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Systematic review with network meta-analysis: pharmacological prophylaxis against post-ERCP pancreatitis

V. S. Akshintala*, S. M. Hutfless*, E. Colantuoni†, K. J. Kim*, M. A. Khashab*, T. Li‡, B. J. Elmunzer§, M. A. Puhan‡, A. Sinha*, A. Kamal*, A. M. Lennon*, P. I. Okolo*, M. K. Palakurthy¶, A. N. Kalloo* & V. K. Singh*

*Division of Gastroenterology, Johns Hopkins Medical Institutions, Baltimore, MD, USA.
†Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
‡Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
§Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI, USA.
¶Department of Gastroenterology, Andhra Medical College, Visakhapatnam, India.

Correspondence to:
Dr V. K. Singh, Division of Gastroenterology, Johns Hopkins Hospital, 1830 East Monument Street, Room 428, Baltimore, MD 21205, USA.
E-mail: vsingh1@jhmi.edu

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SUMMARY

Background
The efficacy of many pharmacological agents for preventing post-ERCP pancreatitis (PEP) has been evaluated in randomised controlled trials (RCTs), but it is unclear which agent(s) should be used in clinical practice. Network meta-analyses of RCTs are used to simultaneously compare several agents to determine their relative efficacy and identify priority agents for comparison in future RCTs.

Aim
To evaluate pharmacological agents for the prevention of PEP by conducting a network meta-analysis of RCTs.

Methods
We searched MEDLINE, EMBASE and Cochrane Library databases for RCTs that evaluated the efficacy of agents for preventing PEP. RCTs were simultaneously analysed using random-effects network meta-analysis under the Bayesian framework to identify the best agents. The efficacy of agents was ordered according to the probability of being ranked as any of the top three best performing agents.

Results
The network meta-analysis included 99 RCTs evaluating 16 agents in 25 313 patients. Topical epinephrine (adrenaline) was the most efficacious agent with 85.9% probability of ranking among the top three agents, followed by nafamostat (51.4%), antibiotics (44.5%) and NSAIDs (42.8%). However, in a sensitivity analysis including only rectal NSAIDs, NSAIDs moved from fourth rank to second (58.1%). Patients receiving topical epinephrine, compared with placebo, had a 75% reduced risk of PEP (OR 0.25, 95% probability interval 0.06–0.66).

Conclusions
Topical epinephrine and rectal NSAIDs are the most efficacious agents for preventing post-ERCP pancreatitis, based on existing RCTs. Combinations of these agents, which act on different steps in the pathogenesis of post-ERCP pancreatitis, should be evaluated in future trials.

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INTRODUCTION

Post-ERCP pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), with an estimated incidence of 3–7% among average-risk patients and 15–20% among patients at high risk for developing PEP.[1–4] There has been an interest in the pharmacological prevention of PEP since 1977, when randomised controlled trials (RCTs) using aprotinin[5] and calcitonin[6] were published.

Only one of three professional societies with guidelines has recommended a pharmacological agent for PEP prophylaxis. The Japanese Guidelines (JPN)[7] and American Society of Gastrointestinal Endoscopy[8] have emphasised the lack of efficacy of certain pharmacological agents to prevent PEP, but they have not advocated in favour of any single pharmacological agent. However, the 2010 guidelines of the European Society of Gastrointestinal Endoscopy[9] recommended rectal NSAIDs for the prevention of PEP based on five placebo-controlled RCTs. A landmark multicentre RCT published in 2012 also demonstrated the superiority of rectal NSAIDs over placebo in high-risk patients.[10]

While seven RCTs have demonstrated the efficacy of rectal NSAIDs, these were all compared with placebo and it is unknown if rectal NSAIDs are better for the prevention of PEP when compared with other pharmacological agents studied in RCTs. Given the lack of head-to-head RCTs between the numerous pharmacological agents studied for PEP prophylaxis, statistical techniques, such as network meta-analyses (NMAs),[11, 12] can be used to perform direct and indirect comparisons of agents evaluated in prior RCTs to determine which agent(s) is(are) most efficacious for preventing PEP. The objective of this study was to conduct a NMA of RCTs of pharmacological agents for preventing PEP among patients undergoing ERCP.

MATERIALS AND METHODS

Literature Search

We searched PUBMED, EMBASE and Cochrane Central Register of Controlled Trials using a combination of MESH terms, EMTREE terms and keywords that describe ERCP (Appendix S1). We used the Cochrane Highly Sensitive Search Strategy and the RCT filter for EMBASE as recommended by the Cochrane Handbook 6.4.11 to identify RCTs.[13] The search had no language restrictions and included the period since inception of each database to June 2013. We also hand searched the bibliographies of relevant systematic reviews[14–31] and scanned the titles of journals that publish high-impact gastroenterology trials, including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Gastroenterology*, *Gut*, *American Journal of Gastroenterology*, *Gastrointestinal Endoscopy*, *Clinical Gastroenterology and Hepatology*, *Endoscopy*, *Alimentary Pharmacology and Therapeutics*, *Pancreas and Pancreatology* journals, published between January 2013 and June 2013 to identify additional trials for inclusion.

