

Comparative effectiveness of pharmacologic and endoscopic interventions for prevention of post-ERCP pancreatitis: a network meta-analysis




Authors

Basile Njei^{1,*}, Thomas R. McCarty^{2,3,*}, Thiruvengadam Muniraj¹, Prabin Sharma⁴, Priya A. Jamidar¹, Harry R. Aslanian¹, Shyam Varadarajulu⁵, Udayakumar Navaneethan⁵

Institutions

- 1 Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, United States
- 2 Department of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts, United States
- 3 Harvard Medical School, Boston, Massachusetts, United States
- 4 Department of Gastroenterology and Hepatology, Yale New Haven Health-Bridgeport Hospital, Bridgeport, Connecticut, United States
- 5 Center for Interventional Endoscopy, Florida Hospital, University of Central Florida College of Medicine, Orlando, Florida, United States

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Corresponding author

Basile Njei, MD, MPH, Yale University School of Medicine,
 333 Cedar St, New Haven, CT 06520
 Fax: +1-860-679-3159
basile.njei@yale.edu

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ABSTRACT

Background and study aims While several interventions may decrease risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, it remains unclear whether one strategy is superior to others. The purpose of this study was to compare the effectiveness of pharmacologic and endoscopic interventions to prevent post-ERCP pancreatitis among high-risk patients.

Methods A systematic review was performed to identify randomized controlled trials from PubMed, Embase, Web of Science, and Cochrane database through May 2017. Interventions included: rectal non-steroidal anti-inflammatory drugs (NSAIDs), aggressive hydration with lactated ringer's (LR) solution, and pancreatic stent placement compared to placebo. Only studies with patients at high-risk for post-ERCP pancreatitis were included. Bayesian network meta-analysis was performed and relative ranking of treatments was assessed using surface under the cumulative ranking (SUCRA) probabilities.

Results We identified 29 trials, comprising 7,862 participants comparing four preventive strategies. On network meta-analysis, compared with placebo, rectal NSAIDs ($B = -0.69$, 95% CI $[-1.18; -0.21]$), pancreatic stent ($B = -1.25$, 95% CI $[-1.81$ to $-0.69]$), LR ($B = -0.67$, 95% CI $[-1.20$ to $-0.13]$), and combination of LR plus rectal NSAIDs ($B = -1.58$; 95% CI $[-3.0$ to $-0.17]$), were all associated with a reduced risk of post-ERCP pancreatitis. Pancreatic stent placement had the highest SUCRA probability (0.81, 95% CI $[0.83$ to $0.80]$) of being ranked the best prophylactic treatment.

Conclusions Based on this network meta-analysis, pancreatic stent placement appears to be the most effective preventive strategy for post-ERCP pancreatitis in high-risk patients.

Introduction

Although endoscopic retrograde cholangiopancreatography (ERCP) is commonly performed for diagnosis and management of pancreato-biliary disease, the procedure itself may result in a host of potential adverse events (AEs) – the most common of

* Drs. Njei and McCarty: These authors contributed equally.

which is post-ERCP pancreatitis [1–3]. While the current literature estimates incidence of post-ERCP pancreatitis to be between 3% to 5%, a recent systematic review including over 2000 high-risk patients who underwent ERCP demonstrated an incidence of 14.7% with an associated 0.2% mortality rate [4–6].

Given this high incidence of post-ERCP pancreatitis in association with substantial morbidity, mortality, and healthcare costs of \$ 200 million annually in the United States, it is not surprising that several preventive strategies, both pharmacologic and endoscopic, have been employed [7]. Currently, there are several studies evaluating a variety of pharmacologic prophylaxes for post-ERCP pancreatitis in high-risk patients that include administration of rectal non-steroidal anti-inflammatory drugs (NSAIDs) or aggressive hydration with lactated ringer's solution (LR) [8–13]. In addition, several studies have demonstrated the efficacy of prophylactic pancreatic stent placement in reducing the rate of post-ERCP pancreatitis and more importantly in reducing the risk of severe post-ERCP pancreatitis [14–16].

However, due to paucity of data, it remains unclear whether pharmacologic, endoscopic, or a combination of both approaches is the preferred strategy to prevent post-ERCP pancreatitis. While previous direct pairwise meta-analyses have attempted to answer this question about prevention of post-ERCP pancreatitis, these types of studies are only able to provide partial information due to inherent design limitations. The primary aim of this study is to design a network meta-analysis, simultaneously analyzing direct and indirect evidence, to compare the effectiveness of pharmacologic and endoscopic treatment approaches to prevent post-ERCP pancreatitis.

Methods

Study design

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline for reporting systematic reviews and meta-analyses and was conducted following a priori established protocol [17, 18]. We utilized a network meta-analysis and Bayesian framework to combine direct and indirect evidence comparing the relative efficacy of pharmacologic and endoscopic prophylaxis treatments for post-ERCP pancreatitis. This method was chosen to compare multiple interventions and synthesize evidence across a network of randomized controlled trials [19, 20]. In brief, this method allows for simultaneous analysis of direct evidence from comparator trials as well as indirect evidence from different treatments compared to a common comparator (i.e., placebo or no intervention) [21].

Selection criteria and study outcomes

Only randomized controlled trials for high-risk patients were included in this network meta-analysis. High-risk patients were defined in randomized controlled trials by procedure-related factors such as difficult cannulation, pancreatic duct injection, pancreatic sphincterotomy, and pre-cut sphincterotomy in ad-

dition to patient-associated factors including female sex, those with sphincter of Oddi dysfunction, and patients with recurrent pancreatitis or prior history of post-ERCP pancreatitis [22–24]. Only trials involving high-risk patients were included.

