ORIGINAL ARTICLE

Aggressive hydration with Lactated Ringer's solution as the prophylactic intervention for postendoscopic retrograde cholangiopancreatography pancreatitis: A randomized controlled double-blind clinical trial

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Background: Pancreatitis is a serious complication of endoscopic retrograde cholangiopancreatography (ERCP) and may cause significant morbidity and even death. There is no effective prophylactic intervention for patients with average risk yet. This study aims to investigate preventive effect of aggressive hydration for post-ERCP pancreatitis. **Materials and Methods:** In a double-blind controlled setting, 150 patient were randomly assigned to receive either aggressive hydration with lactated Ringer's solution (3 mL/kg/h during ERCP, followed by a 20 mL/kg bolus and 3 mL/kg/h for 8 h after the procedure, $n = 75$) or standard amount of hydration (1.5 mL/kg/h during and for 8 h after ERCP, $n = 75$). Patients were observed for volume overload as well as pancreatic pain and serum levels of amylase at baseline and 2, 8, and 24 h after ERCP. Post-ERCP pancreatitis was defined as hyperamylasemia (level of amylase >300) and pancreatic pain during the 24 h follow-up. Hyperamylasemia and pancreatic pain were the secondary end points. **Results:** Mean age of the patients was 50.8 ± 13.5 years. Most of the patients were female (66%). Pancreatitis developed in 21 patients, including 22.7% of patients receiving standard hydration and 5.3% patients receiving aggressive hydration ($P = 0.002$). Hyperamylasemia was detected in 44.0% of patients receiving standard hydration and 22.7% of patients aggressive hydration ($P = 0.006$). The pancreatic pain was reported by 5.3% of patients receiving aggressive hydration and 37.3% of patients receiving standard hydration ($P \leq 0.005$). **Conclusion:** Aggressive hydration with lactated Ringer's solution may effectively prevent post-ERCP pancreatitis as well as hyperamylasemia and pancreatic pain in patients with average risk.

Key words: Aggressive hydration, endoscopic retrograde cholangiopancreatography, pancreatitis, prevention

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has become one of the foundations of diagnosing and the treatment of hepatobiliary and pancreatic diseases. Even with technical progressions and improved knowledge about risk factors after a nearly half a century, complication of ERCP remain an essential concern.[1] Patients may face a higher rate of major complications when undergo therapeutic ERCP procedures versus diagnostic practice.[2] Among major complications that may be associated with technical issues or patient related factors,[2,3] pancreatitis is known as the most important.[4,5] Post-ERCP pancreatitis may cause significant morbidity and even death.

Based on the previous studies, post-ERCP hyperamylasemia or pancreatitis is more likely to occur in presence of patient-related factors such as age under 40 or 50 years[3,6] as well as technique-related characteristics

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such as multiple cannulation attempts, pancreatic brush cytology, and pain during the procedure.[3,7] However, a more important concern is not answered yet that is the best method to prevent this complication.

Several attempts have been made to find an effective prophylactic intervention. The standard of care for high-risk patients is a prophylactic pancreatic duct stents, but the best care for unselected patients remains unclear. After promising early results, studies found either somatostatin or gabexate mesylate ineffective for the prevention of post-ERCP pancreatitis.[8-11] Corticosteroid was not effective as a prophylactic agent either.[12,13] The only effective prophylactic pharmacologic treatment to date, seem to be the rectal indomethacin or diclofenac which could prevent pancreatitis both in high-risk and unselected patients.[14,15]

However, a recent pilot study introduced aggressive hydration protocol ($n = 23$) for the prevention of post-ERCP pancreatitis and compared it with standard intravenous fluid administration ($n = 23$).[16] Results showed the method to be effective and safe. None of the patients receiving aggressive hydration developed pancreatitis compared to 17% in standard hydration. This promising outcome obviously needs to be replicated in further studies overcoming the limitations.

The aim of this trial was to evaluate the effect of aggressive hydration for the prevention of hyperamylasemia, pancreatic pain, and post-ERCP pancreatitis in patients with an average risk.