Eligibility criteria

We included RCTs that enrolled patients undergoing ERCP and that compared at least two agents, including placebo, for preventing PEP. We excluded conference abstracts, as the information required for the assessment of study quality as well as details related to the agent and outcome could not be adequately obtained. We also excluded studies reporting the incidence of hyperamylasaemia without reporting on the clinical signs of PEP. For studies published in languages other than English, we recruited native speakers of the respective language with a scientific background, to assist with determining trial eligibility and data abstraction. Agents were required to be evaluated in at least two eligible RCTs for inclusion in the NMA.

Article review and data abstraction

We employed a systematic approach for reviewing the search results in accordance with the Cochrane guidelines[32] and Agency for Healthcare Research and Quality Methods Guide.[33] Two reviewers independently reviewed titles, abstracts and full texts. In the title review stage, any study having a title potentially related to ERCP was included. In the abstract review stage, any study evaluating pharmacological agents in the setting of ERCP was included. During the full-text review, RCTs that compared at least two agents for the prophylaxis of PEP were eligible for data abstraction. We included articles that reported on the incidence of PEP, even if the number of events was zero. During the abstract and full-text review stages, we resolved conflicts by consensus. We consulted with an epidemiologist, biostatistician and/or endoscopist when necessary during the review process.

One reviewer abstracted data that were verified by a second reviewer, using pilot-tested data extraction sheets containing all the variables of interest, including study design, population and agent characteristics, as well as the incidence, severity and mortality of PEP. We assessed study quality in terms of random sequence generation, allocation concealment, blinding of the patients and

investigators, bias introduced by the investigators due to placement of pancreatic duct stents, and a summary of assessment of bias across the study using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[34]

Outcomes of interest

The incidence of PEP was the primary outcome of interest. Secondary outcomes were the severity and mortality of PEP.

Statistical analysis

We used a Bayesian random-effects model for network meta-analysis (NMA) in WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK) with an adjustment provided for three-arm trials as described by Ades *et al.*[35] For RCTs that compared multiple doses of the same agent in different arms, the results from different arms were pooled for analysis. This pooling was carried out to allow our model to attain equilibrium (see below). We created a model for each outcome of interest: incidence, severity and mortality of PEP.

To model the most efficacious agent in the NMA, the Bayesian algorithm utilised data from the RCTs with non-informative priors and was simulated to run 160 000 draws of probable results. Each draw provided an estimate of the incidence, severity or mortality rate for each agent and this was used to determine the ranking of each agent in relation to the other agents in the NMA. The percentage of times each agent ranked among the top three performing agents (maximum of 300%), among all the draws, was used to identify the most efficacious agent. The initial 80 000 draws were excluded to avoid the influence of the initially unstable values.[36] We summarised the ranking results using rankograms.[37] We also calculated pairwise odds ratios (OR) with 95% probability intervals (PI)[38] to compare the relative odds of incidence, severity or mortality with placebo as the reference agent. The direction of the point estimate ($OR < 1$ or $OR > 1$) that provides the rank is accorded greater importance than the absolute value of the OR or the 95% PI for our interpretation of the results in this NMA. The attainment of equilibrium of the model, i.e. a state in which the model gives stable results after running multiple iterations, was evaluated by examining the Markov chain (MC) error for each outcome. The model was considered to be stable if the MC error was less than 5% of the standard deviation (s.d.) of the corresponding rank or OR.

We evaluated heterogeneity and consistency within the NMA by quantitative assessment using statistical methods. Heterogeneity was quantified by including a random intercept for study within the Bayesian NMA model. The variance of the random intercept represents the variation across studies in the agent–outcome relationship. Because high-risk status was thought to be the most likely source of potential heterogeneity, an analysis that excluded RCTs that only included patients at high risk of developing PEP was conducted.

A Bayesian approach for a multivariate meta-regression model[39] was used to assess consistency of the model across different designs of comparison between the same pairs of agents, i.e. agents A and B can be compared by calculating OR from a trial comparing A vs. B vs. C or A vs. B (Appendix S1). The consistency was treated as a fixed effect and represents the difference in expected outcomes comparing the possible trial designs. A Wald test with degrees of freedom equal to the number of consistency fixed effects was used.

Sensitivity analyses

Multiple separate analyses were conducted to evaluate the certainty of results. The most efficacious agent was excluded from the analysis and the model was rerun to assess the influence of the excluded agent on the ranking order. The agents that were evaluated only among high-risk patients were compared in a separate analysis to determine if the rank order of the most efficacious agents was similar in this subgroup. To assess for the influence of route of administration and dosage on the efficacy of these agents, the 16 agents were broken down into 30 categories and a separate analysis was conducted. Considering the clinical guidelines' recommendation of using rectal NSAIDs[9] over other routes of NSAIDs, RCTs evaluating oral and intramuscular route for NSAIDs were excluded to evaluate the efficacy of rectal NSAIDs over other agents.

