 years, personal history of recurrent acute pancreatitis, PD injection leading to “acinarization” or over three PD injections, or PD guidewire insertion twice or more [4,9]. These inclusion factors are associated with high risk for PEP [2,5].

**Intervention**

Once written informed consent was obtained, patients were randomized in a 1:1 ratio to receive either NS infusion or LR infusion. Each ERCP procedure was performed by 1 of 3 therapeutic endoscopists who perform>200 ERCPs per year. Postgraduate year-6 and postgraduate year-7 gastroenterology fellows were involved in all cases and were allowed up to seven attempts at cannulation. All patients that were eligible for randomization and that received pre-procedural fluids were given 100 mg rectal indomethacin just prior to start of ERCP proce-
dure. Prophylactic PD stents were placed if the PD was cannulated twice or more, and/or at the discretion of the endoscopist.

**Administration of intravenous fluid**

The IVF infusion was initiated by nurses in the pre-procedure area prior to the procedure. The infusion was started at a rate of 3mL/kg/h, and this was continued throughout the procedure. A 20mL/kg bolus was then given at the end of the procedure. After this bolus was complete, the infusion was continued at a rate of 3mL/kg/h. If the patient remained hospitalized, the post-procedure infusion was continued for 8 hours [17,18]. The maximum rate of the intravenous fluids was set at 500mL/h. If the patient was discharged home after the procedure, then the infusion was only continued for the duration that the patient remained in our post-procedure area. In our institution, these patients are monitored for 45–60 minutes based on alertness, vital signs, and appropriate verbal response before being discharged home.

**Outcomes**

The primary study outcome was the occurrence of PEP. This was defined by: (1) new or worsening abdominal pain that is clinically consistent with acute pancreatitis, combined with (2) associated pancreatic enzymes elevation ≥3 times the upper limit of normal 24 hours after the procedure, and (3) resultant or prolongation of existing hospitalization of ≥2 nights [2]. Secondary study outcomes included: severe acute pancreatitis (persistent organ failure ≥48 hours), localized AEs (pseudocyst formation or walled off pancreatic necrosis), and death. Other recorded events were AEs related to IVF: peripheral/pulmonary edema and hypoxia. Also recorded were AEs related to NSAIDs: anaphylaxis, gastrointestinal bleeding, and acute kidney injury.

Inpatient participants were all seen and examined within 24 hours following the procedure and asked/evaluated for new abdominal pain, shortness of breath, chest pain, and/or extremity swelling. Outpatient participants were called by one investigator (RP) on the phone within 72 hours after the procedure. Patients were asked if they experienced any new abdominal pain, new shortness of breath, extremity swelling, or chest pain.

**Sample size**

It was estimated that a total of 242 subjects would have been required to detect a difference in PEP rates of 0.16 in the NS group versus 0.05 in the LR group assuming a medium effect size with 80% power using Fisher’s exact test.

**Methods to reduce bias**

The randomization sequence was generated using a computer. Randomization was performed as block randomization in random block sizes in a 1:1 allocation ratio using sealed envelopes. Patients, nurses, endoscopists, outcome assessors and data analysts were blinded to the treatment assignment. Both types of intravenous fluids (LR and NS) were available in the pre-procedural area. The pre-op nurse covered the intravenous fluid bag with a dark opaque bag which obscured the name/type of fluid from vision. The endoscopists, investigators, and patients were therefore not aware of the allocation.

**Statistical analysis**

Patient and demographic characteristics were summarized as mean and standard deviation for continuous variables and as rates for categorical variables. All analyses were performed following the intent-to-treat principle for benefits. The difference in primary outcomes across compared groups was assessed using a Fisher’s exact test and summarized as relative risk (RR) along with 95% CI. Additional measures of relative (RRR), absolute risk reduction (ARR) and number needed to treat (NNT) along with 95% CI was also calculated. The statistical significance was set at 5% for all comparisons. The adjusted and unadjusted difference in primary outcomes was assessed using the binary logistic regression. All analyses were performed using the IBM SPSS version 25 statistical analysis package.