Included studies involved adult patients (age ≥ 18 years) who underwent ERCP involving use of rectal NSAIDs (i.e., indomethacin or diclofenac), aggressive hydration with LR solution (defined as ≥ 3 mL/kg/h during the procedure and post-procedure intravenous bolus or high-rate infusion), prophylactic pancreatic stent placement, or placebo. Studies evaluating these treatments alone or in combination as well as studies evaluating direct comparator studies to placebo were included. Observational studies and trials evaluating prevention or reduction of post-ERCP pancreatitis were excluded. Post-ERCP pancreatitis was defined by the consensus criteria as a clinical syndrome consistent with pancreatitis as typical epigastric abdominal pain with an amylase or lipase level at least three times [25].

Data sources and literature search strategy

Two authors (BN and TRM) independently conducted a comprehensive search of the literature to identify articles that examined multiple electronic databases. Systematic searches of PubMed, EMBASE, Web of Science, the Cochrane Library databases, and major annual gastroenterology conference proceedings were performed from inception through May 31, 2017. Published abstract proceedings were extracted from major gastrointestinal meetings from January 2010 to May 2017. Scientific meetings included Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), and the American College of Gastroenterology (ACG) annual meeting.

Search terms included: “post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis,” “rectal non-steroidal anti-inflammatory drugs (NSAIDs),” “lactated ringer's (LR),” “prophylactic pancreatic stent,” and “post-ERCP pancreatitis prophylaxis.” All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. Titles and abstracts of all potentially relevant studies were screened for eligibility. Reference lists of studies of interest were then manually reviewed for additional articles with additional references acquired through cross-checking bibliographies of retrieved full-text papers. Any differences were resolved by mutual agreement and in consultation with the third reviewer (UN). In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Data abstraction and quality assessment

Study data were abstracted by two authors (BN and TRM) independently. Risk of bias of individual studies was evaluated and assessed in the context of the primary outcome (i.e., development of post-ERCP pancreatitis) using the Cochrane Risk of Bias assessment tool [26]. The GRADE approach to rate the quality of evidence of estimates derived from this network meta-analysis was also performed [27, 28]. Direct evidence from randomized controlled trials was initially identified as high quality; however, it could be down-graded based on risk of bias, indirectness, imprecision, heterogeneity, or publication bias. Rating

of indirect estimates began at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate but could be down-graded further for imprecision or intransitivity. If direct and indirect estimates were similar (i.e., coherent), then the higher of their rating was assigned to the network meta-analysis estimates.

Statistical analysis

Direct meta-analysis was performed using DerSimonian and Laird random effects model to estimate pooled odds ratio (OR) and 95% confidence interval (CI) [29]. Multivariate random-effects meta-regression was utilized to present results using the Stata `mvmeta` command extension [30]. Heterogeneity was assessed using I^2 statistic with values >50% indicating substantial heterogeneity [31]. With regard to publication bias, funnel plot asymmetry and Egger's regression test were performed as well [32]. Direct comparisons were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark) [33].

Indirect comparisons using a fixed effects Bayesian network meta-analysis was performed using a Markov chain Monte Carlo method in WinBUGS statistical analysis program version 1.4.4 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK) and Network Plots were created in Stata SE-13 [31,34]. The Bayesian meta-analysis approach offers greater flexibility for the use of more complex models and different outcome types, thereby enabling the simultaneous comparison of all treatment options [35]. Comparative effectiveness of any two treatments were modeled as a function of each treatment in relation to the reference treatment (i.e., placebo or no intervention) to assume consistency of treatment effects across all included randomized controlled trials. This thereby ensures the direct and indirect effect estimates are the same effects.

With regard to network consistency, direct and indirect estimates were evaluated using a node-splitting technique. Posterior distribution of all parameters was estimated using non-informative priors to limit inference to data derived from the trials. No assumptions about efficacy of rectal NSAIDs, aggressive resuscitation with LR, or prophylactic pancreatic stent placement from data external to the trials was included in this systematic review and network meta-analysis.

We used the Markov chain Monte Carlo method to obtain pooled effect sizes [35]. All chains were run with 50,000 simulated draws after a burn-in of 5,000 iterations. The median of the posterior distribution based upon 50,000 simulations was obtained using the 2.5th and 97.5th percentiles, after adjusted for multiple arms. Risk of post-ERCP pancreatitis was reported using the estimate of the beta coefficient and calculated the 95% credible interval.

Information on the relative effects was converted into a probability that a treatment was best, (i.e., first-best, second-best, etc) and into a ranking for each treatment, called the surface under the cumulative ranking curve (SUCRA) [36, 37]. A SUCRA value of 1.0 guarantees when a treatment is certainly the best and 0 when a treatment is certainly the worst. SUCRA values enable overall ranking of treatments for a particular outcome. SUCRA simplifies the information about the effect of

each treatment into a single number, thereby assisting the decision-making process.

Sensitivity analysis

Sensitivity analyses were also performed to assess the robustness and generalizability of our findings. Sensitivity analysis was performed for high-quality studies as determined by GRADE assessment. Low-quality studies were excluded. Additional sensitivity analysis was performed for full-text manuscripts. Abstracts that did not result in full manuscript publication were excluded.

Results

Based on previously discussed literature search criteria, a total of 29 trials were included in this study – comprising 7,862 participants comparing four preventive strategies for post-ERCP pancreatitis. A PRISMA flow chart of search results is shown in ► **Fig.1**. A network plot of network meta-analysis comparisons of included studies is highlighted in ► **Fig.2**.