The number needed to treat (NNT) was calculated for each of the 16 agents by using the OR between the agent and placebo obtained from NMA based on the methods described by Chatellier *et al.*[40] The pooled incidence of PEP among the placebo groups of all RCTs weighted by the sample size of each RCT was calculated for this purpose.

RESULTS

Search results and study characteristics

The electronic searches resulted in 9094 titles, of which 94 RCTs met the inclusion criteria for NMA. We identified an additional five RCTs from hand searching,

resulting in a total of 99 RCTs for this analysis (Figure 1). A total of 25 313 patients were randomly assigned to one of 16 agents or placebo, among whom 13 285 (52.5%) were women. The mean age of the patients in these RCTs ranged from 42 to 70 years. Among the RCTs that met the inclusion criteria for NMA, the first RCT was published in 1984 and the most recent publication was from 2012.

The 16 pharmacological agents that met the inclusion criteria for the NMA included allopurinol, antibiotics (cefotaxime, ceftazidime, ciprofloxacin, metronidazole or ofloxacin), corticosteroids (prednisone, methyl prednisolone and hydrocortisone), epinephrine (adrenaline), gabexate, glyceryl trinitrate, heparin, interleukin (IL)-10, NSAIDs (indomethacin, diclofenac), N-acetylcysteine (NAC), nafamostat, nifedipine, octreotide, secretin,

