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PANCREAS, BILIARY TRACT, AND LIVER

Vigorous Periprocedural Hydration With Lactated Ringer's Solution Reduces the Risk of Pancreatitis After Retrograde Cholangiopancreatography in Hospitalized Patients

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BACKGROUND & AIMS: **Vigorous intravenous fluid resuscitation (IVFR) was reported to reduce post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in a pilot study. We performed a randomized, double-blind controlled trial to establish whether periprocedural vigorous IVFR reduces the risk of post-ERCP pancreatitis.**

METHODS: **A total of 510 patients with native papilla at 3 tertiary referral centers in Korea were randomly assigned (1:1) to groups given vigorous IVFR (lactated Ringer's solution in an initial bolus of 10 mL/kg before the procedure, 3 mL/kg/h during the procedure, for 8 hours after the procedure, and a post-procedure bolus of 10 mL/kg) or a standard IVFR (lactated Ringer's solution at 1.5 mL/kg/h during and for 8 hours after the procedure). The primary end point of the study was the development of post-ERCP pancreatitis, and the secondary end point was severity of pancreatitis, hyperamylasemia, and fluid overload.**

RESULTS: **The main indications for ERCP were choledocholithiasis (58%) and malignant biliary stricture (27%). Post-ERCP pancreatitis developed in 11 patients in the vigorous IVFR group (4.3%) and 25 patients in the standard IVFR group (9.8%) (relative risk, 0.41; 95% CI, 0.20–0.86; $P = .016$). Moderate or severe acute pancreatitis occurred in a significantly smaller proportion of patients in the vigorous IVFR group (0.4%) than in the standard IVFR group (2.0%; $P = .040$). One patient in the vigorous IVFR group developed peripheral edema.**

CONCLUSIONS: **In a double-blind, randomized controlled trial, we found vigorous periprocedural intravenous hydration with lactated Ringer's solution to reduce the incidence and severity of post-ERCP pancreatitis in average-risk and high-risk cases. IVFR is not associated with increased adverse events. ClinicalTrials.gov number: NCT02308891.**

Keywords: Clinical Trial; Pancreas; Inflammation; Prevention; Complication.

See editorial on page 93.

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure performed in more than 500,000 patients in the United States annually.[1] Pancreatitis remains the most common serious complication of ERCP, with an incidence rate ranging from 8.8% in average-risk to 14.1% in high-risk patients.[2]

Because of the risk of post-ERCP pancreatitis, procedural techniques and pharmacologic interventions have both been studied in an effort to reduce the incidence of post-ERCP pancreatitis. Prophylactic pancreatic stent placement has been shown to reduce the odds of developing post-ERCP pancreatitis in high-risk patients.[3,4] However, in some cases, the ductal anatomy may render deep cannulation of a guidewire and placement of a stent difficult. The consequences of failed pancreatic stent placement after multiple attempts are not desirable, because the risk of post-ERCP pancreatitis then becomes substantially higher.[5] As such, pharmacologic prophylaxis has the benefit of being noninvasive

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Abbreviations used in this paper: ERCP, endoscopic retrograde cholangiopancreatography; IVFR, intravenous fluid resuscitation; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RR, relative risk; SOD, sphincter of Oddi dysfunction.

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and offers a potentially inexpensive and nontoxic approach to preventing post-ERCP pancreatitis. Although several pharmacologic agents have been proposed, the only agents that have been shown to reduce the risk of post-ERCP pancreatitis in high-risk patients are nonsteroidal anti-inflammatory drugs (NSAIDs) per rectum.[6] Three meta-analyses of rectal NSAIDs support their efficacy in post-ERCP pancreatitis prevention, and they are recommended by the European Society of Gastrointestinal Endoscopy.[7–9] Currently, universal prophylaxis by using rectal indomethacin for post-ERCP pancreatitis is controversial.[10,11]

Recently, Buxbaum et al[12] performed a pilot study advocating the use of intravenous fluid resuscitation (IVFR) as an intervention to prevent pancreatitis after ERCP. The purpose of IVFR is to perfuse the pancreatic microcirculation adequately, so that pancreatitis and its subsequent complications can be minimized or even prevented. However, because of the small sample size and the relatively high rate of pancreatitis in the control group, the study is at risk for type 1 errors, and larger clinical trials are needed to validate the observations.[12] Therefore, we conducted a multicenter, randomized controlled clinical trial to evaluate the efficacy of vigorous periprocedural hydration for the prevention of post-ERCP pancreatitis in average-risk cases.