MATERIALS AND METHODS

Study design and participants

This randomized, double-blind, and controlled trial was carried out at Imam Reza Hospital, Tabriz University of Medical Sciences, from November 2014 to April 2015. The study population was all of the inpatients and outpatients referred to ERCP center of the hospital during this period. Therefore, clinical indications for ERCP were choledocholithiasis, bile duct leak, and biliary obstruction, gallstone pancreatitis, and active cholangitis but patients with the latter two indications were not included because of the required particular care. As sphincterotomy could decrease the likelihood of pancreatitis,[3] patient with such a history was excluded. Age over 70 years, pregnancy and clinical signs of fluid overload also led to exclusion which were peripheral or pulmonary edema, hypernatremia or hyponatremia (Na <130 or Na >150 mEq/L). Patients with cardiac insufficiency (New York Heart Association Class II or above), respiratory insufficiency (oxygen saturation <90%), renal insufficiency (creatinine clearance <40 mL/min), or liver dysfunction were also excluded as they were at higher risk for fluid load.

The study protocol was approved by the Institutional Review Board of Tabriz University of Medical Sciences in accordance with the principles of the Declaration of Helsinki. This trial is registered with the Iranian Clinical Trials Registry (IRCT201410161213N3).

A complete explanation was given to each patient regarding current standard of care, potential risks, and benefits of the treatment and written consent was obtained from patients. A complete physical examination was then carried out to exclude patients as described above noticing ankle or upper extremity edema, ascites, pulmonary rales in particular, and measuring oxygen saturation. Patients were examined again right after ERCP as well as 2, 8, and 24 h afterward. Both patient and the evaluator gastroenterologist were blinded to the type of hydration of the patient. Because of the nature of the investigation, this was not kept up during follow-up, after 24 h, the intervention group was still receiving the liquid but controls were not. Imaging studies were only performed when clinically indicated.

Randomization

After giving written consent, a trained staff then gave a number to each selected patient in a continuous order. A schedule was previously generated by RandList and patients were assigned to the target or the control group depending on the number given to each.

Intervention

Lactated Ringer's solution was chosen for hydrating patients in this study.[17] The standard care for patients undergoing ERCP was intravenous lactated Ringer's solution at a rate of 1.5 mL/kg/h during ERCP and the following 8 h. In case of post-ERCP pancreatitis, they received a bolus of 20 mL/kg, followed by a rate of 3 mL/kg/h.

Aggressive hydration was administered for the target group as described by Buxbaum *et al*.[16] Intravenous lactated Ringer's solution was administered at a rate of 3.0 mL/kg/h during ERCP. Patients received a bolus of 20 mL/kg right after ERCP and 3 mL/kg/h of lactated Ringer's solution for 8 h. Then the fluid decreased to 1.5 mL/kg/h, if no pain was reported and stopped when the patient could tolerate a normal diet.

Outcome

Post-ERCP pancreatitis was defined by presence of both pancreatic pain more than three on visual analogue scale (VAS) (epigastric abdominal pain radiating to the back) and hyperamylasemia (amylase more than three times the upper limit of normal [i.e., 300 U/L]) during the 24 h follow-up. In those who already had pain, the pancreatic pain was defined as an increase of three on VAS.

The VAS was used for pain assessment which is by far the most popular tool.[18] Patient with pain before ERCP rated it right before the procedure. All of the patients rated the pain immediately after ERCP as well as 2, 8, and 24 h later.

Statistical analysis

As the occurrence of post-ERCP pancreatitis within the first 24 h was set as the primary outcome, a pilot study with 10 patients in each group was conducted. After ERCP, pancreatitis occurred in 0.4% of patients receiving aggressive hydration and 16.6% of patients receiving standard care. With a power of 80%, type I error of 5% and 1 point difference in the occurrence of post-ERCP pancreatitis, the sample size was calculated to be 114 patients. Allowing for at least 10% drop outs, 155 patients were enrolled.

