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Peri-Procedural Aggressive Hydration for Post Endoscopic Retrograde Cholangiopancreatography (ERCP) Pancreatitis Prophylaxsis: Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: Periprocedural intravenous hydration is suggested to decrease the risk of post-ERCP pancreatitis (PEP). However, quality of evidence supporting this suggestion remains poor. Here we hypothesized that aggressive hydration(AH) could be an effective preventive measure.
Methods: Pubmed, EMBASE, CINAHL, Google Scholar, Clinical Trials. gov, Clinical Key, International Standard Randomized Trial Number registry as well as secondary sources were searched through January 2019 to identify randomized controlled studies comparing AH to standard hydration (SH) for prevention of PEP. Pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated using the random-effects model. RevMan 5.3 was used for analysis.
Results: A total of 9 RCTs, with 2094 patients, were included in the meta-analysis. AH reduced incidence of PEP by 56% compared to SH (OR = 0.44, CI:0.28–0.69; p = 0.0004). The incidence of post-ERCP hyperamylasemia also decreased with AH compared to SH (OR = 0.51; p = 0.001). Length of stay decreased by 1 day with AH (Mean Difference (MD): −0.89 d; p = 0.00002). There was no significant difference in adverse events related to fluid overload between two groups (OR:1.29; p = 0.81) and post-ERCP abdominal pain (OR:0.35; p = 0.17). Numbers of patient to be treated with AH to prevent one episode of PEP was 17. Final results of the meta-analysis were not affected by alternative effect measures or statistical models of heterogeneity.
Conclusion: Aggressive hydration is associated with a significantly lower incidence of PEP and it appears to be an effective and safe strategy for the prevention of Post ERCP pancreatitis.

Introduction

ERCP is an essential diagnostic and therapeutic procedure to investigate and intervene in pancreato-biliary pathologies. It has now become a therapeutic procedure solely due to the availability of other non-invasive modalities such as magnetic resonance cholangiopancreatography (MRCP) and Endoscopic Ultrasound (EUS). A population-based study estimated that therapeutic ERCP increased by 35% and diagnostic ERCP decreased by the 75% from 1998 to 2013 [1]. Although generally considered a safe procedure, manipulation of the pancreato-biliary system leads to complications such as post ERCP pancreatitis (PEP), hemorrhage, perforation, and in some cases infection. PEP is the most common adverse event related to ERCP with an estimated incidence ranging from 1.5 to 15% [2–16]. PEP also weighs significantly on health care cost with an estimated annual burden of 200 million dollars [13]. Overall mortality associated with PEP is 0.7% [13]. Some of the important risk factors for PEP include female gender, younger age [17,18], endoscopist inexperience, difficult cannulation, therapeutic ERCP, ERCP performed

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for sphincter of Oddi dysfunction, and history of prior PEP [8,9]. Most cases of PEP are mild and generally treated with intravenous hydration and short in-hospital stay; severe cases require more extended hospital stay, ICU level care, nutritional support (enteral or parenteral), and other surgical or radiological interventions if complicated by pseudocyst, necrosis or infection [19].

A plethora of research is currently focused on the prevention strategies for PEP. Rectal indomethacin and stent placement in high-risk cases (e.g., with difficult and multiple cannulation attempts) are prophylactic measures recommended by the two leading endoscopy societies, American Society of Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal Endoscopy (ESGE) [20,21]. Multiple insults either independently or simultaneously during ERCP can lead to PEP, which can be mechanical, chemical, thermal, microbiologic, and even allergic [22]. One of the postulated mechanisms of PEP from animal models is pancreatic hypoperfusion leading to ischemic insult [23]. Prior research has tried to evaluate the role of aggressive IV hydration for the prevention of PEP. Results of such studies remain mixed with variable sample size. Meta-analyses conducted for further consolidation of evidence showed positive outcome [24–26]. Most such studies used LR solution as the preferred hydration fluid based on the reasoning that intravenous hydration with normal saline can worsen acidosis and activate pancreatic enzymes, and in a patient with already developed acute pancreatitis it reduces SIRS at 24 h [27]. However, a recent meta-analysis shows no significant effect of mortality [28]. Impact of the type of intravenous hydration fluid in the prevention of PEP is unclear. The ASGE and ESGE currently suggest aggressive peri-procedural hydration with LR to prevent PEP based on very poor quality of evidence [21]. We conducted this meta-analysis with the hypothesis that aggressive hydration with either RL or NS can be an effective strategy for the prevention of PEP with minimal to no risk.

Material and methods

Data sources and literature search

A comprehensive search strategy was developed with the assistance of a health sciences librarian with expertise in searching for systematic reviews. We queried Pubmed, CENTRAL, CINAHL, Google Scholar, Clinical Key, ClinicalTrial.gov, and International Standard Randomized Trial Number registry to identify potential randomized controlled trial (RCTs) investigating aggressive hydration with either normal saline or Ringer's lactate to prevent post-ERCP pancreatitis (PEP) in patients undergoing ERCP for any indication. Following search terms were used in combination with boolean operators “AND” and “OR”: Endoscopic retrograde cholangiopancreatography, ERCP, Ringer's lactate, Normal Saline, Hydration, Ringer's solution, Lactated Ringer, pancreatitis, Post-ERCP pancreatitis and Post Endoscopic retrograde cholangiopancreatography pancreatitis. All searches were conducted during January 2019, and the selection process is shown in Fig. 1. Additionally, reference lists of included studies and other review articles found during search were manually searched to identify additional studies. No language or other database limitation was imposed at any time during the search process. All results were imported into EndNote (Thompson ISI Research Soft, Philadelphia, PA), a bibliographic database manager and duplicate studies were identified and removed.