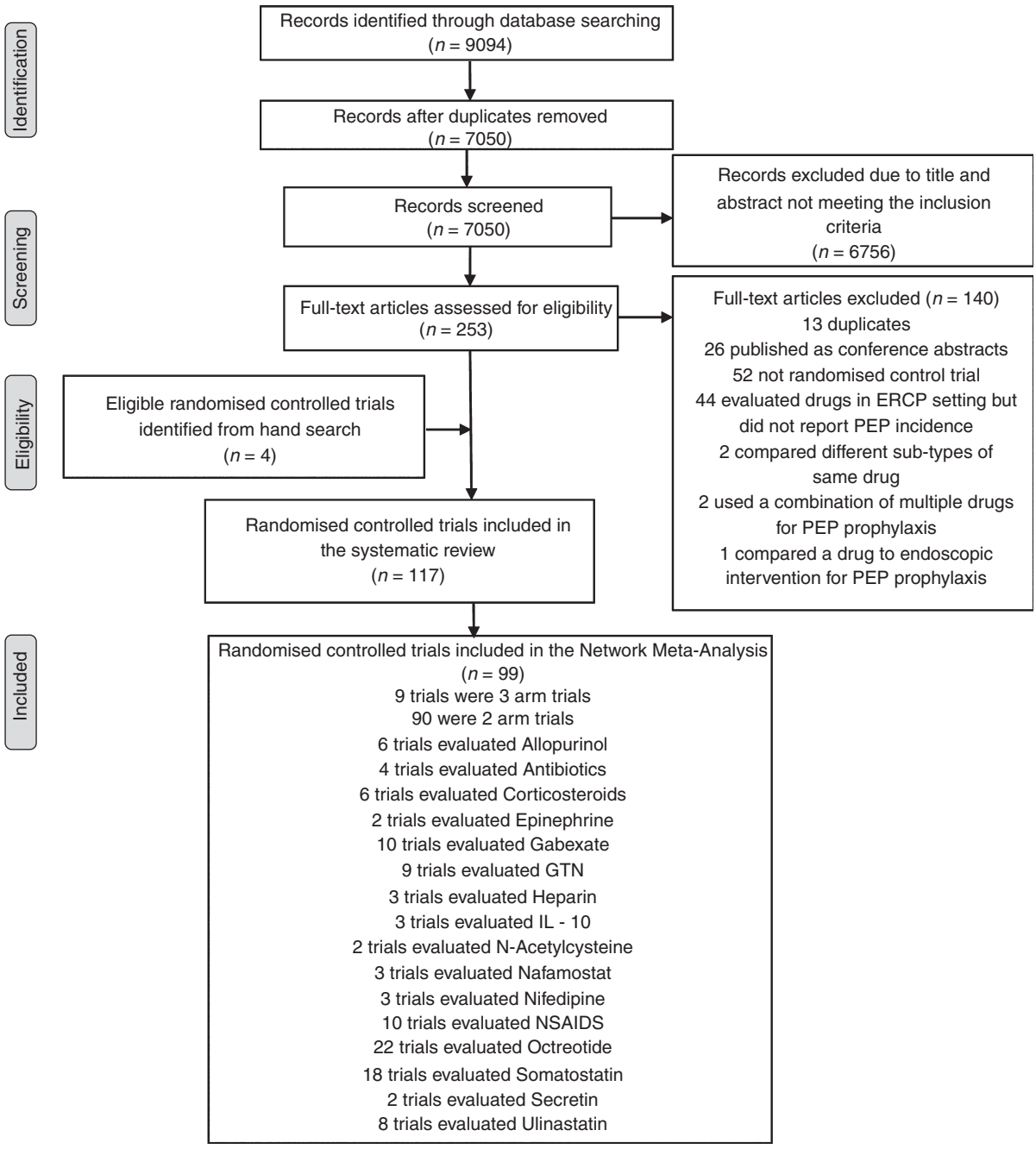

Figure 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing the inclusion of studies from literature review through network meta-analysis.

somatostatin and ulinastatin (Appendix S2, References). There were another 20 agents that did not meet the inclusion criteria for NMA because they were evaluated in a single RCT. The 20 excluded trials are further described in Appendix S2 (Table S1). None of the 20 agents showed statistically significant efficacy based on the singe trial and are unlikely to have influenced the results of NMA if included in the analysis.

The NMA included 12 head-to-head trials and 87 placebo-controlled trials. There were nine three-arm RCTs[41–49] that evaluated two different agents with placebo and seven RCTs[50–56] that evaluated single agents at different dosages with placebo. There were 85 RCTs published in English, 5 in Chinese,[44, 45, 48, 57] 2 in Italian,[58, 59] 2 in Spanish,[60, 61] 2 in German,[62, 63] 1 in Hungarian,[64] 1 in Korean[46] and 1 in Japanese.[65] On assessing the quality of RCTs, there were 62 (62.6%) RCTs that had adequate random sequence generation, 53 (53.5%) that had adequate allocation concealment and 60 (60.6%) that had adequate blinding of patients and study personnel (Appendix S2, Figure S1). However, 19 (19.2%) had a high risk of bias due to the placement of pancreatic duct stents in some of their study patients. A total of 73 (73.7%) RCTs were conducted at tertiary care or referral centres. Of the 47 RCTs that reported on conflicts of interest, there were 14 (29.8%) RCTs that reported receiving support from industry.

The definition of PEP was variable across studies (Appendix S2, Table S2), but 74 (74.7%) of the 99 RCTs defined PEP using a consensus definition as 'clinical pancreatitis with serum amylase at least three times normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission'.[66] Twenty-four (24.2%) studies reported using definitions similar to the consensus definition for PEP. Amylase and lipase were used to define PEP in 15 (15.2%) studies, while two (2%) studies used the results of abdominal imaging in addition to elevations in pancreatic enzymes. The results of abdominal imaging consistent with PEP, without regard to enzyme levels, were used by one study to define PEP.

Efficacy of pharmacological agents to prevent PEP

Figure 2 displays a network figure of all the agents included in this NMA and the number of RCTs comparing different agents. Figure 3 provides a graphical representation of the ranking order, which reflects efficacy. Among the 16 agents, topical epinephrine was the most efficacious agent to prevent PEP, with an 86.5% probability of being ranked in the top three positions followed by nafamostat (52%), antibiotics (45.4%), NSAIDs (40.9%),

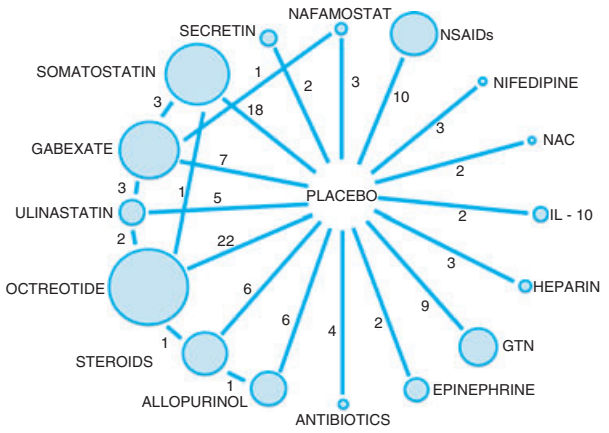

Figure 2 | Network of randomised controlled trials (RCT) comparing different pharmacological agents for their efficacy to prevent post-ERCP pancreatitis. The size of each node is proportional to the number of randomised patients (sample size). The number adjacent to the lines connecting agents indicates the number of RCTs. NAC, N-acetylcysteine; IL, interleukin; GTN, glyceryl trinitrate.

secretin (26.6%) and somatostatin (20.5%). The corresponding ORs for these six agents compared with placebo were 0.25 (95% PI 0.06–0.64), 0.41 (95% PI 0.17–0.86), 0.46 (95% PI 0.15–1.06), 0.42 (95% PI 0.26–0.64), 0.62 (95% PI 0.18–1.60) and 0.47 (95% PI 0.30–0.69) respectively. The OR comparing the top two agents, topical epinephrine and nafamostat, with each other was 0.42 (95% PI 0.13–2.18) (Appendix S2, Table S3).