Methods

Study Design

This multicenter, randomized controlled trial was performed between November 2014 and October 2015 at 3 tertiary referral centers in Korea, each performing more than 500 ERCPs per year; endoscopy trainees were not involved in the study period. The study was approved by the institutional review board of each institution, and written informed consent was obtained from all study patients. An independent data and safety monitoring board consisting of 2 specialists provided regulatory oversight by reviewing the subject data. This trial was registered with ClinicalTrials.gov (NCT 02308891). All authors had access to the study data and had reviewed and approved the final manuscript.

Patients

All patients undergoing their first ERCP and meeting eligibility criteria were invited to participate in the study. Exclusion criteria included (1) age younger than 18 years or older than 75 years, (2) inability to provide informed consent, (3) anticipated low risk of post-ERCP pancreatitis (chronic calcific pancreatitis), (4) concomitant acute pancreatitis, and (5) prior Billroth II surgery or Roux-en-Y reconstruction. Patients older than the age of 75 were excluded because older patients have higher risk of undiagnosed comorbidities that might increase the risk of vigorous hydration. Patients were also excluded if they met any of the following criteria: known history of severe cardiovascular, hepatic, renal, or respiratory disease or electrolyte disturbances defined as (1) greater than New York Heart Association class II heart failure, (2) recent myocardial ischemia within 3 months, (3) history of cirrhosis, (4) renal insufficiency with creatinine clearance <40 mL/min, (5) chronic obstructive pulmonary disease with requirement for home oxygen, or (6) hypernatremia (serum sodium >150 mEq/L) or hyponatremia (serum sodium <130 mEq/L).

Randomization

All potentially eligible patients were required to be screened and enrolled within 6 hours of initial presentation to be randomized. After providing informed consent, eligible subjects were randomly assigned in a 1:1 ratio to receive either a vigorous or standard hydration regimen by using concealed computer-generated block randomization with a balanced number in each group. The endoscopists, investigators, and patients were blinded to the randomization allocation. The independent physicians who were not involved in the trial (non-study staff) determined the rate of fluid administration. No patients were lost to follow-up (Supplementary Figure 1).

Endoscopic Retrograde Cholangiopancreatography Procedure

The patients were placed under conscious sedation with intravenous pethidine and midazolam and/or propofol. All of the patients underwent ERCP on admission. Biliary cannulation was first attempted with a conventional cannula (ERCP cannula; Boston Scientific, Athens, Greece) and a guidewire. Contrast medium was injected only when selective deep cannulation was expected to be in the direction of the common bile duct. If the endoscopist failed after 5 minutes, a pull-type sphincterotome was used for an additional 5 minutes with a guidewire. A precut papillotomy was attempted as a rescue method if the wire-guided cannulation by using a pull-type sphincterotome failed. The use and type of pancreatic duct stents were at the discretion of the treating endoscopist.

Intervention

Consecutive patients with a native papilla undergoing therapeutic ERCP at 3 tertiary referral centers were randomized in a 1:1 ratio to receive a vigorous IVFR (lactated Ringer's solution in an initial bolus of 10 mL/kg before procedure, 3 mL/kg/h during and for 8 hours after procedure, and a post-procedure bolus of 10 mL/kg) or a standard IVFR (lactated Ringer's solution at a rate of 1.5 mL/kg/h during and for 8 hours after the procedure). After the examination, the patient did not

eat, and serum amylase and lipase levels were measured before and at 8 and 24 hours after the examination. If the 8-hour serum amylase or lipase level was more than 3 times the upper normal limit and the patient developed abdominal pain, then the patient was kept fasting and received a continuous infusion of 3 mL/kg/h. Patients in the vigorous IVFR arm who exhibited no abdominal pain at 8 hours had their fluids decreased to 1.5 mL/kg/h, and diet was allowed.