**Results**

**Patients**

A total of 763 subjects were screened (Fig. 1). Of these, 596 met exclusion criteria. The remaining 167 patients were enrolled and provided written informed consent. Six of these patients did not show up after consent was obtained and were not able to be reached via telephone despite multiple attempts. One hundred sixty-one patients underwent randomization to either LR or NS and all received rectal nonsteroidal anti-inflammatory drugs (NSAIDS). After the procedure, another 25 patients were excluded as they did not meet patient or procedural risk factors that were high-risk for developing PEP. Thus, a total of 136 patients were included in the final data analysis. Baseline characteristics of the 136 included patients were similar across the two randomized groups (Table 1). The mean age was 51.9 years in the LR group and 51.8 years in the NS group (P=0.97). There were a similar percentage of females and males enrolled in the LR (64% and 36%, respectively) and NS groups (61% and 39%, P=0.72). Both the major criteria and minor criteria of risk factors for developing PEP were similar between the two groups. The distribution of PD stent placement between LR and NS groups was 21 (29%) and 13 (20%), respectively. Finally, there were 43 (50.5%) ambulatory cases in the LR group, and 41 (53.9%) in the NS group.

**Outcomes**

As highlighted in Table 2, the incidence of PEP was 4% (3/72 patients) in the LR group versus 11% (7/64 patients) in the NS group resulting in a RR of 0.38 (95% CI 0.10 to 1.42; P=0.19). The relative risk reduction (ARR) was 0.62 (95% CI –0.41 to 0.90) along with an ARR of 0.07 (95% CI –0.025 to 0.17) and an NNT of 15 (95% CI –41 to 6). Given the difference in PD stent placement between groups, we performed a multivariate analysis which showed that PD stent did not have an impact on the rate of pancreatitis (RR adjusted 0.34, 95% CI (0.08–1.26); P=0.11).

Regarding secondary outcomes (Table 3), there was one case of pancreatitis leading to pseudocyst formation in the NS group. Otherwise, there were no cases of severe pancreatitis, walled off pancreatic necrosis, death, events related to IVF infu-
sion, or events related to NSAID use. There were reports of procedural related events: two cases of bacteremia in the NS group, one case of fever/sepsis in each group, one case in the LR group of post-sphincterotomy bleed, and three cases in the LR group and two cases in the NS group of post-procedural abdominal discomfort leading to admission to the hospital for observation.

**Table 4** gives a breakdown of the risk factors of each patient with PEP. Each PEP patient had at least three risk factors (minor or major). The most common risk factors were bilirubin < 1, more than eight cannulation attempts, or more than 10 minutes spent cannulating, female gender, PD injection, and PD wire insertion × 2.

**Discussion**

The topic of our research study is the optimal type of intravenous hydration peri-procedure to prevent PEP in patients who are at high risk of PEP. To date, there has not been a study on prevention of PEP with a head-to-head comparison of aggressive IV NS compared to aggressive IV LR for specifically high-risk patients who all received rectal indomethacin. We think it is important to specifically examine patients at a high risk of PEP who are all receiving rectal indomethacin, since this group can benefit the most from establishing the optimal way to administer IVF. With this in mind, we performed a RCT to assess aggressive LR infusion compared to aggressive NS infusion for the prevention of PEP in high-risk patients undergoing ERCP. Overall, the incidence of PEP was lower in the group receiving an aggressive LR infusion (4%) compared to NS infusion (11%), with a RRR of 62%, an ARR of 7% and NNT of 15. However, the...
Moderate- to high-risk patients all receiving prophylactic rectal NSAIDs. They included 826 patients receiving prophylactic rectal NSAIDs assessed the value of aggressive hydration in patients receiving prophylactic rectal NSAIDs. A large, multicenter, RCT such as the FLUYT trial may overpower our efforts to determine the efficacy of aggressive hydration. Nonetheless, our study shows that there is no statistical difference between the two forms of aggressive hydration, which is congruent with their findings. In addition, while the aforementioned trial compares aggressive LR to maintenance NS, it does not evaluate the role of aggressive NS infusion and its comparison to aggressive LR infusion, which is unique to our study. Aggressive NS (as opposed to maintenance NS) was used in our study to equalize the effect of aggressive hydration between both groups, and thus create a more direct comparison between LR and NS.