Characteristics of included studies

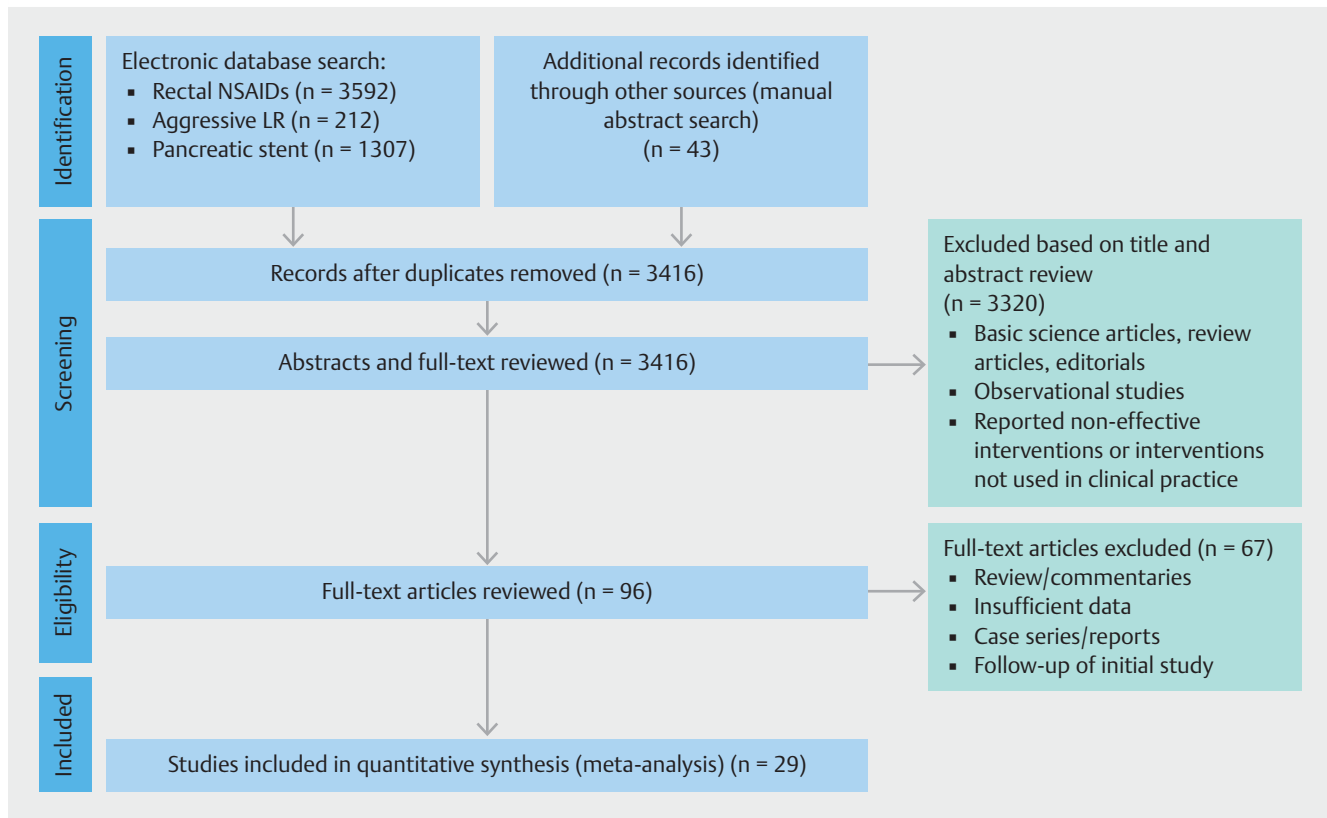
The primary outcome of post-ERCP pancreatitis was reported in all studies (► **Table 1**). Thirteen studies, including 5,955 patients with rectal NSAID use for prevention of post-ERCP pancreatitis were included [8–10,17,38–46]. All but one study (abstract) were fully published manuscripts [45]. Eight studies involving 754 patients evaluated use of aggressive hydration with LR solution in the prophylaxis of post-ERCP pancreatitis [11–13,47–51]. Four studies were fully published manuscripts, three studies were major gastroenterology meeting abstracts, and a final study was a RCT identified through ClinicalTrials.gov. One of the fully published manuscripts was a double-blinded, placebo-controlled trial that included both LR solution independently, as well as in combination with rectal NSAID use (n=96) [51]. Nine studies, including a total of 1057 participants, evaluated use of prophylactic pancreatic stent placement [14–16,52–57].

Quality assessment

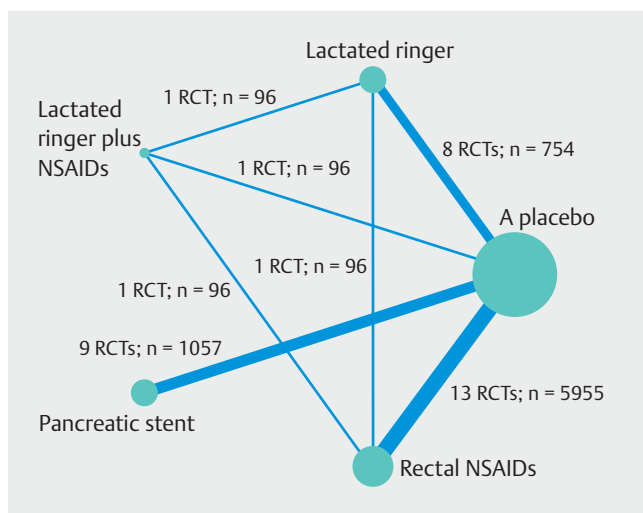
GRADE assessment was performed for all included studies. These review authors' judgements about each risk of bias item for each included study is highlighted in **Supplemental Fig. 1**. A risk of bias summary graph is also available in **Supplemental Fig. 2**.