Data were analyzed by SPSS (version 21, SPSS Inc., Chicago, IL). Chi-square test was used to evaluate difference between qualitative variables (gender, pancreatic pain, and hyperamylasemia) and the student's *t*-test to evaluate differences in means (age, level of pain, amylase, liver enzymes, bilirubin, creatinine, hematocrit, and hospitalization days). A two-way repeated measures analysis of variance (time-treatment interaction) was also performed. The type of hydration as a between-subjects factor (group) and time of measurements as the within-subjects factor (time) were considered in pain and amylase parameters. Descriptive information is presented as a mean ± standard deviation and the level of significance was considered at 0.05.

RESULTS

Procedure

From the total of 303 patients, 162 patients were eligible but 12 declined to participate and 150 were randomized as participants. The mean age of these patients was 50.8 ± 13.5 years (range: 20-70), 66% were females. Baseline characteristics of participants are described in Table 1, which also shows the results of comparison between the target and the control group. As described within the table patients in the two groups were matched in terms of age, gender distribution, and number of young females (under 40 years old).

Sphincterotomy was performed for all of the patients. Balloon dilatation was performed for 65 (86.7%) patients receiving aggressive hydration and 68 (90.7%) of controls ($P = 0.440$). Stone extraction baskets were utilized for 61 (81.3%) patients receiving aggressive hydration and 59 (78.7%) of controls ($P = 0.683$). A plastic stent was placed for 7 (9.3%) patients receiving aggressive hydration and 8 (10.7%) of controls ($P = 0.785$). Only 2 (2.7%) patients in target group received metal stent ($P = 0.497$). The ERCP procedure was prolonged because of several cannulation attempts in of five patients whose data were excluded because of the increased risk for post-ERCP pancreatitis.

Complications of ERCP other than pancreatitis occurred in four patients (perforation, incomplete stone removal, and impaction of stone retrieval basket). Clinical evidence of overload was not observed in any.

End points

From the total of 150, post-ERCP pancreatitis developed in 21 patients. Their mean age was 51.9 ± 13.4 years. Duration of hospitalization was longer for those who developed pancreatitis (4.2 ± 3.4 vs. 1.2 ± 0.8 days, $P = 0.001$).

Post-ERCP pancreatitis developed in 17 out of 75 patient (22.7%) receiving standard hydration (mean age of 49.5 ± 17.9 years). This rate was significantly lower ($P = 0.002$) in patients receiving aggressive hydration with Ringer's solution and only 4 out of 75 (5.3%) developed post-ERCP pancreatitis (mean age of 52.1 ± 11.9 years).

Hyperamylasemia was detected in 33 patients (44.0%) receiving standard hydration and 17 patients (22.7%)

Table 1: Baseline characteristics on patient undergoing endoscopic retrograde cholangiopancreatography

	Standard care ($n = 75$)	Aggressive hydration ($n = 75$)	*P*
Male/female (*n*)	24/51	27/48	0.605*
Age*** (year)	52.24 (12.12)	49.60 (15.05)	0.239**
Young female (*n*)	10	16	0.196*
Indication: Bile duct stone (%)	96.0†	94.7†	–
Bilirubin (total) (mg/dL)	2.67 (4.09)	3.67 (5.74)	0.225**
Bilirubin (direct)	1.51 (2.54)	2.07 (3.64)	0.276**
Hematocrit (%)	37.88 (4.69)	38.54 (5.04)	0.412**
Creatinine (mg/dL)	1.18 (1.46)	0.9 (0.22)	0.108**
Aspartate aminotransferase (IU/L)	76.68 (78.79)	69.02 (84.99)	0.568**
Alanine aminotransferase (IU/L)	120.23 (133.57)	101.32 (107.44)	0.341**
Alkaline phosphatase (IU/L)	653.30 (615.43)	563.98 (448.46)	0.311**
Hospitalization days	2.13 (2.33)	1.28 (0.74)	0.003**

**P* values from Chi-square test; ***P* value from Student's *t*-test; ***Data are expressed as mean ± SD, unless indicated otherwise; †Other indications were dilated bile duct, hydatic cyst, stent placement; ‡Other indication was dilated bile duct. SD = Standard deviation

receiving aggressive hydration (P = 0.006). Figure 1 shows, how the level of amylase fluctuated within three measurements. The repeated measurement analysis showed a significant different for the type of intervention ($F_{(1,148)}$ = 7.210, P = 0.008, power = 80%) but the changes in the levels of amylase between three measurements was not significant in both groups ($F_{(2,72)}$ = 2.720, P = 0.067, power = 80%). However, as shown in Figure 1, the time-group interaction was not significant ($F_{(1,148)}$ = 0.44, P = 0.500, power = 80%).