Study selection

Inclusion criteria

Prospective randomized controlled trials conducted on adult humans comparing aggressive hydration with standard hydration for PEP prevention with either normal saline or Ringer's lactate used in each arm and incidence of PEP reported in each arm were included.

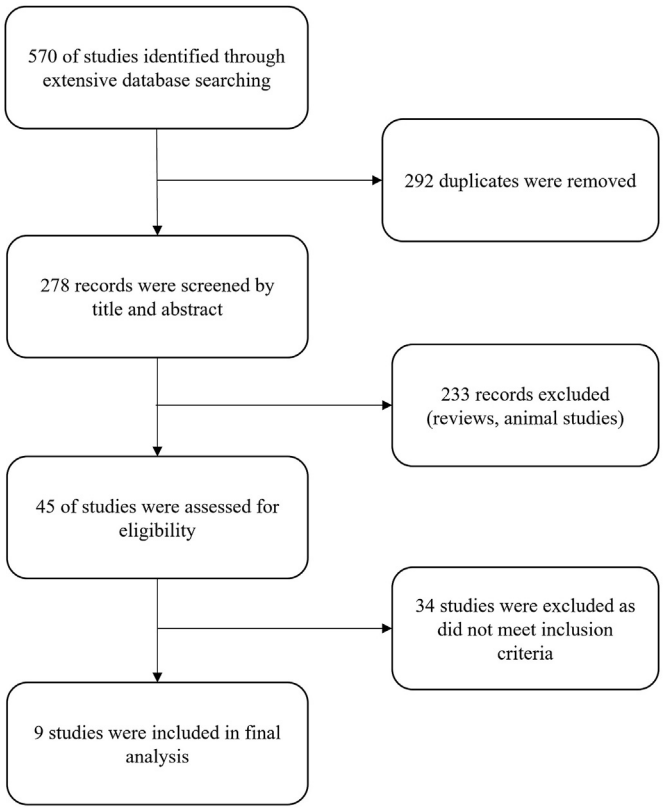

Fig. 1. Study selection flow diagram.

Exclusion criteria

Studies were excluded if they were duplicate publications, non-randomized non-prospective clinical trials, involved non-human subjects or any other prevention treatment used in any study arms such as indomethacin or other agents and studies without incidence of PEP reported.

Data extraction

All data extraction and quality assessment of the included studies was performed by two of the authors (D.R. & K.D.) independent of each other according to a prespecified protocol. In case of discrepancy, third author, fourth author and fifth author (S.A., C.R. & M.Y.) were consulted, and a final decision reached through consensus after discussion.

A standard data extraction form created in MS-Excel was used to extract data by two reviewers (D.R. & K.D.). Extracted items included first author, publication year, sample size, criteria for PEP diagnosis, definition of adverse event, the incidence of PEP, hyperamylasemia incidence, post-procedure abdominal pain incidence, adverse event rate, and length of stay.

Quality assessment

The two reviewers (D.R. and K.D.) assessed the quality of studies according to Cochrane Handbook Recommendations. Total of seven domains were used for risk assessment: 1) random sequence

generation (selection bias), 2) allocation concealment (selection bias), 3) blinding of participants and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective outcome reporting (reporting bias).

Outcomes included in the analysis

Primary end-point of the studies: incidence of acute pancreatitis.

Secondary outcomes were: (i) Incidence of Hyperamylasemia, (ii) Incidence of abdominal pain, (iii) Adverse event rate (e.g., Fluid overload), and (iv) Length of Stay.

Statistical analysis

We used Review Manager 5.3 software [29] (The Cochrane Collaboration, Oxford, UK) for this meta-analysis. Continuous variables were analyzed using the mean difference, while for dichotomous variables the odds ratio was calculated. Random effects model with the Mantel-Haenszel method was used for meta-analysis with the assumption that heterogeneity existed among study articles. We determined the statistical heterogeneity among studies using the I^2 statistic. The I^2statistic was used to assess the level of heterogeneity assigning the categories no risk, low, moderate and considerable heterogeneity to I^2 values of 0%–40%, 30%–60%, 50%–90%, and 75%–100% respectively [30]. The I^2 statistic <50% was used as the threshold to determine heterogeneity existence in this meta-analysis [31]. Funnel plot [32] and the Egger's test [33] were used to examine publication bias. P-values <0.05 were considered statistically significant for meta-analysis and the Egger test. Sensitivity analysis was performed with alternative effect measures, pooling methods, and statistical models. In addition, the sequential omission of individual study at a time was done to evaluate the change in effect size. We also explicitly excluded research abstracts during the sensitivity analysis. Calculated power of meta-analysis as whole for primary outcome was 0.999 (99.9%). Chances of Type I and II errors were 0.0004 (0.04%) and 0.001 (0.1%), respectively. When we excluded abstracts and included only full manuscripts power of meta-analysis for primary outcome remained comparable, (0.984 or 98.4%). Chance of type I and type II errors was 0.00001(0.001%) and 0.016 (1.6%), respectively.