Direct treatment comparisons

For direct treatment comparisons, all pharmacologic and endoscopic modalities were compared to placebo or no intervention (**Supplemental Table 1**). Compared to placebo, use of rectal NSAID therapy significantly reduced odds of post-ERCP pancreatitis by 49% (OR=0.51, 95% CI [0.33 to 0.77]) (► **Fig.3**). With regard to the effect of aggressive LR solution, this strategy was also effective in significantly reducing post-ERCP pancreatitis by 52% (OR=0.48, 95% CI [0.24 to 0.97]) (► **Fig.4**). When these two modalities were combined and compared to placebo, use of rectal NSAID and aggressive LR solution demonstrated



► **Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of search results for the prevention of post-ERCP pancreatitis.



► **Fig. 2** Network meta-analysis design of included studies for the prevention of post-ERCP pancreatitis.

75% reduced odds of developing post-ERCP pancreatitis; however, this was not statistically significant (OR=0.25, 95% CI [0.06 to 0.99]). Prophylactic pancreatic duct stent placement was effective in decreasing post-ERCP pancreatitis by 71% (OR = 0.29, 95% CI [0.17 to 0.48]) (► **Fig. 5**).

Sensitivity analyses

Results from sensitivity analyses are reported in the **Supplemental Table 1**. Overall, for the primary outcome, the results were largely similar to the main analysis.

Publication bias

There was no evidence of publication bias, based upon either qualitative on funnel-plot asymmetry or quantitative (i.e., Egger regression test, $P > 0.05$ for all comparisons) (**Supplemental Fig. 3, Supplemental Fig. 4, Supplement Fig. 5**).

Network meta-analysis comparisons

With this network meta-analysis, we calculated the mixed effect estimate as a weighted average of both direct and indirect treatment effects. On direct network meta-analysis, all strategies (i.e., both pharmacologic and endoscopic treatments) were associated with a reduced risk of post-ERCP pancreatitis. In a direct network meta-analysis, compared with placebo, use of rectal NSAIDs (B = -0.69, 95% CI [-1.18 to -0.21]), pancreatic stent (B = -1.25, 95% CI [-1.81 to -0.69]), high-volume LR solution (B = -0.67, 95% CI [-1.20 to -0.13]), and combination of LR plus rectal NSAIDs (B = -1.58, 95% CI [-3.0 to -0.17]), were all associated with a reduced risk of post-ERCP pancreatitis. Summary results of our network meta-analysis are summarized in ► **Table 2**. Indirect comparisons were largely similar to those obtained in direct meta-analysis for treatment

► **Table 1** Summary characteristics of included studies for prevention of post-ERCP Pancreatitis.

Author	Year, place of study	Place of study	Type of manuscript	Study design	Sample size	Mean age of treatment group (years)	Female gender (%)	Primary ERCP indication of bile duct stone (%)	Trial-specific treatment details
Rectal NSAID Therapy									
Murray et al.	2003	Scotland	Full text	Single-center comparator to placebo	220	55	65 %	25.45 %	Diclofenac 100 mg immediately post-ERCP
Sotoudehmanesh et al.	2007	Iran	Full text	Single-center comparator to placebo	490	58.4	53.90 %	53.26 %	Indomethacin 100 mg immediately pre-ERCP
Otsuka et al.	2012	Japan	Full text	Multicenter comparator to placebo	104	75	49.04 %	77.88 %	Diclofenac 25 – 50 mg immediately pre-ERCP
Elmunzer et al.	2012	United States	Full text	Multicenter comparator to placebo	602	44.4	79.07 %	–	Indomethacin 100 mg immediately post-ERCP
Dobronte et al.	2012	Hungary	Full text	Single-center comparator to placebo	228	–	–	–	Indomethacin 100 mg 10 – 15 minutes pre-ERCP
Alabd and Abo	2013	Sudan	Abstract	Single-center comparator to placebo	240	–	–	–	–
Dobronte et al.	2014	Hungary	Full text	Single-center comparator to placebo	665	66.8	–	–	Indomethacin 100 mg 10 – 15 minutes pre-ERCP
Andrade-Davila et al.	2015	Mexico	Full text	Single-center comparator to placebo	166	51.59	66.27 %	39.76 %	Indomethacin 100 mg immediately post-ERCP
Patai et al.	2015	Hungary	Full text	Single-center comparator to placebo	574	66.25	67.16 %	58.63 %	Indomethacin 100 mg 60 minutes pre-ERCP
Lua et al.	2015	Malaysia	Full text	Single-center comparator to placebo	151	50.3	59.03 %	56.25 %	Diclofenac 100 mg immediately post-ERCP
Luo et al.	2016	China	Full text	Multicenter comparator to placebo	2014	62	52.42 %	77.50 %	Indomethacin 100 mg 30 minutes pre-ERCP
Levenick et al.	2016	United States	Full text	Single-center comparator to placebo	449	64.9	52.56 %	27.72 %	Indomethacin 50 mg × 2 during ERCP
Ucar et al.	2016	Turkey	Full text	Single-center comparator to placebo	100	59	66.66 %	83 %	Diclofenac 100 mg 30 – 90 minutes pre-ERCP
Aggressive LR solution									
Buxbaum et al.	2014	United States	Full text	Single-center comparator to standard hydration	62	43	51.61 %	74.20 %	IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 20 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h

► **Table 1** (Continuation)