Study Outcomes and Definition

The primary outcome of the study was the occurrence of post-ERCP pancreatitis. Post-ERCP pancreatitis was diagnosed on the second day of hospitalization when there was a new onset of epigastric pain, an increase in pancreatic enzymes of at least 3 times the upper limit of the normal range within 24 hours after ERCP, and hospitalization for at least 2 nights.[6,7] Severity of pancreatitis was defined according to the revised Atlanta classification.[13]

Secondary outcomes were the incidence of post-ERCP hyperamylasemia, the development of moderate or severe pancreatitis, and fluid overload. Patients were monitored for signs and symptoms of fluid overload every 8 hours during the first 24 hours, such as peripheral edema, neck vein distention, weight gain, and pulmonary crackles. Data regarding the length of hospital stay for patients with post-ERCP pancreatitis were prospectively collected. Patients were followed up at 30 days to assess for late adverse events and to determine the severity of post-ERCP pancreatitis.

The following conditions were considered to represent a high risk for post-ERCP pancreatitis[7,14]: <50 years of age and female sex; a history of recurrent pancreatitis; clinical suspicion of sphincter of Oddi dysfunction (SOD), normal bilirubin ($\leq$1 mg/dL); pancreatic sphincterotomy; pancreatic duct injection; instrumentation of the pancreatic duct (eg, brush cytology); precut sphincterotomy; pneumatic dilation of an intact biliary sphincter; ampullectomy; or difficult cannulation (the presence of any of the following variables: duration of cannulation attempts >5 minutes, more than 5 attempts, or more than 2 pancreatic guidewire passages).[7]

Safety Evaluation

All patient beds were elevated at a 30° angle during the hydration protocol to decrease the likelihood of pulmonary sequestration. All checkpoints included a clinical assessment for signs of volume overload (ie, tachypnea, abnormal breath and heart sounds, and enlarged neck veins). Other post-ERCP adverse events in addition to pancreatitis, including bleeding, perforation, and cholangitis, were recorded. If a patient developed signs of volume overload, the physicians halted their fluids, and the patient was managed at the discretion of the treating physicians. Adverse events were reported to the institutional review board and data and safety monitoring board.

Sample Size Calculation

On the basis of the incidence rates of post-ERCP pancreatitis reported in the literature,[14–16] we assumed a 7.7% incidence rate of pancreatitis in the standard IVFR group and a reduction to 2.5% in the vigorous IVFR group (relative reduction of 67.5%). Therefore, by using a two-tailed test and with alpha and beta values of 0.05 and 0.2, respectively, we estimated that 255 patients would be required per group.

Statistical Analysis

Continuous variables were described as mean and standard deviation and were compared by using the Student *t* test or Mann-Whitney test, when appropriate. Categorical variables were described as numbers and percentages, and differences between groups were tested for significance by using the χ^2 (or Fisher exact) test.

Logistic regression analysis was used to control confounding variables and to estimate the odds ratio (OR) associated with each variable for development of pancreatitis. All variables with $P < .1$ in the univariate analysis were selected for the final mode. Treatment effect was calculated by relative risk (RR) reduction, absolute risk reduction, and number needed to treat, which were computed with corresponding 95% CI. A P value <.05 was considered significant in all tests. Statistical analyses were performed by using SPSS software, version 17 (SPSS Inc, Chicago, IL).

Results

Patients

During the study period, a total of 1512 patients were assessed for eligibility, and 1002 patients were excluded from the study because of previous biliary sphincterotomy (n = 632), acute pancreatitis (n = 97), advanced age (n = 91), comorbidities (n = 71), declined participation (n = 65), prior Billroth II surgery or Roux-en-Y reconstruction (n = 32), and other reasons (n = 14) (Supplementary Figure 1). Ultimately, 510 patients were randomized to each treatment arm and included in the analysis; 255 patients received the aggressive hydration regimen, and 255 patients received the standard hydration regimen. The 2 groups were comparable in terms of age, sex, indications for therapeutic ERCP, and risk factors for post-ERCP pancreatitis (Table 1 and Supplementary Table 1). The main indications for therapeutic ERCP were choledocholithiasis (57.3%) and malignancies (27.5%).