Results

Literature search

A total of 570 potential studies were identified in the preliminary search from the databases mentioned in the method section. 292 dupicates were removed after initial search. After excluding guidelines, review articles, animal studies, non-randomized clinical trials, retrospective studies, and case reports, 45 articles remained. We included 9 RCTs (4 published studies [34–37], 1 unpublished study [38], and 4 abstracts [39–42]) which matched our all inclusion criteria. The baseline characteristics of individual studies are presented in Table 1. Flow diagram of the selection process is depicted in Fig. 1

Study and population characteristics

Study characteristics are shown in Table 1. A sample size of the study population ranged from 14 to 326 in the aggressive hydration (AH) group and 12 to 326 in standard hydration (SH) group. Majority of included studies originated from the USA, Thailand, and Korea. Mean age of AH group ranged from 43 to 59 years with female proportion varied from 36 to 85%. Mean age of the SH group ranged from 45 to 59 years with female proportion varied from 32 to 83%. However, 3 studies did not report specific numbers for mean age and female proportions but stated that the demographics of both groups were comparable. One study just reported a mean age of overall population but no gender distribution. Definitions of secondary outcomes as reported by different studies are shown in Table 2.

Assessment of risk of bias

In accordance with the Cochrane systemic review of intervention guidelines risk of bias summary and graph is depicted in Fig. 2. Four studies used computer generated random numbers as the method for randomization with adequate allocation concealment. Blinding of participants and personnel was done in 5 RCTs. Single blinding was done in 2 studies. Attrition bias was seen in 2 studies. Selective reporting was done in one unpublished RCT, five RCTs had no reporting bias.

Primary outcomes

Incidence of PEP

PEP was reported as a primary outcome in all studies included in the analysis. Out of 2094 patients, 165 (7.9%) patients developed PEP. The incidence of PEP was significantly lower in aggressive hydration group overall 5.1% (108/969) compared to 11.1%(57/1125) in the standard. The number of patients needed to receive aggressive hydration in order to prevent one case of PEP is 17. Analysis using the Mantel-Haenszel method with random effects model showed that aggressive hydration decreased the risk of PEP reduced to half compared to standard hydration (OR = 0.44; 95% CI: 0.28–0.69, P = 0.0004) and no significant heterogeneity existed among RCTs ($I^2 = 31\%$) as shown in Fig. 3. Sensitivity analyses showed similar findings. The exclusion of 1 RCT conducted by Chang et al. changed I^2 static to 0%, but no significant change in overall estimate was seen (OR = 0.37; 95% CI: 0.25–0.53; P < 0.00001). We also performed a sensitivity analysis by excluding all 5 research abstracts to study the primary outcomes, and similar results were observed with even profound decrease in the incidence of PEP (OR: 0.34; CI:0.21–0.54; p < 0.000001) as shown in Fig. 4.

Secondary outcomes

Incidence of hyperamylasemia

Five studies compared aggressive hydration with standard hydration in the prophylaxis of post-ERCP hyperamylasemia. The incidence of hyperamylasemia was 17% in the aggressive hydration group and 28.5% in the standard hydration group. Analysis using the Mantel-Haenszel method with a random effects model showed that aggressive hydration resulted in a 50% reduction in post ERCP hyperamylasemia (OR = 0.51; 95% CI: 0.34–0.77, P = 0.001). However, the heterogeneity among studies included in the analysis was moderate ($I^2 = 57\%$); forest plot is shown in Fig. 5. The conclusion was not affected while performing sensitivity analysis. The exclusion of 1 RCT conducted by Park et al. changed I^2 static to 0%, but no significant change in overall estimate was seen (OR = 0.43; 95% CI, 0.33–0.56; P < 0.00001).

The incidence of post-ERCP abdominal pain

Three studies reported the incidence of abdominal pain as a secondary outcome. The overall incidence of abdominal pain was 18% and 25% in the aggressive hydration group and standard

Table 1
Study and population characteristics with definition of PEP.