Efficacy of pharmacological agents to prevent severe PEP

There were 48 RCTs that reported the severity of PEP. These RCTs evaluated 15 agents in 15 671 patients. All studies reported the severity of PEP using the consensus criteria. Severe PEP includes hospitalisation for ≥10 days or development of any of the following during hospitalisation: haemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, percutaneous drainage or surgery.[66] Overall, severe PEP was reported in 0.49% and 0.53% of patients in the pharmacological agent and placebo groups respectively (Appendix S2, Table S2). Too few events occurred to perform a NMA or identify trends in efficacy based on individual trial ORs for severe PEP.

Efficacy of pharmacological agents to prevent PEP mortality

There were 62 RCTs that reported on mortality due to complications arising from PEP. These RCTs evaluated

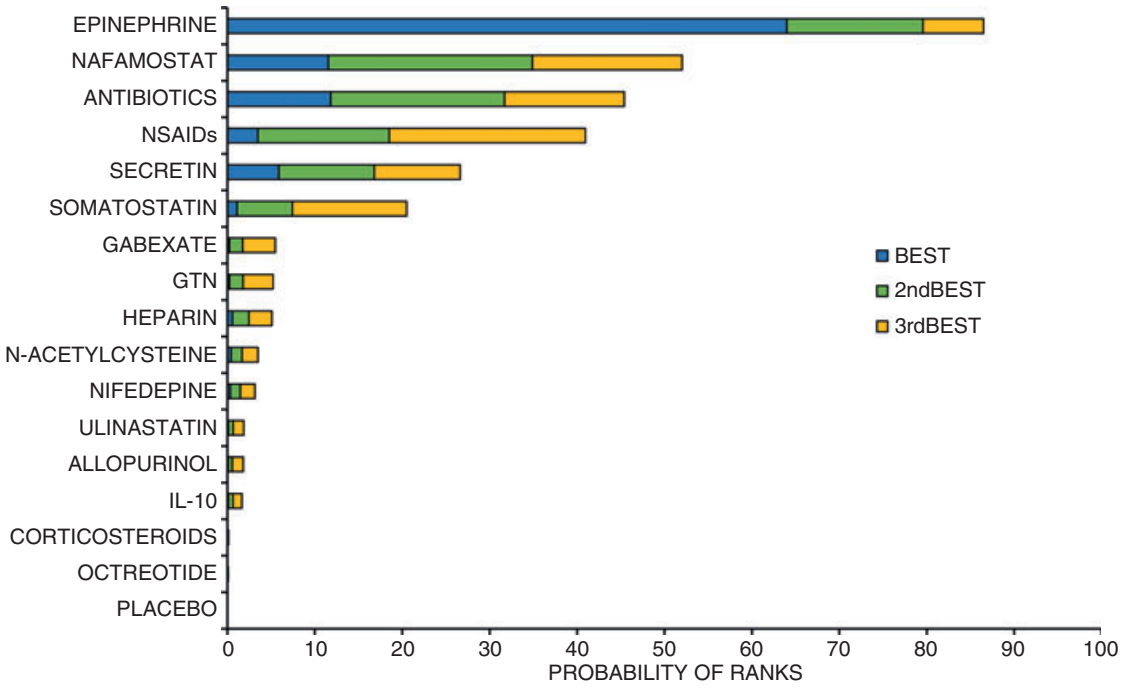

Figure 3 | Rankograms comparing the pharmacological agents to prevent post-ERCP pancreatitis. The vertical axis lists the agents evaluated. The horizontal axis lists the probability of achieving the best, second best or the third best rank based on repeated draws of the algorithm. The agent with the longest bar indicates the most efficacious agent. The total probability for top three ranks together is 300%.

13 agents in 16 264 patients. A total of nine deaths were reported: three in patients receiving pharmacological agents and six in patients receiving placebo (Appendix S2, Table S2). Too few events occurred to perform a NMA or identify trends in efficacy to prevent PEP related mortality.

Evaluation of consistency and heterogeneity

The Wald test for consistency (χ^2) was 18.90 with a P value of 0.98, indicating that the primary outcome model did not demonstrate inconsistency across designs. The heterogeneity parameter was 0.39 (s.d. 0.12), indicating the presence of heterogeneity. Our qualitative assessment of heterogeneity led us to suspect that RCTs that included only high-risk patients may be an important component of the heterogeneity. After excluding RCTs that had only high-risk patients, there was less heterogeneity 0.23 (s.d. 0.09) and the rank order of remaining top-ranking agents did not change when compared with the initial ranking (Appendix S2, Figure S2).