Table 1. Demographic and Baseline Characteristics of Patients

	All patients	Vigorous hydration (n = 255)	Standard hydration (n = 255)
Age, *y*, mean (SD)	57.6 (12.1)	57.0 (11.9)	58.2 (12.4)
Female sex, n (%)	232 (45.5)	115 (45.1)	117 (45.9)
Body mass index, kg/m^2, mean (SD)	22.1 (1.9)	22.0 (1.8)	22.1 (1.9)
Hematocrit, %, mean (SD)	36.1 (2.9)	36.5 (3.0)	35.5 (2.9)
Creatinine, *mg/dL*, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)
Primary indication			
Choledocholithiasis	292 (57.3)	155 (60.8)	137 (53.7)
Malignancies	140 (27.5)	64 (25.1)	76 (29.8)
Benign strictures	52 (10.2)	23 (9)	29 (11.4)
Others	26 (5.1)	13 (5.1)	13 (5.1)

NOTE. *P* values for comparison were not significant.
SD, standard deviation.

Primary and Secondary Outcomes

The volume of fluid administered during the initial 8-hour period was 2744 ± 364 mL and 741 ± 63 mL ($P < .001$) in the vigorous IVFR and standard IVFR groups, respectively.

Post-ERCP pancreatitis occurred in 36 of 510 patients (7.1%). This study did not find a statistically significant difference in the rate of post-ERCP pancreatitis between endoscopists ($P = .734$). The primary outcome of post-ERCP pancreatitis was significantly lower in the vigorous hydration group (4.3%, 11 of 255) than in the standard group (9.8%, 25 of 255) ($P = .016$; RR, 0.41; 95% CI, 0.2–0.86) (Figure 1). On the basis of our data, 18 patients need to be treated with aggressive hydration to prevent 1 case of post-ERCP pancreatitis. Among patients with post-ERCP pancreatitis, the median length of hospital stay was 1 day shorter in the vigorous IVFR group than in the standard IVFR group (4 vs 5 days, $P = .039$).

All 36 patients with post-ERCP pancreatitis completed the 30-day follow-up necessary to determine the severity of pancreatitis. Moderate or severe post-ERCP pancreatitis occurred in 6 patients, one (0.4%) in the vigorous IVFR group and five (2.0%) in the standard IVFR group ($P = .040$) (Figure 1). Hyperamylasemia was also observed less frequently in the vigorous IVFR group (6.7%) than in the standard IVFR group (16.1%) ($P = .001$).

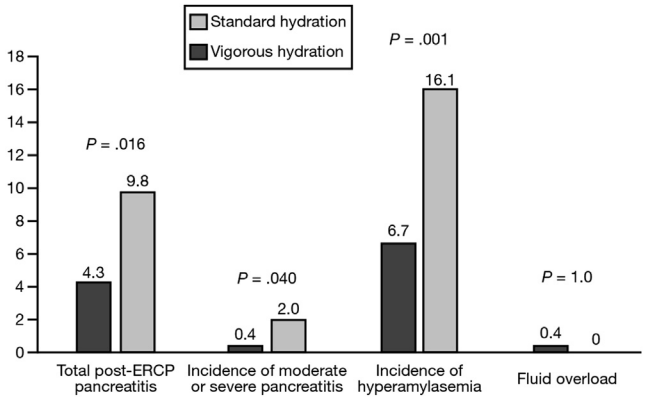

Figure 1. Impact of hydration strategy on clinical outcomes.

Adverse Events

The rate of total adverse events was 1.2% (6 of 510) (3 in the standard hydration group and 3 in the vigorous hydration group, with no significant difference between groups). Sphincterotomy site bleeding occurred in 4 patients (2 from each group), and all patients recovered with endoscopic hemostasis. No perforation or death occurred during the study. One patient in the vigorous IVFR group developed peripheral edema; the symptoms resolved spontaneously within 24 hours after withdrawal of fluid.