Study Authors (year)	Location	Sample Size (AH/SH)	Intervention between two groups	Definition of PEP	Mean Age ±SD (year)	Female (%)	Full Text
Buxbaum et al [34] (2014)	USA	39/23	**AH:** intravenous lactated Ringer solution at a rate of 3.0 cc/kg/h during the procedure, a bolus of 20 cc/kg immediately after ERCP, followed by a post-ERCP rate of 3.0 cc/kg/h for 8 h **SH:** intravenous lactated Ringer solution at a rate of 1.5 cc/kg/h during ERCP and for 8 h after ERCP without a bolus	Hyperamylasemia (amylase >3 times the upper limit of normal) and pancreatic pain (epigastric abdominal pain radiating to back scored by patient as development of or increase of pain ≥3 on 0–10 visual analogue scale and persisting for ≥24 h	43 ± 14 45 ± 17	48.7 56.5	Yes
Chuankrekkul et al [40] (2015)	Thailand	30/30	**AH:** intravenous lactated Ringer solution at a rate of 3.0 cc/kg/h during ERCP, 10 mL/kg bolus, and 3.0 cc/kg/h for 8 h after ERCP **SH:** intravenous lactated Ringer solution at a rate of 1.5 cc/kg/h during ERCP and 8 h after ERCP	Not described (stated that standardized criteria was use)	61.9 (overall population)	_	No
Shygan-Nejad et al [35] (2015)	Iran	75/75	**AH:** intravenous lactated Ringer solution at a rate of 3.0 cc/kg/h during ERCP, a bolus of 20 mL/kg right after ERCP and 3.0 cc/kg/h of lactated Ringer solution for 8 h **SH:** intravenous lactated Ringer solution at a rate of 1.5 cc/kg/h during ERCP and the following 8 h	Pancreatic pain more than three on visual analogue scale (VAS) (epigastric pain radiating to back) and hyperamylasemia (amylase ≥3 times of upper limit of normal during 24 h follow up	49.6 ± 15 52.2 ± 12.1	36 32	Yes
NCT02050048 [38] (2016)	USA	14/12	**AH:** initial bolus of LR prior to ERCP of 7.5 cc/kg over 1 h, LR fluid infusion during the procedure at 5 cc/kg/hr and Post-procedure bolus of 20 cc/kg over 90 min **SH:** LR infusion at 1.5 cc/kg/hr during ERCP and continued through the 90 min post-procedure	Abdominal pain and elevation in amylase and lipase (no limit specified) after 24 h of procedure	59 ± 12 55.7 ± 18	85 83	No
Rosa at el [41] (2016)	Portugal	35/33	**AH:** intravenous lactated Ringer solution at a rate of 3.0 cc/kg/h during ERCP, 20 cc/kg bolus after ERCP, and 3 cc/kg/h for 8 h after ERCP **SH:** intravenous lactated Ringer solution at a rate of 1.5 cc/kg/h during and for 8 h after ERCP	Epigastric pain plus either amylase or lipase levels >3 times the upper limit of normal at 24 h	_	_	No
Choi at el [36] (2016)	Korea	255/255	**AH:** lactated Ringer solution in an initial bolus of 10 cc/kg before ERCP, 3.0 cc/kg/h during and for 8 h after ERCP, and a post-ERCP bolus of 10 cc/kg **SH:** lactated Ringer solution at a rate of 1.5 cc/kg/h during and for 8 h after ERCP	New onset of epigastric pain, pancreatic enzymes >3 times the upper limit of normal within 24 h after ERCP	57 ± 12 58.2 ± 12.4	45.1 45.9	Yes
Chang at el [42] (2016)	Thailand	85/86	**AH:** intravenous lactated Ringer solution at a rate of 150 cc/h starting 2 h before ERCP, and continued during and after ERCP to complete 24 h **SH:** intravenous lactated Ringer solution calculated by the Holliday-Segar method given peri-ERCP	New or Increased epigastric pain persisting for >24 h, amylase or lipase >3 times the upper limit of normal	_	_	No
Park at el [37] (2018)	Korea	266/129	**AH:** intravenous hydration (3 mL/kg/h during ERCP, a 20-mL/kg bolus and 3 cc/kg/h for 8 h after ERCP) with either lactated Ringer's solution or normal saline **SH:** intravenous hydration with LRS (1.5 cc/kg/h during and for 8 h after ERCP).	Increase in pancreatic enzymes of at least three times the upper limit of normal, persisting epigastric pain for over 24 h after the ERCP, and hospitalization for at least 2 nights	58.5 ± 15.2 59 ± 15.1	54 55	Yes
M Alciva-Leon at el [39] (2018)	Ecuador	326/326	**AH:** intravenous lactated Ringer solution at a rate of 3.0 cc/kg/h during ERCP, 20 cc/kg bolus after ERCP, and 3 cc/kg/h for 8 h after ERCP **SH:** intravenous lactated Ringer solution at a rate of 1.5 cc/kg/h during and for 8 h after ERCP	Hyperamylasemia(amylase >3 times upper limit of normal) and epigastric pain persisting for >24 h after the procedure	_	_	No

hydration group, respectively. Analysis using the Mantel-Haenszel method with random effects model showed no statistically significant difference between incidence of abdominal pain among aggressive hydration group and standard hydration group (OR = 0.35, 95% CI:0.08–1.58, P = 0.17). Considerable heterogeneity was observed among studies in this analysis ($I^2 = 73\%$). Forest plot is shown in Fig. 6. During Sensitivity analyses effect estimate changed showing statistical difference between two groups when model was modified to fixed effect (OR = 0.24; 95% CI: 0.12–0.50, P < 0.00001) and method of analysis changed to peto (OR = 0.26; 95% CI:0.14–0.50, P < 0.0001), which confirms that heterogeneity existed between studies. Sensitivity analysis with the sequential omission of studies from the analysis did not change the conclusion, but the exclusion of study performed by Shygad et al. resulted in heterogeneity $I^2 = 0\%$, which can be a potential source of heterogeneity in the analysis. Subsequently when the analysis was done on the remaining two studies under fixed effect did not show any statistical difference between two groups for incidence of abdominal pain (OR = 0.72; 95% CI:0.26–2.05, P = 0.54).

Length of hospitalization

Three studies reported a difference between the length of stay in the aggressive and standard hydration group. The analysis using a random-effects model showed that minimal but statistically significant reduction in length of stay (approx. 1 day) was seen in a patient with aggressive hydration group. (mean difference = −0.89 day; 95% CI, −1.36 to −0.43, P = 0.0002). No heterogeneity was noted among studies included in the analysis ($I^2 = 0\%$) as shown in Fig. 7. Sensitivity analyses showed that an alternate statistical model (fixed model) did not affect the result. Sensitivity analysis with the sequential omission of individual studies from the analysis did not change the conclusion.

Table 2
Definitions of secondary outcomes.