Sensitivity analyses

When the RCTs evaluating topical epinephrine were excluded, the ranking of the remaining agents remained mostly unchanged (Appendix S2, Figure S3). After excluding topical epinephrine, the most efficacious agent was nafamostat with 61.8% probability of ranking among top three agents followed by antibiotics (59.3%) and NSAIDs (59.3%).

A separate analysis of the RCTs that included only high-risk patients had six RCTs evaluating gabexate,[41] NSAIDs,[10] octreotide,[67] somatostatin,[41, 68] ulinastatin[69] and IL-10[56] (Appendix S2, Figure S4). NSAIDs ranked as the most efficacious agent to prevent PEP in these RCTs evaluating high-risk patients (Appendix S2, Figure S5). Topical epinephrine and nafamostat have not been evaluated in a trial of only high-risk patients.

The model to evaluate the agents based on the route of administration and dose did not reach equilibrium after 1 000 000 iterations, prohibiting the report of quantitative comparisons.[36] Instead of relying on statistical results, we examined the direction and magnitude of the individual RCT ORs. There was no clear trend in efficacy by dose or route (Appendix S2, Table S4).

After excluding RCTs that evaluated oral NSAIDs and intramuscular NSAIDs, leaving only rectal NSAIDs, the rank order of the agents changed. Topical epinephrine continued to be the most efficacious agent to prevent

Table 1 | Odds ratios and number needed to treat of each agent compared with placebo ordered based on the results of the rankogram

Rank	Agent	Number of RCTs comparing the agent with placebo	Number of patients in treatment arm	OR of agent compared with placebo (95% PI)	NNT
1	Topical epinephrine	2	646	0.25 (0.06–0.65)	15
2	Rectal NSAIDs	8	1017	0.37 (0.21–0.59)	19
3	Nafamostat	3	626	0.41 (0.17–8.34)	20
4	Antibiotics	4	1082	0.46 (0.15–1.07)	21
5	Secretin	2	429	0.62 (0.18–1.61)	31
6	Somatostatin	18	1759	0.47 (0.30–0.70)	22
7	Gabexate	7	1631	0.59 (0.35–0.95)	29
8	GTN	9	1082	0.61 (0.36–0.97)	30
9	Heparin	3	313	0.91 (0.32–2.04)	135
10	N-acetylcysteine	2	179	1.1 (0.34–2.67)	123
11	Nifedipine	3	205	1.03 (0.36–2.35)	408
12	Ulinastatin	5	678	0.82 (0.40–1.49)	67
13	Allopurinol	6	986	0.76 (0.41–1.26)	50
14	IL-10	2	383	0.95 (0.41–1.89)	243
15	Steroids	6	1221	0.97 (0.55–1.59)	406
16	Octreotide	22	2179	0.79 (0.53–1.13)	57

RCT, randomised controlled trial; GTN, glyceryl trinitrate; IL, interleukin; OR, odds ratio; PI, probability intervals; NNT, number needed to treat.

Odds ratio of less than 1 indicates the pharmacological agent to be protective.

PEP, with an 85.4% probability of being ranked in the top three positions; however, rectal NSAIDs moved from a fourth to second rank (58.1%) followed by nafamostat (48.4%), antibiotics (42.6%), secretin (24.5%) and somatostatin (16.7%).

The NNT for topical epinephrine was 15, while it was 19 for rectal NSAIDs. The corresponding NNT values for each of the other agents are listed in Table 1.

DISCUSSION

Despite the numerous agents evaluated in prior RCTs and in clinical use for the prevention of PEP, the majority of agents have not been compared in head-to-head RCTs. We conducted a NMA of 16 pharmacological agents evaluated in 99 RCTs involving 25 313 patients as well as several sensitivity analyses and found that topical epinephrine and rectal NSAIDs are the most efficacious agents for the prevention of PEP.

The top six agents, from most to least efficacious for preventing PEP, were topical epinephrine, rectal NSAIDs, nafamostat, antibiotics, secretin and somatostatin (Figure 4). The sharp demarcation in the probability of ranks, between topical epinephrine and the other agents, indicates that topical epinephrine should be further evaluated in future studies. Similarly, the difference between the sixth ranking agent, somatostatin, and the seventh ranking agent, gabexate, highlights the limited efficacy of those agents ranking from seventh to 16th and suggests that future clinical trials should exclude these agents from further study.