Subgroup Analyses

Table 2 shows the significant risk factors for developing post-ERCP pancreatitis on univariate and multivariate analysis: difficult cannulation (OR, 3.9; 95% CI, 1.7–8.6; $P = .001$), pneumatic dilation of an intact biliary sphincter (OR, 3.9; 95% CI, 1.5–9.9; $P = .003$), and non-use of vigorous hydration (OR, 2.4; 95% CI, 1.1–5.0; $P = .016$).

Vigorous hydration was also protective in patients at high risk for post-ERCP pancreatitis (8.7%, 8 of 92 in the vigorous IVFR group and 25.0%, 20 of 80 in the standard IVFR group; $P = .004$; RR, 0.28; 95% CI, 0.12–0.69; $P = .004$).

Discussion

The findings of this randomized controlled trial show that vigorous periprocedural IVFR with lactated Ringer's solution significantly reduced the incidence and severity of post-ERCP pancreatitis. The number of ERCP patients who needed to be treated to prevent 1 episode of pancreatitis was 18. The use of vigorous hydration might also be effective for preventing pancreatitis in high-risk patients.

Freeman et al[1,17] reported that the risk factors for post-ERCP pancreatitis were both patient-related factors (ie, female sex, young age, suspected SOD) and procedure-related factors (ie, difficult cannulation, pancreatic duct injection, and precut sphincterotomy). In the present study, the multivariate analyses of independent risk factors for post-ERCP pancreatitis demonstrated statistical association with cannulation difficulty (OR, 3.9; 95% CI, 1.7–8.6), dilation of an intact biliary sphincter (OR, 3.9; 95% CI, 1.5–9.9), and non-use of vigorous hydration (OR, 2.4; 95% CI, 1.1–5.2). The frequency of some known risk

Table 2. Univariate and Multivariate Analysis of Risk Factors for Post-ERCP Pancreatitis

	Pancreatitis (n = 36)	No pancreatitis (n = 474)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female sex and younger than 50 y	2 (5.6)	24 (5.1)	1.1 (0.2–4.8)	.704		
Suspected SOD	1 (2.8)	7 (1.5)	1.9 (0.2–15.9)	.446		
Normal bilirubin (≤1 mg/dL)	4 (11.1)	33 (7.0)	1.7 (0.5–5.0)	.319		
History of recurrent pancreatitis	0 (0)	6 (1.3)	0.98 (0.9–0.99)	.497		
Difficult cannulation, n (%)	17 (47.2)	79 (16.7)	4.4 (2.2–8.9)	<.001	3.9 (1.7–8.6)	.001
Precut sphincterotomy, n (%)	5 (13.9)	31 (6.5)	2.3 (0.8–6.3)	.164		
Pancreatic injection, n (%)	6 (16.7)	10 (2.1)	9.2 (3.1–27.2)	<.001	3.3 (0.9–11.7)	.063
Pancreatic sphincterotomy, n (%)	2 (5.6)	15 (3.2)	1.8 (0.4–8.1)	.341		
Instrumentation of pancreatic duct, n (%)	1 (2.8)	6 (1.3)	2.2 (0.3–19.0)	.485		
Pneumatic dilation of intact biliary sphincter, n (%)	9 (25.7)	35 (7.4)	4.3 (1.8–9.9)	.002	3.9 (1.5–9.9)	.003
Ampullectomy, n (%)	1 (2.8)	8 (1.7)	1.6 (0.2–13.6)	.485		
Placement of pancreatic stent, n (%)	5 (13.9)	69 (14.6)		.913		
Absence of vigorous hydration, n (%)	25 (69.4)	230 (48.5)	2.4 (1.1–5.0)	.016	2.4 (1.1–5.2)	.024

factors evaluated was too low to reveal statistical significance.