Study Authors (year)	Hyperamylasemia	Pancreatic/Abdominal pain	Volume Overload	Other Complications of ERCP
Buxbaum et al (2014)	amylase ≥3 times the upper limit of normal	pancreatic pain (epigastric abdominal pain radiating to back scored by patient as development of or increase of pain ≥3 on 0–10 visual analogue scale and persisting for ≥24 h	defined by the development of ankle or upper extremity edema, ascites, pulmonary rales,and/or decreased oxygen saturation	None reported
Chuankrekkul et al (2015)	Outcome not reported	Outcome not reported	Not defined (no patient had volume overload)	None reported
Shygan-Nejad et al (2015)	Amylase more than three times the upper limit of normal (i.e., 300 U/L)	Epigastric pain radiating to back with score of 3 or more on visual analogue scale	Not clearly defined (Mentioned that no clinical evidence of volume overload in any group)	Occurred in 4 patients (Perforation, incomplete stone removal, and impaction of stone retrieval basket)
NCT02050048 (2016)	Outcome not reported	Reported without any specific definition	Not clearly defined (Mentioned as edema)	None reported
Rosa at el (2016)	Outcome not reported	Outcome not reported	Not clearly defined (Mentioned as no complications as a consequence of intensive hydration)	None reported
Choi at el (2016)	amylase ≥3 times the upper limit of normal	Outcome not reported	Peripheral edema, neck vein distention, weight gain and pulmonary crackles	No perforation or death during study
Chang at el (2016)	Outcome not reported	Outcome not reported	One patient in SH developed leg edema; insufficient outcome report	None reported
Park at el (2018)	Amylase at least three times upper limit of the normal range	Reported as Epigastric pain	Defined as symptoms like dyspnea, peripheral edema, neck vein distention, and pulmonary crackles	AH: post-sphincterotomy bleeding (15 patients), Post-ERCP cholangitis (2 patients) SH: post-sphincterotomy bleeding (2 patients) No perforation or death reported
M Alciva-Leon at el (2018)	amylase ≥3 times the upper limit of normal	Outcome not reported	Not clearly defined (no patient had volume overload)	None reported

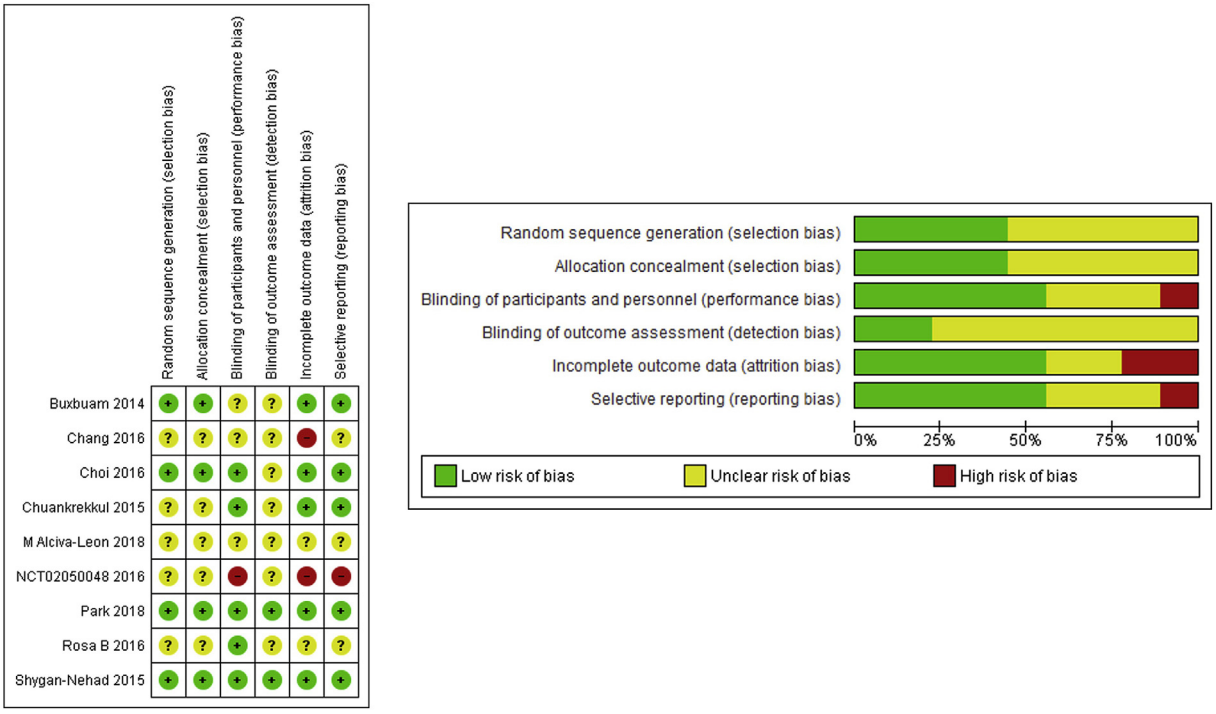

Fig. 2. Risk Bias graph and Summary.

Adverse effect incidence

Total seven studies reported incidence of adverse outcome in both treatment arms, but we only included only 3 studies in the final analysis as remaining five had zero events in both aggressive and standard hydration group as such studies do not provide any indication of either the direction or magnitude of effect between two groups. The overall incidence of adverse events was 0.5% in aggressive hydration arm and 0.3% in standard hydration group. Analysis using the Mantel-Haenszel method with random effects model showed no statistical difference in adverse event rate between two groups (OR:1.29; 95% CI:0.16–10.69, P = 0.81) as shown Fig. 8. Sensitivity analyses did not significantly affect pooled OR. Sequential removal of individual studies one by one showed similar results.