There were agents that share a similar mechanism of action, but had widely discrepant ranks. For example, nafamostat, gabexate and ulinastatin are all protease inhibitors, but nafamostat ranked higher than gabexate and ulinastatin. This is probably because of the higher potency[70] and longer duration of action[71] of nafamostat. Somatostatin and octreotide are also similar for their anti-secretory properties, but somatostatin ranked higher, potentially because octreotide causes constriction,[72, 73] while somatostatin causes relaxation of the sphincter of Oddi.[74]

There were two RCTs comparing topical epinephrine with placebo and these were conducted at different centres in Asia.[75, 76] The primary limitations of these studies were that they included only patients undergoing diagnostic ERCP and both utilised an ERCP protocol that mandates that a more experienced endoscopist complete difficult procedures. While patients undergoing diagnostic ERCP are typically considered to be at low risk for PEP,[2] it should be noted that, in the epinephrine trial conducted by Xu *et al.*,[75] 9% of the patients had acinarisation and the mean number of pancreatic duct contrast injections was 4.6. This suggests that many patients became high risk due to procedural interventions. How-

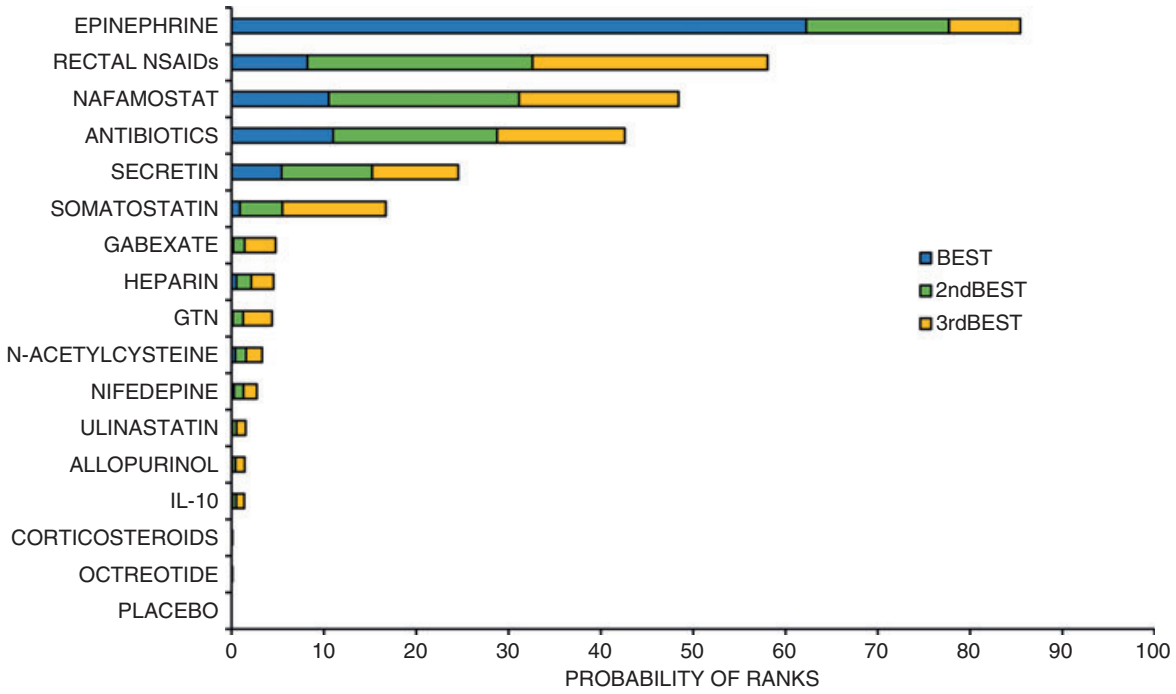

Figure 4 | Sensitivity analysis: after exclusion of trials evaluating oral, intramuscular NSAIDs and inclusion of only rectal NSAIDs; rankograms comparing pharmacological agents to prevent post-ERCP pancreatitis. The vertical axis lists the agents evaluated. The horizontal axis lists the probability of achieving the best, second best or the third best rank based on repeated draws of the algorithm. The agent with the longest bar indicates the most efficacious agent. The total probability for top three ranks together is 300%.

ever, these particular limitations and other methodological limitations can be similarly found in all of the trials evaluating the other top-ranking agents in the present NMA. It should be highlighted that we conducted several sensitivity analyses and found that the rank order of the top six agents did not change after excluding each individual agent from the analysis. Interestingly, when we excluded only the epinephrine trials and re-evaluated the rank order, nafamostat ranked in the top position followed by antibiotics and then NSAIDs.

There are several possible explanations for why topical epinephrine was found to be the most efficacious agent for the prevention of PEP. Although the pathophysiology of PEP is not well understood,[77–79] several human[2–4, 80–82] and animal[83] studies support the important role that pancreatic ductal outflow obstruction due to papillary oedema plays in the development of PEP. Topical application of epinephrine induces arteriolar vasoconstriction in the papillary vasculature that reduces oedema and subsequent pancreatic ductal outflow obstruction.[84, 85] Topical epinephrine has also been shown to relax duodenal musculature[86] and the sphincter of Oddi,[87] both of which also reduce pancreatic outflow obstruction. The concept of pancreatic ductal outflow obstruction as an early step in the pathogenesis of PEP has been espoused in prior reviews.[77, 78] By reducing pancreatic ductal outflow obstruction, topical epinephrine acts at an early point in the pathogenesis of PEP. In addition, the local application of epinephrine increases the likelihood of it acting within this early therapeutic window and represents a clear advantage over other agents, which act on a more downstream point in the pathogenesis of PEP when the inflammatory cascade may no longer be attenuated. A topical agent also carries certain advantages over agents that are administered through different routes. For example, rectally administered agents may be expelled due to endoscopic air insufflation of the bowel or incomplete absorption.[88, 89] Rectal agents can also be difficult for endoscopy staff to administer when patients undergo ERCP in the supine position.