Pancreatic pain (pain scoring 3 or more on VAS) was reported by four patients (5.3%) receiving aggressive hydration and 28 patients (37.3%) receiving standard hydration ($P \leq 0.005$). A repeated measurement analysis showed a significant effect for the type of intervention ($F_{(1.148)}$ = 25.001, $P < 0.001$, power = 80%) and the reported pain score also significantly decreased in both groups ($F_{(2,72)}$ = 28.610, $P < 0.005$, power = 80%). The time-group interaction was also significant ($F_{(1.148)}$ = 8.885, P = 0.003, power = 80%). These are illustrated in Figure 2.

DISCUSSION

The primary aim of this study was to evaluate the preventive effect of aggressive hydration on reducing the incidence of post-ERCP pancreatitis in a double-blind setting. The results added to the evidence that aggressive hydration with lactated Ringer's solution could decrease the prevalence of post-ERCP pancreatitis as well as hyperamylasemia and pancreatic pain.

ERCP is one of the well-known causes of iatrogenic pancreatitis. The incidence of post-ERCP pancreatitis ranges is reported between 1.3% and 24.4%[19] depending on the patient and procedure related factors. Studies continue to find a better preventive method. Prophylactic pancreatic duct stent placement is mainly valuable for preventing the development of severe pancreatitis in high-risk patients.[20] For those with low or average risk, rectal nonsteroidal anti-inflammatory drug (NSAID) is the available and most effective preventative approach. NSAIDs probably inhibit phospholipase A2, cyclooxygenase, and neutrophil-endothelial interactions which are contributed to the pathogenesis of pancreatitis.[14] Both methods have side effects, and stents are associated with higher morbidity compared to rectal NSAIDs.[21]

Based on evidences, clinical practice guidelines recommend intravenous volume infusion as the main intervention in the early management of acute pancreatitis.[22,23] Furthermore, recent studies indicate that fluids may prevent pancreatitis as well as reducing the risk of severe pancreatitis.[16] Sufficient hydration could probably improve perfusion of the tissue at risk. Studies have shown an association between greater risks of developing post-ERCP pancreatitis with higher blood urea nitrogen levels.[24] Fasting state of patients undergoing ERCP may worsen their situation.[25]

Studies on animal models of pancreatitis show that the improvement of pancreatic microcirculation can reduce the histopathologic damage of the tissue, especially when given prophylactically.[26] Pancreatic hypoperfusion induced by physiologic changes due to proinflammatory cytokines plays an important role in the early phase of acute pancreatitis development.[26,27] Clinical evidences suggest that the consequent systemic inflammatory response is the basis of pancreatitis, pancreatic necrosis, and infection[28] and this may be a good cue to find preventive interventions for this chain.

Results of the current study are compatible with a previous pilot study which was the first and the only study suggesting the use of IV fluids as a prophylactic intervention

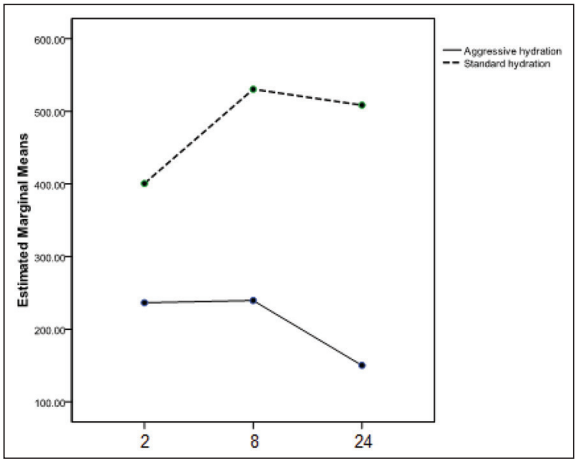

Figure 1: Mean level of amylase as measured in 2, 8 and 24 h postendoscopic retrograde cholangiopancreatography in participants