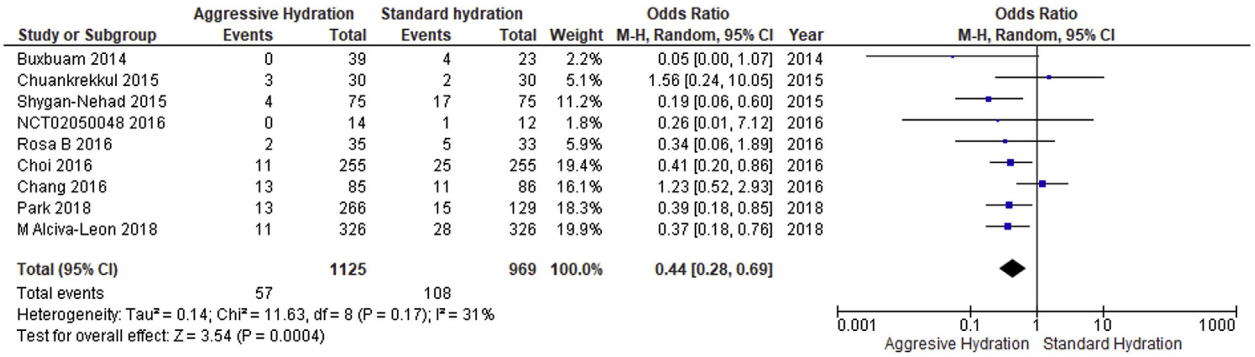

Fig. 3. Effect of hydration strategies on post-ERCP pancreatitis.

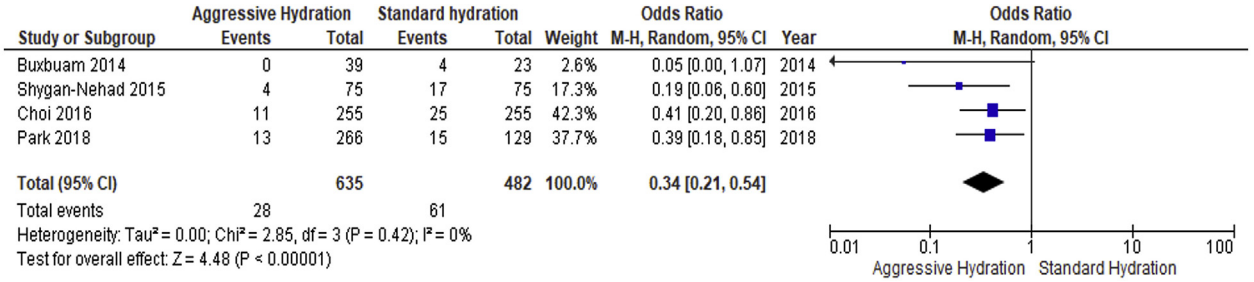

Fig. 4. Effect of hydration strategies on post-ERCP pancreatitis (only full articles).

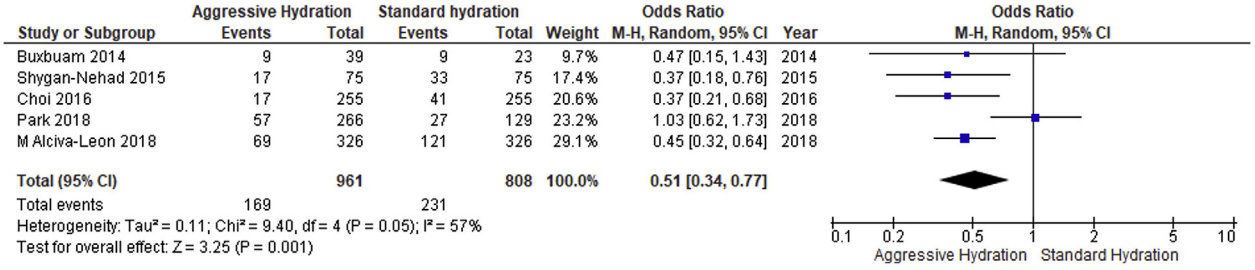

Fig. 5. Effect of hydration strategies on post-ERCP Hyperamylasemia.

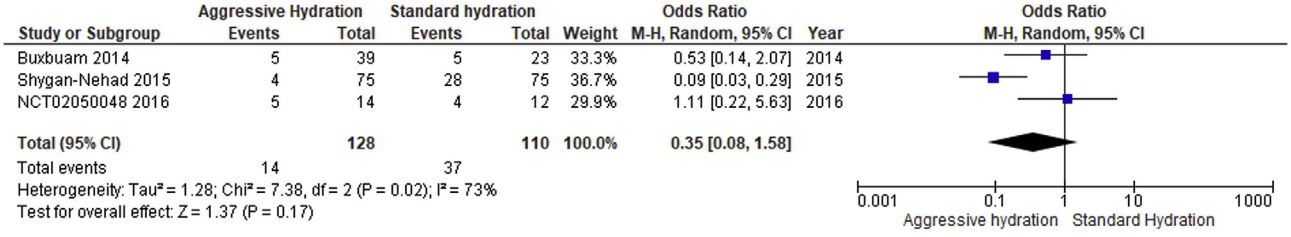

Fig. 6. Effect of hydration strategies on Abdominal pain.

Publication bias

No publication bias was noted on the funnel plot (Fig. 9) and with Egger's regression test (P = 0.315) for our primary outcome (incidence of pancreatitis). In addition, Egger's test performed for the included studies to estimate effect size secondary outcomes and also revealed no significant publication bias.