Due to its ability to reduce pancreatic ductal outflow obstruction, topical epinephrine essentially acts as the 'pharmacological equivalent' of a pancreatic stent. Numerous RCTs have shown the superiority of pancreatic stents over no stent for preventing PEP in high-risk patients.[90] The key difference between topical epineph-

rine and pancreatic stents is the short duration of action of epinephrine. However, one RCT reported that 60% of prophylactic pancreatic stents spontaneously migrate within 24 h[91] with no difference noted in the incidence of PEP between this group and those in whom the pancreatic stents remained *in situ*. Another study reported that the mean time for spontaneous pancreatic stent dislodgement can be as little as 2.1 days.[92] These studies suggest that pancreatic stents may also act within a narrow therapeutic window. In addition, pancreatic stents have many drawbacks, including technical difficulty with placement as well as the cost of stents and follow-up endoscopy commonly required for stent removal.

When only RCTs evaluating rectal NSAIDs were included in the model, rectal NSAIDs ranked second after topical epinephrine. Rectal NSAIDs are the only pharmacological agents currently recommended in clinical guidelines[9] based on their efficacy, low cost, favourable safety profile and widespread availability. While nafamostat and antibiotics ranked in the third and fourth positions, there are several reasons limiting their use in clinical practice. Nafamostat is intravenously administered over an extended time period before, during and after ERCP. One study administered nafamostat for as long as 24 h.[55] The primary limitation of antibiotics is microbial resistance, which is already a significant global health problem.[93]

A closer examination of route of administration, dose, cost, advantages and disadvantages of each of the six top-ranking agents from the present NMA suggests that topical epinephrine and rectal NSAIDs are both inexpensive, widely available, easy to administer and associated with few side effects. The costs of rectal NSAIDs and topical epinephrine, $1.12 and $0.24,[94] respectively, are much lower than the cost of prophylactic pancreatic duct stent placement, which can range from $160 to $508.[95, 96] Given that topical epinephrine and rectal NSAIDs act to counter different steps in the pathogenesis of PEP, i.e. pancreatic ductal outflow obstruction and the inflammatory cascade, respectively, they can potentially be used in combination for a synergistic effect. A recent meta-analysis concluded that NSAIDs are only able to reduce the incidence of PEP from 13.9% to 8%.[29] It is possible that the concomitant use of topical epinephrine and rectal NSAIDs could further reduce the incidence of PEP.

There are several limitations to the present NMA. The first is the inclusion of RCTs that enrolled patients with wide discrepancies of risk for developing PEP, as this results in statistical heterogeneity. However, when we excluded trials of only high-risk patients from our NMA, there was less heterogeneity and the rank order of agents did not change. A separate analysis of the trials that included only high-risk patients showed a similar ranking of agents, although topical epinephrine was not evaluated in high-risk patients. It is also important to emphasise that there is currently no method to quantify the risk of developing PEP based on known demographic, clinical and procedural risk factors. This limitation essentially affects not only our NMA but also all RCTs conducted in this field. The second limitation is the use of pancreatic duct stents, in addition to drugs, for PEP prophylaxis in some of the trials. While we were not able to control for the effect of pancreatic stenting in our NMA, pancreatic stenting was performed in only a small percentage of patients, equally distributed in the intervention and placebo arms, and in more recent trials and, therefore, did not significantly impact the performance of the drugs in the NMA.

It must be emphasised that the objectives of NMA differ from conventional meta-analyses. While conventional meta-analyses summarise evidence from RCTs for a particular agent(s) and provide evidence for framing management guidelines, NMA summarises evidence from multiple competing interventions simultaneously and provides direction for future research and clinical practice. Our study identified potential sources of heterogeneity across trials and recommends exclusion of relatively poor performing agents and further evaluation of better performing agents.

In conclusion, the present network meta-analysis found that topical epinephrine and rectal NSAIDs are the best performing agents to prevent PEP. Future trials are needed to determine whether topical epinephrine, alone or in combination with rectal NSAIDs, can effectively reduce or further reduce the incidence of PEP.

AUTHORSHIP

Guarantor of the article: Dr Vikesh K. Singh.

Author contributions: Venkata S. Akshintala – study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; administrative, technical and material support; study supervision. Susan M. Hutfless – study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Elizabeth Colantuoni – analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy and WinBUGS code for Bayesian multivariate meta-regression model.

Appendix S2. Supplementary data and analyses.

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