Author	Year, place of study	Place of study	Type of manuscript	Study design	Sample size	Mean age of treatment group (years)	Female gender (%)	Primary ERCP indication of bile duct stone (%)	Trial-specific treatment details
Chuankekkul et al.	2015	Thailand	Abstract	Single-center comparator to standard hydration	60	61.9	–	–	IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 10 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h
Shaygan-Nejad et al.	2015	Iran	Full text	Single-center comparator to standard hydration	150	49.6	66%	95.35%	IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 20 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h
Rosa et al.	2016	Portugal	Abstract	Multicenter comparator to standard hydration	68	–	–	–	IV LR solution at a rate of 3.0 mL/kg/h during ERCP, a bolus of 20 mL/kg immediately post-ERCP, followed by post-ERCP rate of 3.0 mL/kg/h for 8 h
NC-T0205004-8	2016	United States	–	Multicenter comparator to standard hydration	26	59.1	84.62%	–	Initial bolus LR solution of 7.58 mL/kg pre-ERCP, IV LR solution of 5.0 mL/kg/h during ERCP, following by post-ERCP bolus of 20 mL/kg for 90 minutes
Chang et al.	2016	Thailand	Abstract	Single-center comparator to standard hydration	171	–	–	50%	IV LR solution at a rate of 150 mL/h starting 2 h pre-ERCP, and continued during and post-ERCP for 24 h
Choi et al.	2016	Korea	Full text	Multicenter comparator to standard hydration	510	57.6	45.50%	53.70%	Initial bolus LR solution of 10 mL/kg pre-ERCP, IV LR solution of 3.0 mL/kg/h during ERCP and continued 8 h post-ERCP, following by post-ERCP bolus of 10 mL/kg
Mok et al.	2017	United States	Full text	Single-center comparator with multiple therapies*	48	60.25	60.60%	–	Treatment arms included standard normal saline solution vs normal saline plus indomethacin versus LR versus LR plus indomethacin

► **Table 1** (Continuation)

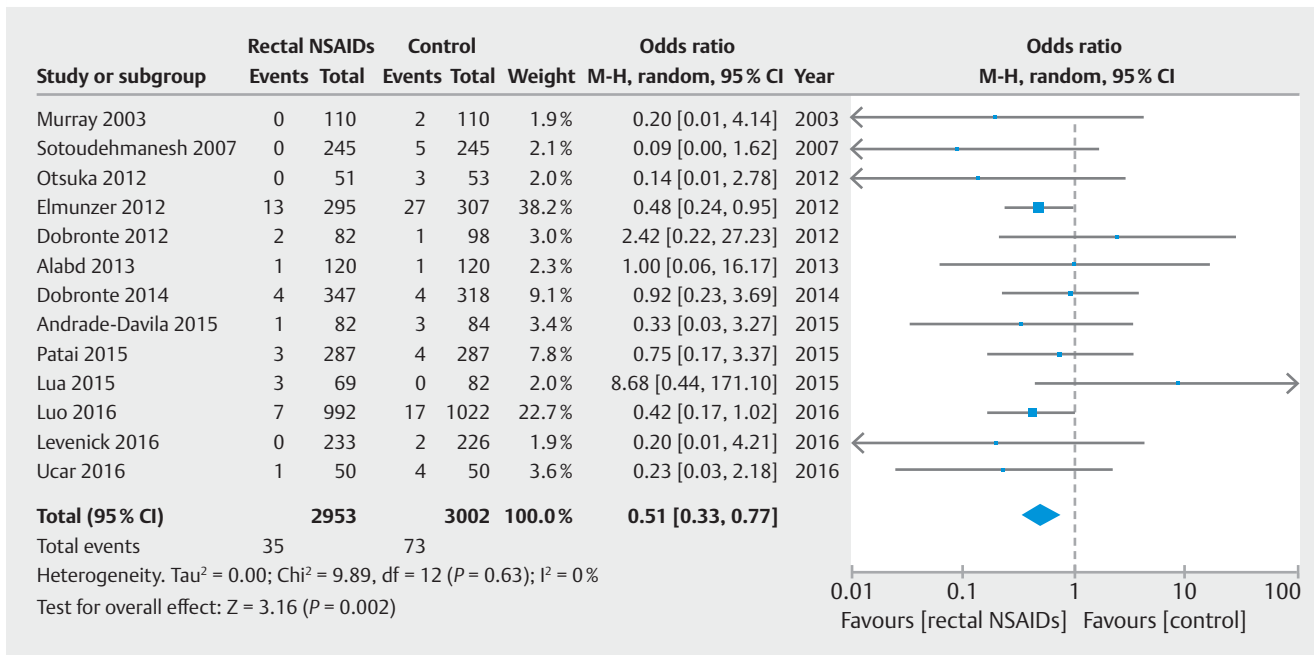
Author	Year, place of study	Place of study	Type of manuscript	Study design	Sample size	Mean age of treatment group (years)	Female gender (%)	Primary ERCP indication of bile duct stone (%)	Trial-specific treatment details
Rectal NSAIDs + LR solution									
Mok et al.	2017	United States	Full text	Single-center comparator with multiple therapies*	48	60.25	60.60 %	–	Treatment arms included standard normal saline solution vs normal saline plus indomethacin versus LR versus LR plus indomethacin
Pancreatic stent placement									
Smithline et al.	1993	United States	Full text	Single-center comparator to placebo	99	46	78.79 %	–	5–7 Fr stent, 2–2.5 cm in length
Tarnasky et al.	1998	United States	Full text	Single-center comparator to placebo	80	46.05	–	–	5–7 Fr stent, 2–2.5 cm in length
Fazel et al.	2003	United States	Full text	Single-center comparator to placebo	74	44.7	86.49 %	–	Nasopancreatic 5 Fr catheter or 5 Fr stent, 2 cm length, 2 barbed
Harewood et al.	2005	United States	Full text	Single-center comparator to placebo	19	48.75	63.16 %	–	Straight, single flanged, polyethylene 5 Fr stent, 3–5 cm length
Sofuni et al.	2011	Japan	Full text	Multicenter comparator to placebo	201	66.4	37.81 %	–	Straight, 5 Fr stent, 3 cm in length
Pan et al.	2012	China	Full text	Single-center comparator to placebo	40	58.3	52.50 %	–	Single pigtail, 5 Fr stent
Lee et al.	2012	Korea	Full text	Single-center comparator to placebo	101	57.5	62.38 %	66.33 %	Single pigtail unflanged 3 Fr stent, 4–8 cm length
Kawaguchi et al.	2012	Japan	Full text	Single-center comparator to placebo	120	67	56.67 %	35.83 %	Unflanged on pancreatic duct side, 2 flanges on duodenal side 5 Fr stent, 3 cm length
Cha et al.	2013	United States	Full text	Single-center comparator to placebo	151	56.6	58.94 %	15.89 %	Straight or external 3/4 pigtail 5–7 Fr stent, 2–2.5 cm length