Discussion

The main finding of this meta-analysis show that vigorous periprocedural hydration with either NS or LR significantly reduced the incidence of PEP by 56%, in other words 17 patients have to receive aggressive periprocedural hydration to prevent one case of PEP. Also, aggressive hydration was associated with reduced length of inpatient hospital stay and lower adverse events (fluid overload).

Currently, rectal Indomethacin and pancreatic stent placement (particularly in high-risk patients) are well-studied and recommended measures for PEP prophylaxis. The ASGE suggests to use periprocedural hydration with LR, but the body of evidence remains sparse, and results are mixed. Additionally, there is no clear benefit of using one hydration fluid type over another (NS vs. RL). We

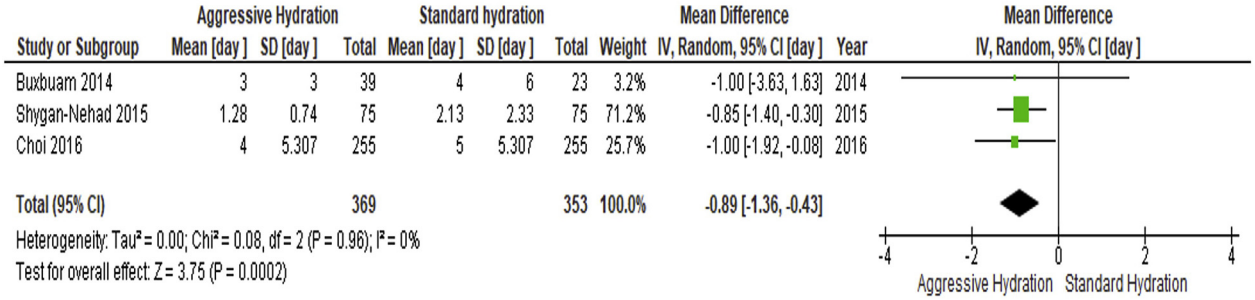

Fig. 7. Effect of hydration strategies on Length of Stay.

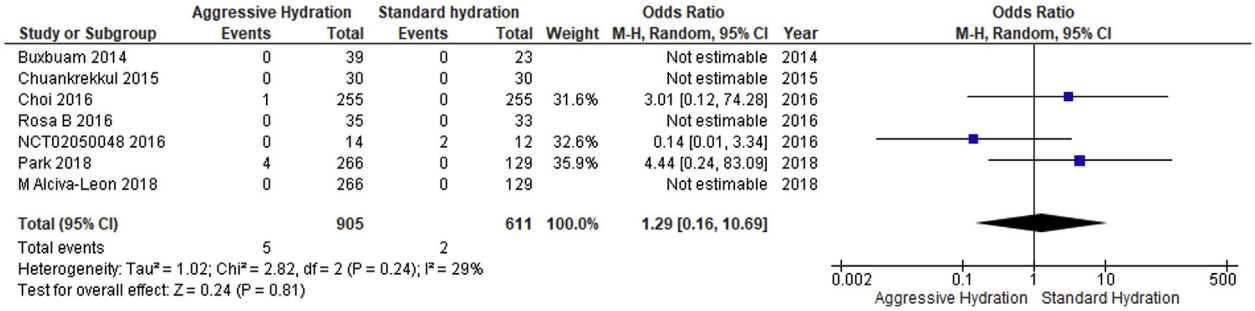

Fig. 8. Effect of hydration strategies on Fluid overload.

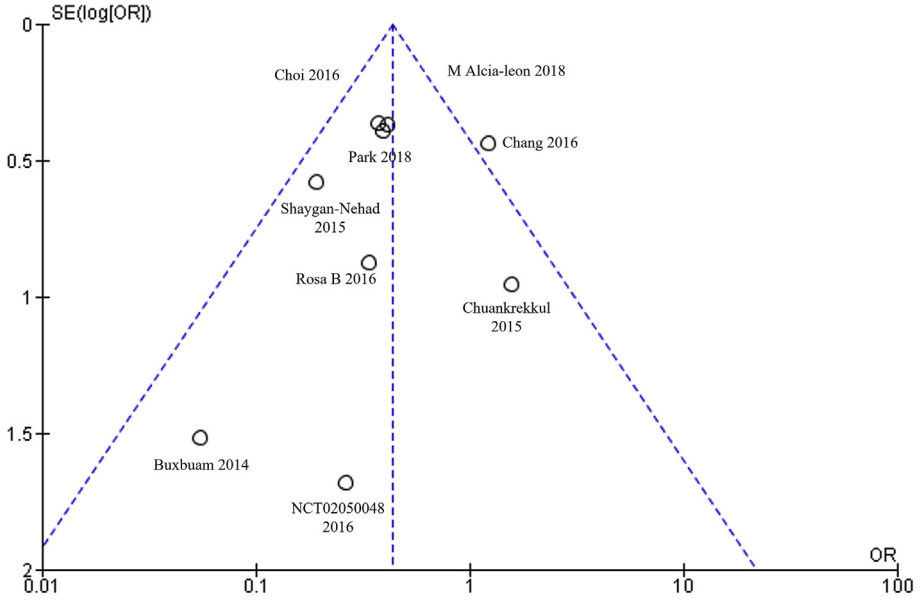

Fig. 9. Funnel plot for publication bias among studies for primary outcome (post-ERCP pancreatitis).