There were several strengths of this study. First, the study design of an RCT reduces the risks of known and unknown biases that can potentially confound results. This is the first study to compare aggressive LR hydration with aggressive NS hydration in specifically high-risk patients for PEP. The endoscopists were blinded to which fluid was given, limiting any bias on their part. However, there are few limitations as well. A key limitation of the study is unexpected poor accrual of patients. We planned for 242 patients with expected rates of pancreatitis being 5% in the lactated Ringer’s arm versus 16% in the NS arm. However, the enrollment was stopped at 136 patients within the given timeframe of the study (2 years). The poor accrual can be attributed to several factors including the limited timeframe of fellowship training, as this study was led by a trainee in a 3-year fellowship program, and lack of resources including personnel etc. However, these findings are important to inform power calculations for future studies to provide reliable answers. For example, based on the estimates from previous studies we powered the study for an absolute difference of 11% for the rate of pancreatitis which was higher than the observed rate of 7% resulting in post hoc power of 35% versus the planned rate of 80% at a significance level of 5%. Nevertheless, this is one of the largest RCTs on this issue. We have also considered patient allocation after randomization as a limitation of our study. Due to the nature of the study in capturing only high-risk patients, we had to exclude patient’s that did not meet procedural criteria for high-risk after randomization. Some high-risk factors for PEP cannot be determined until after the ERCP is complete, and thus, those patients that did not meet procedural criteria for PEP had to be excluded after randomization. However, the number of patients who were excluded was similar between groups. Another possible limitation is the study being performed at a single institution and all procedures performed under the supervision of three endoscopists. The single institution participation and limited number of endoscopists may be associated with reduced practice variation. This same issue possibly limits the generalizability of these findings. However, these findings provide real-world evidence of the efficacy of LR versus NS for the prevention of PEP.

### Table 2 Primary outcome: occurrence of PEP.

<table>
<thead>
<tr>
<th>Lactated Ringer’s (n = 72)</th>
<th>Normal saline (n = 64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP cases</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>4.2%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Outpatient PEP cases</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>(discharged home)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient PEP cases</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(returned to hospital floor)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEP, post-ERCP pancreatitis.

### Table 3 Secondary outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Lactated Ringer’s</th>
<th>Normal saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute pancreatitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pseudocyst formation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Peripancreatic abscess formation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Walled off pancreatic necrosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reported events related to intravenous fluid infusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reported events related to NSAID use</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Presented within 2 days with bacteremia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Presented within 2 days with fever/sepsis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sphincterotomy bleed requiring repeat EGD</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Outpatient admitted to hospital after ERCP due to post-procedural abdominal discomfort</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography.
Conclusions

In conclusion, there is insufficient evidence to support the use of aggressive LR infusion over aggressive NS peri-procedure in patients receiving rectal NSAIDs and known to be at high risk for PEP.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

ClinicalTrials.gov  NCT0321586
TRIAL REGISTRATION: Randomized blinded controlled trial at http://www.clinicaltrials.gov/

References


Table 4. Risk factors for PEP present in each of 10 patients who experienced PEP, as well as the type of IVF they received.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fluid received</td>
<td>NS</td>
<td>LR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>LR</td>
<td>NS</td>
<td>LR</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Prophylactic PD stent placed</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>SOD dysfunction suspicion</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Personal history of PEP</td>
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<tr>
<td>Bilirubin &lt; 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>More than 8 cannulation attempts OR more than 10 minutes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Precut sphincterotomy</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Balloon dilation of intact sphincter</td>
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<tr>
<td>PD sphincterotomy</td>
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<tr>
<td>Ampullectomy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Female</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Age &lt; 50</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Personal history of recurrent acute pancreatitis</td>
<td>X</td>
<td>X</td>
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<td>PD injection</td>
<td>X</td>
<td>X</td>
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<tr>
<td>PD cannulation with wire × 2</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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