ERCP, endoscopic retrograde cholangiopancreatography; NSAID, nonsteroidal anti-inflammatory drug; IV, intravenous; LR, lactated ringer's

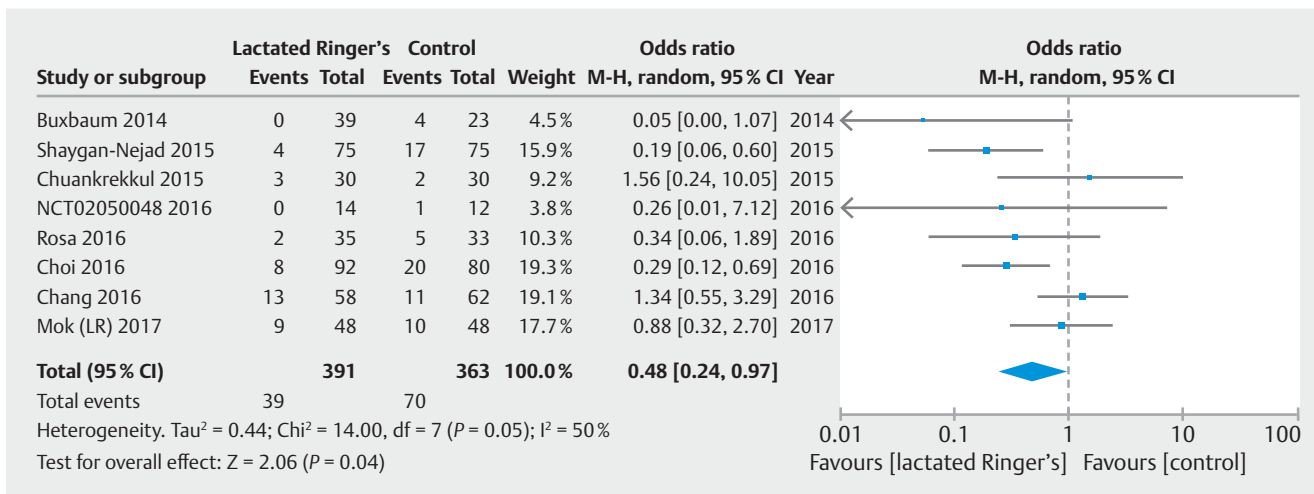
modalities compared to placebo. However, in indirect network meta-analysis, there was no statistically significant difference when treatment modalities were compared with each other. There were overlapping confidence intervals, although differences were observed in effect size.

Ranking probability

Ranking probability based on SUCRA indicated that prophylactic pancreatic duct stent placement had the highest probability (SUCRA=0.81, 95% CI [0.83 to 0.80]) of being ranked the best prophylactic treatment (► Fig. 6). As highlighted in the SUCRA probabilities figure, a combined strategy of LR solution plus rectal NSAIDs was the second most effective treatment to prevent post-ERCP pancreatitis (SUCRA=0.76, 95% CI [0.79 to 0.72]), followed by aggressive infusion of LR solution alone (SU-



► **Fig. 3** Direct treatment comparison of rectal NSAIDs to placebo for the prevention of post-ERCP pancreatitis.



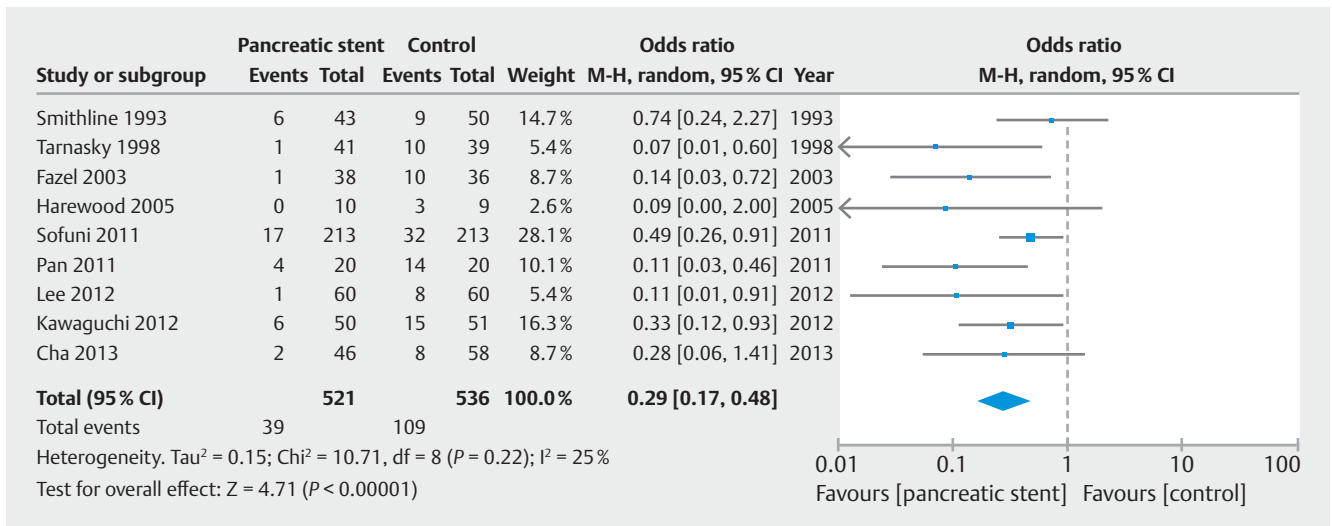
► **Fig. 4** Direct treatment comparison of aggressive LR solution to placebo for the prevention of post-ERCP pancreatitis.