performed a meta-analysis on 9 RCTs to assess the effectiveness of periprocedural aggressive hydration for the prevention of PEP. Out of 9 included RCTs, five RCTs reported no significant change in events of PEP between aggressive and standard hydration. Four RCTs reported a decrease in PEP incidence with aggressive hydration. Our pooled analysis showed there is a statistically significant reduction in PEP with aggressive hydration. Of the studies included in our analysis, one RCT used NS in the aggressive hydration group, while others used NS in the standard hydration group. Among 9 RCTs, 5 different types of hydration rates were used in the aggressive hydration group which are evidenct in Table 1. The RCT by Park et al. included 3 groups: aggressive LR, aggressive NS, and standard LR. In the analysis, we used the pooled event rate by combining aggressive groups. Overall AH strategy with the initial fluid rate of 3 cc/kg/hr during the procedure with 20 cc/kg bolus immediately after procedure with 3 cc/kg/hr for 8 h following procedure seems a good fluid rate as evident among studies in which AH is preferred over SH. Traditionally, it is believed that NS potentiates acidosis [27] and lead to more pancreatic enzyme activation, which is the rationale behind using LR. However, there is no strong evidence supporting particular hydration fluid type or rate, and this needs to be explored in the future.

Post-ERCP hyperamylasemia occurs in three-fourths of patients regardless of symptoms [43]. Patient with lower than 1.5 times of ULN amylase level after 2–4 h of procedure are unlikely to develop PEP [44]. Only 5 RCTs reported an incidence of hyperamylasemia as a secondary outcome and evident from the I^2 statistic, heterogeneity exists between these studies. Two RCTs reported no difference between two groups, while the remaining 3 showed a reduction. Our pool estimate effect shows almost 50% reduction which is in agreement with previous meta-analyses result [24,25], which showed almost 60% reduction. Exclusion of study by Park et al. (which used NS in the aggressive arm as well) dropped heterogeneity to 0% but there was no significant change in reduction in hyperamylasemia.

Abdominal pain is a commonly reported symptom post-ERCP. Although abdominal pain can point to more grave complications such as pancreatitis, duodenal perforation, cholangitis, it can also be related to air insufflation. Necessary work-up guided by clinical suspicion should be the next step. Three RCTs reported abdominal pain as a secondary outcome. While two RCTs reported no difference, a RCT by Shygan-Nehad (with the largest sample among 3) showed a reduction in the incidence of abdominal pain. However, no significant difference was observed on the pooled estimate.

In practice, one issue with aggressive hydration strategy would be side effects of volume overload specifically in patients with heart failure, lung disease or chronic kidney disease. Seven RCTs reported adverse event rates in both hydration groups. Out of these, four RCTs reported zero adverse events in both groups; hence the odds ratio could not be calculated. The pooled estimate of the remaining 3 studies showed no statistically significant difference between the two groups. Moreover, adverse events rate was stated under wide banner of “clinical volume overload” and no separate rate per type of volume overload (e.g., pedal edema, pulmonary edema etc) was provided. However, one major issue that exists with all studies is the fact that patients who are particularly at risk for volume overload were excluded from analyses. Although evident from the meta-analysis, no significant difference noted between two groups in terms of adverse effects, but one should also acknowledge that it is only in people with a low risk for volume load. Future research should assess adverse event rate in patients with high risk for volume overload and evaluate if potential benefit of prevention of PEP can outweigh the risk associated with volume overload or not.

Length of stay is commonly used as an quality improvement measure. Only 3 studies reported the effect of aggressive hydration compared to standard hydration on the length of stay. One RCT reported that there was no significant difference in length of stay, while two RCTs conducted afterwards reported a reduction in hospitalization length. Pooled analysis showed that aggressive hydration strategy could reduce hospital stay from half day to one and a half day, which can ultimately favorably impact the cost of hospitalization. The previous meta-analysis with 2 studies showed the same difference in length of hospitalization as well.

Our meta-analysis has its own merits. We conducted analysis with the presumption that study samples are different in various ways rather than checking heterogeneity first and selecting model afterwards. Also, we included all the RCTs available in the form of full articles or abstracts (even one unpublished RCT) to minimize any publication bias. In addition to the funnel plot, we evaluated publication bias with Egger test across all outcomes due to a different number of studies included for different outcomes. However, our meta-analysis has the following limitations. We included research abstracts, quality of which cannot be fully evaluated as information available regarding methods is limited. However, a sensitivity analysis was performed for the primary outcome by excluding research abstracts, and similar results were seen. Furthermore, not all studies provide information on secondary outcomes. Although adverse event rates are provided in some studies, there are a specific description on them which limits analysis by type of adverse event. Moreover, these studies used variable rate of fluid hydration and also varied in the definition of PEP. Also, we could not analyses other outcomes such as mortality, cost associated with hospitalization and effect of hydration strategy on severity of pancreatitis because of limited data available from these studies.

In conclusion, our meta-analysis shows that aggressive hydration can be a supportive measure to rectal NSAIDs, and pancreatic stent in patients with low risk for volume overload. More research in the form of randomized controlled trials is needed to further elucidate the role of the type of the hydration fluid and the rate of the fluid. Also, the safety of aggressive hydration in the particularly subset of patients at high risk for volume overload should be explored.

Author contributions

Conception and Design: DR, KD, SA, PC, BB, MY, CR.

Analysis and Interpretation: DR, KD, SA,PC, BB, MY, CR.

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