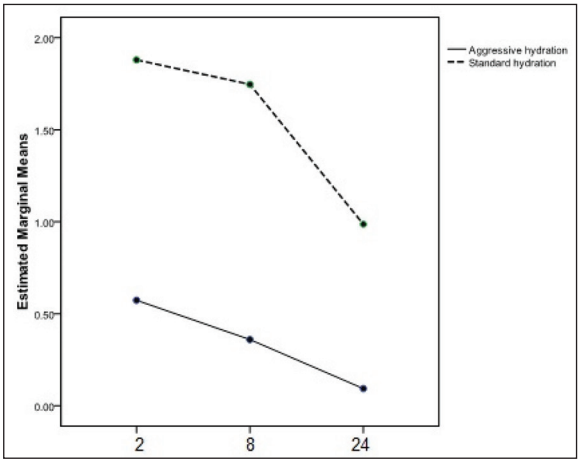

Figure 2: Mean level of pain reported by patients in 2, 8 and 24 h postendoscopic retrograde cholangiopancreatography

for post-ERCP pancreatitis. Buxbaum *et al.*[16] randomized 62 patients to the standard (n = 23) and aggressive (n = 39) protocol and reported that aggressive hydration with lactated Ringer's solution could decrease the prevalence of post-ERCP pancreatitis. They hydrated patients with lactated Ringer's solution as well. Lactated Ringer's solution (vs. saline) may be the best choice for hydrating patients with acute pancreatitis as it probably decreases the chance of systemic inflammatory response syndrome[29] and may stimulate an anti-inflammatory immune reaction.[17]

The preventive effect on hyperamylasemia and persistent pain did not reach the significance. The current study could address some of the limitations of Buxbaum *et al.* by recruiting a higher number of patients (more than threefold), with a different ethnicity (all Caucasian), and making patients and investigators blind to the allocation. However, because of the nature of the study, the rating investigators were not blind at the third measurement.

The current study has limitations. Patients were selected by relatively strict inclusion criteria to ensure their safety after receiving aggressive hydration. As a result patients with major comorbid illness were excluded and this limits generalization of the results. Consequently, while these results are obtained from patients with an average risk for post-ERCP pancreatitis, they were at low risk for adverse effects of aggressive hydration. Although aggressive hydration has been shown to be an effective factor in the prevention of severe pancreatitis and necrosis,[30] this study did not specifically address the clinical outcomes. Larger trials are needed to evaluate the preventive effect of aggressive hydration on the severity of post-ERCP pancreatitis. A bigger sample size could also reveal the significance of changes in levels of amylase between three measurements in both groups by increasing the power. However, this was not possible in this study.

The center, where this study was performed is a tertiary referral hospital. Rate of post-ERCP pancreatitis is higher than most of the referred articles. As mentioned by previous studies, this may be explained by the fact that a referral and high volume center admits a larger proportion of patients at high-risk of pancreatitis.[31] Imam Reza Hospital, where this study was carried out is a University Teaching Hospital, and low experience of operators may also play a part. However, all of the known risk factors were equally distributed between the two groups and might not influence the main outcome.

CONCLUSION

Acute pancreatitis is a serious complication of ERCP. While hydration is the mainstay of treatment of acute pancreatitis, the current study adds to the evidence that aggressive hydration with Ringer's solution may be an effective prophylactic method of post-ERCP pancreatitis in nonselected patients.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

AS contributed to the conception of the work, conducting the study, preparation and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AM contributed to the conception of the work, approval of the final version of the manuscript, and agreed for all aspects of the work. AG contributed in the conducting the study, revising the draft, and agreed for all aspects of the work. MG contributed to the conception of the work, statistical analysis, approval of the final version of the manuscript, and agreed for all aspects of the work. MK contributed to the conception of the work, conducting the study, preparation and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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