CRA = 0.51, 95% CI [0.55 to 0.49]), and finally independent use of rectal NSAID use (SUCRA = 0.41, 95% CI [0.44 to 0.38]). A rankogram of interventions to prevent post-ERCP pancreatitis based upon cumulative SUCRA probabilities is highlighted in **Supplemental Fig. 6**.

Discussion

In this systematic review and network meta-analysis, compared to other treatment approaches, pancreatic duct stent placement appears to be the most effective strategy for the prevention of post-ERCP pancreatitis followed by prophylaxis using aggressive LR hydration and rectal NSAIDs, followed by high-volume LR infusions alone, and finally use of rectal NSAIDs.

Pancreatic duct stents reduce post-ERCP pancreatitis by relieving pancreatic ductal hypertension that may develop as a result of transient procedure-induced stenosis [58]. The most recent European Society of Gastrointestinal Endoscopy (ESGE) guideline on prophylaxis of post-ERCP pancreatitis recommends placement of a 5 Fr prophylactic pancreatic stent in high-risk cases [59]. However, pancreatic stent placement is technically challenging. Pancreatic stent requires deep cannulation of the duct and placement of a guidewire. Attempting to place a pancreatic duct stent with subsequent failure actually increases risk of post-ERCP pancreatitis by inducing injury to the pancreatic orifice. Hence, it is these authors' belief that pancreatic stent placement should only be attempted by providers with familiarity and expertise, in individuals deemed to be



► **Fig. 5** Direct treatment comparison of pancreatic stent placement to placebo for the prevention of post-ERCP pancreatitis.

► **Table 2** Summary results from network meta-analysis in the prevention of post-ERCP pancreatitis.

Post-ERCP treatment	Beta coefficient (β)	95% credible interval (CI) ¹	Quality of evidence
Lactated ringer's vs placebo	-0.69	-0.77 to -2.15	⊕⊕⊕ Moderate ²
Lactated ringer's + rectal nsaid vs placebo	-0.82	-1.45 to -0.19	⊕⊕⊕⊕ High
Pancreatic stent vs placebo	-1.37	-2.98 to -0.23	⊕⊕⊕⊕ High
Rectal NSAIDs vs placebo	-1.27	-2.30 to -0.70	⊕⊕⊕⊕ High
Lactated ringer's + rectal NSAIDs vs lactated ringer's	-0.55	-2.28 to 1.17	⊕⊕⊕ Low ³
Pancreatic stent vs lactated ringer's	-0.45	-1.30 to 0.39	⊕⊕⊕ Low ³
Rectal NSAIDs vs lactated ringer's	0.21	-1.32 to 1.74	⊕⊕⊕ Low ³
Pancreatic stent vs lactated ringer's + rectal NSAIDs	0.10	-1.61 to 1.80	⊕⊕⊕ Low ³
Rectal NSAIDs vs lactated ringer's + rectal NSAIDs	0.76	-0.92 to 2.44	⊕⊕⊕ Low ³
Rectal NSAIDs vs pancreatic stent	0.66	-0.84 to 2.17	⊕⊕⊕ Low ³

ERCP, endoscopic retrograde cholangiopancreatography; NSAID, nonsteroidal anti-inflammatory drug

¹ If the CI estimates are either all positive or negative (i. e., does not include a zero), it indicates that results are statistically significant.

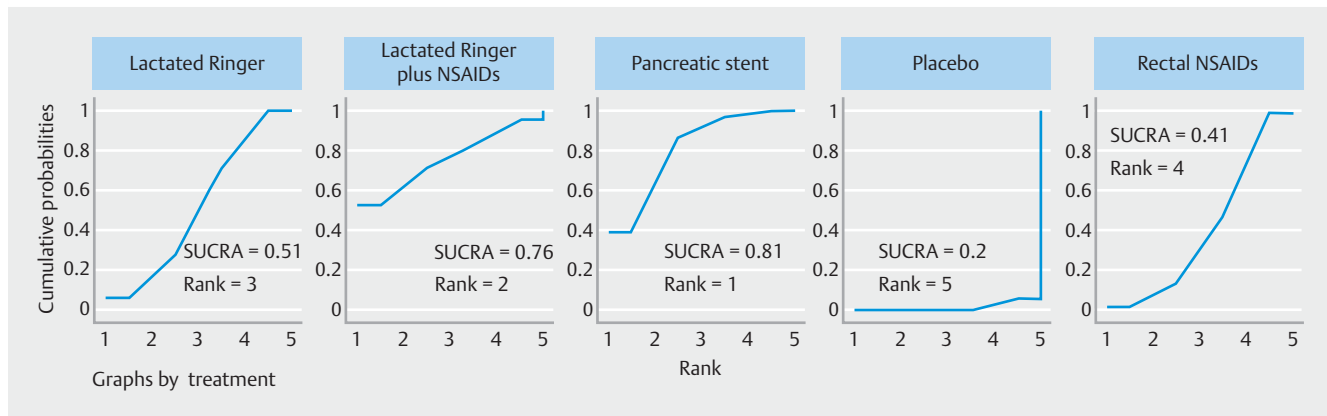
² Due to risk of bias in imprecision of summary results.