Although early vigorous hydration is advocated for treatment of acute pancreatitis, there is no direct evidence suggesting that it is superior to less vigorous or standard fluid resuscitation.[18–21] Most previous studies that reported beneficial as well as adverse outcomes by using aggressive hydration are limited by their retrospective study design and suffer from reverse causation bias.[18–21] The rationale for hydration is based on the need to resolve the hypovolemia.[19] Compared with other crystalloid preparations, IVFR with lactated Ringer's solution may promote a more favorable acid-base balance and may stimulate an anti-inflammatory response.[22–24] The beneficial effect of IVFR can be maximized during the first 24 hours of acute pancreatitis, when proinflammatory cytokines are thought to induce numerous physiological changes that lead to pancreatic hypoperfusion.[22,23] In addition, most patients undergoing ERCP are in a fasting state for a minimum of 8–12 hours before the procedure because of their illness or according to instructions, and thus, relative volume depletion may influence their susceptibility to post-procedure pancreatitis. A vigorous periprocedural hydration strategy would be an effective intervention for preventing pancreatitis because an at-risk population is identifiable before the onset of acute pancreatitis. In addition, IVFR provides the rare opportunity to initiate adequate hydration at the time of the initial insult, thereby possibly reducing the severity of pancreatitis.

Several prophylactic interventions have proven to be effective in minimizing the risk of post-ERCP pancreatitis, including pancreatic stent placement and rectal NSAIDs.[6,7,25] In the present study, pancreatic stents were used in 14.5% of all patients. The placement of the pancreatic stent was not associated with a reduced incidence of pancreatitis in our study. This finding could be explained by the fact that pancreatic stent placement was usually attempted in patients considered at high risk for developing post-ERCP pancreatitis. The administration of rectal NSAIDs has shown promise in reducing the risk of post-ERCP pancreatitis.[2,6] However, NSAID suppositories are not readily available in some countries including Korea. Combinations of these prophylactic interventions, which act on different steps in the pathogenesis of pancreatitis, might complement one another by working in completely different ways. Further clinical trials should be designed to explore the potentially favorable interaction of vigorous hydration with NSAIDs or pancreatic stent placement.

Several studies have raised concerns regarding the safety of aggressive hydration. A recent study conducted in China reported that in patients with severe acute pancreatitis, rapid hemodilution is associated with increased sepsis and mortality.[26] In the current study, we found that most patients in the vigorous hydration group were hydrated safely, with a mean volume of 2744 mL during the first 8-hour period. One patient in the vigorous hydration group developed peripheral edema, which was managed conservatively. No major adverse events such as hypoxemia and pulmonary edema were detected in our study. Patients with risk factors for volume overload were excluded from our study, which might explain the lower rate of adverse events. Combined with careful patient selection and ongoing monitoring, vigorous IVFR may help reduce the risk of post-ERCP pancreatitis without increasing the rate of adverse events.

Because the revised Atlanta classification is the most up-to-date definition for severe acute pancreatitis, we defined severity of post-ERCP pancreatitis by using the revised Atlanta classification and not the consensus definition.[13,27] The consensus definition of severity stratification emphasizes the length of inpatient hospitalization.[27] The distribution of moderate-severe post-ERCP pancreatitis remains the same with statistical significance if the consensus definition for severity had been used.

There was no trainee involvement in the present study, and it might have impacted the results. In a pilot study by Buxbaum et al,[12] trainees were involved in all cases. These patients were thus much more likely to fulfill the high-risk criterion in this study in which aggressive IVFR decreased the risk of pancreatitis from 25% to 8.7% in patients at high risk for post-ERCP pancreatitis.

There are several limitations to the current study. We used stringent exclusion criteria to enroll patients in whom we believed vigorous hydration could be safely implemented. Use of these strict inclusion criteria resulted in the exclusion of patients with major comorbidities. Strict eligibility criteria may limit the external validity of this clinical trial, but physicians should be able to select similar patients for intervention in clinical practice. Another limitation is that the incremental benefit of intravenous hydration in addition to the combination of rectal NSAIDs was not elucidated because NSAID suppositories are not yet available in our country. Dosing of fluid in obese patients is more complicated and will require further study; it likely should be based on ideal rather than actual body weight.