³ Due to risk of bias in individual studies, indirectness, and imprecision of summary results.

a high-risk, and in cases in which cannulation is not intentional and stent placement would be recommended in case of inadvertent cannulation. In patients in whom pancreatic stent placement is not feasible, use of alternative measures to reduce post-procedure pancreatitis should be employed.

Based on our study, aggressive hydration with LR appears to be effective when combined with rectal NSAIDs rather than

using rectal NSAIDs alone or LR alone. Use of rectal NSAIDs, potent inhibitors of phospholipase A2, has been increasingly adopted in to clinical practice [59, 60]. Current ESGE guidelines recommend routine rectal administration of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication [59]. Aggressive hydration with LR, which attenuates the acidosis that appears to promote zymogen acti-



► **Fig. 6** SUCRA cumulative probability plots for the prevention of post-ERCP pancreatitis.

vation and pancreatic inflammation, may be an effective intervention for preventing post-ERCP pancreatitis. Given the different mechanisms to prevent pancreatitis, it is not surprising that both work synergistically. Moreover, as both rectal NSAID therapy and LR infusion are inexpensive with relative few AEs, combination strategy is now has become a preferred strategy for post-ERCP pancreatitis prevention.

Our study observations are different from a previous network meta-analysis which reported that use of rectal NSAIDs when indirectly compared with pancreatic stent placement alone were associated with lower odds for developing post-ERCP pancreatitis [61]. However, that analysis included both observational studies and randomized controlled trials, which may have contributed to the divergent results. Furthermore, this previous study examined the efficacy of rectal NSAIDs and prophylactic pancreatic duct stent placement among both average-risk and high-risk cohorts. Our study specifically included only high-quality randomized controlled trials in high-risk patients and demonstrates the superiority of pancreatic stent placement as the best prophylactic measure for post-ERCP pancreatitis. Importantly, these findings do not take into account the cost-effectiveness of various therapies (i. e., rectal NSAIDs are inexpensive, easy to use, efficacious, and low risk). Despite our findings, questions still remain about whether all high-risk patients should receive a pancreatic stent—especially individuals who require multiple cannulation attempts of the biliary orifice.

It is important to note that the current systematic review and network meta-analysis is not without limitations. There were no studies comparing treatment strategies other than placebo except for one study that compared aggressive LR hydration to use of rectal NSAIDs. No currently published studies have examined the role of pancreatic duct stent versus rectal NSAIDs; although it should be pointed out there is an actively recruiting clinical trial designed to directly compare these two treatment modalities [62]. This study, with an expected enrollment of over 1400 patients, is a comparative effectiveness multicenter, non-inferiority trial of rectal indomethacin alone versus the combination of rectal indomethacin and prophylactic

pancreatic stent placement for prevention of post-ERCP pancreatitis.

While we included indirect comparison in a Bayesian network meta-analysis design, we cannot discount the possibility of conceptual heterogeneity whereby differences may exist in trial design, patient population, intervention (i. e., timing of rectal NSAID administration or operator variability in pancreatic duct stent placement), and outcome assessment which may limit true comparability between included studies [19,27]. Though we performed sensitivity analyses to minimize heterogeneity and generalize our findings, it is important to understand that not all risk factors for post-ERCP pancreatitis are created equal, and combinations or risk factors are not simply additive, but multiplicative [63–66]. Additional limitations include a lack of data on follow-up – though the primary endpoint of post-ERCP pancreatitis lends itself to definitive diagnosis as defined over a discrete period of time as detailed above [25]. Treatment-related AEs were not reported in our systematic review and network meta-analysis as well, which may limit clinical adoption of these strategies, especially pancreatic duct stent placement.

Despite these limitations, our study possesses several strengths. These include the comprehensive and simultaneous assessment of the relative efficacy of four competing or in-combination strategies to prevent post-ERCP pancreatitis in a high-risk cohort. Although SUCRA probabilities may not easily substitute for clinical judgement on a patient-by-patient basis, focusing on summary effect estimates and GRADE to rate overall quality of evidence allows for better approximations [27]. In addition, while conceptual heterogeneity was present in our study, strategies to limit the effect of conceptual heterogeneity included strict inclusion and exclusion criteria and use of multiple sensitivity analyses to assess the robustness of the results.

Furthermore, although there are several available strategies available to potentially reduce incidence post-ERCP pancreatitis, our results validate the current American Society of Gastrointestinal Endoscopy (ASGE) guidelines recommending pancreatic duct stenting in high-risk individuals – strong recommendation [22]. Future trials such as the one discussed above to assess rectal indomethacin alone versus combination therapy

with rectal NSAID and prophylactic pancreatic stent placement may help development of future recommendations; however, these are unlikely to occur [62]. Comparison of these different strategies alone may be of limited benefit clinically because the combination of the different treatments has already readily been adopted in clinical practice and shown to be effective with few complications.

Conclusion

In conclusion, based upon this systematic review and network meta-analysis, prophylactic pancreatic stent placement appears to be the most effective preventive strategy for post-ERCP pancreatitis in high-risk patients. Despite these findings, it is these authors' belief that combination therapy will likely predominate clinical practice. This is in part due to the increased risk of post-ERCP pancreatitis with failed cannulation of the pancreatic duct and the ease and cost of combination therapy with rectal NSAID use and aggressive LR infusion.

Competing interests

Dr. Shyam Varadarajulu is a consultant for Boston Scientific and Olympus. Dr. Udayakumar Navaneethan is a consultant for Janssen, AbbVie, Pfizer and Takeda.

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