If there are no contraindications for fluid administration, vigorous periprocedural hydration seems to be safe and effective in reducing the incidence and severity of post-ERCP pancreatitis in both average-risk and high-risk patients. Although the prophylactic intervention requires continuous infusion for 8 hours, it is easily applicable when hospital admission is scheduled for the same day as the procedure. Additional confirmatory studies will be necessary to support our conclusions and to assess the optimal protocol and volume of IVFR.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.06.007.

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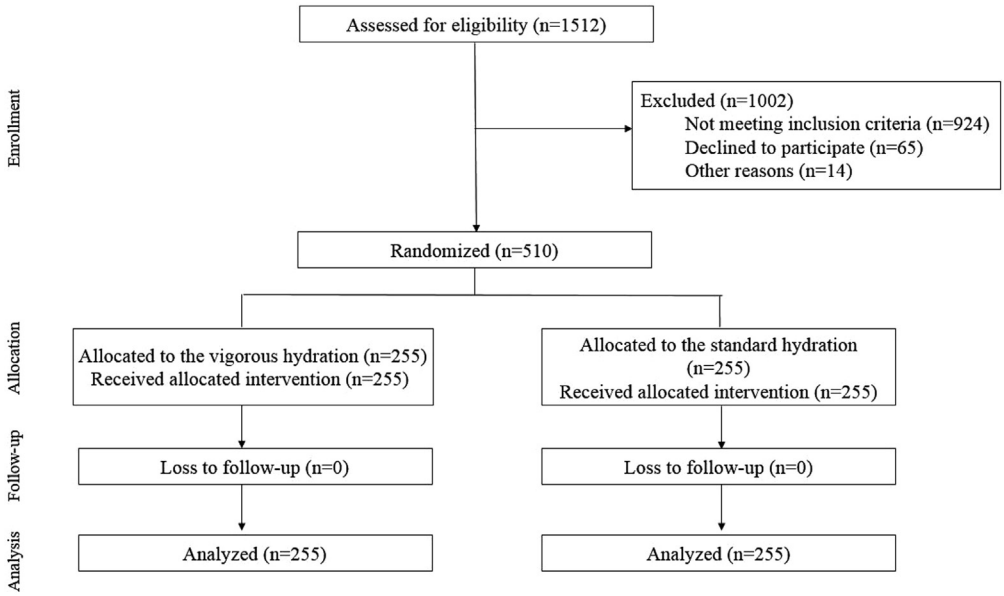
Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Risk Factors for Post-ERCP Pancreatitis

	All patients	Vigorous hydration (n = 255)	Standard hydration (n = 255)
Any risk factor for pancreatitis	172 (33.7)	92 (36.1)	80 (31.4)
Female sex and younger than 50 y	25 (4.9)	12 (4.7)	13 (5.1)
Suspected SOD	8 (1.6)	5 (2.0)	3 (1.2)
Normal bilirubin (≤1 mg/dL)	37 (7.3)	16 (6.3)	21 (8.2)
History of recurrent pancreatitis	6 (1.2)	4 (1.6)	2 (0.8)
Difficult cannulation, n (%)	96 (18.8)	51 (20.0)	45 (17.6)
Precut sphincterotomy, n (%)	35 (6.9)	21 (8.2)	14 (5.5)
Pancreatic injection, n (%)	16 (3.1)	6 (2.4)	10 (3.9)
Pancreatic sphincterotomy, n (%)	17 (3.3)	9 (3.5)	8 (3.1)
Instrumentation of pancreatic duct, n (%)	7 (1.4)	4 (1.6)	3 (1.2)
Pneumatic dilation of intact biliary sphincter, n (%)	46 (9.0)	22 (8.6)	24 (9.4)
Ampullectomy, n (%)	9 (1.8)	5 (2.0)	4 (1.6)
Placement of pancreatic stent, n (%)	74 (14.5)	39 (15.3)	35 (13.7)

P values for comparison were not significant.



Supplementary Figure 1. Enrollment.