Nafamostat Reduces the Incidence of post-ERCP Pancreatitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

István László Horváth[1,2], Dénes Kleiner[1,2], Rita Nagy[1,3,4], Péter Fehérvári[1,5], Balázs Hankó[2], Péter Hegyi[1,4,6] and Dezső Csupor[1,4,7,*]

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). As the management of pancreatitis is limited, clinical approaches focus on the prevention of post-ERCP pancreatitis (PEP). In theory, the serine protease inhibitor nafamostat can reduce circulating inflammatory mediators in pancreatitis. We aimed to investigate the effect of nafamostat in the prevention of PEP in this systematic review and meta-analysis. The protocol for this review was registered in PROSPERO (CRD42022367988). We systematically searched 5 databases without any filters on September 26, 2022. The eligible population was adult patients undergoing ERCP. We compared the PEP preventive effect of nafamostat to placebo. The main outcome was the occurrence of PEP. We calculated the pooled odds ratios (ORs), mean differences, and corresponding 95% confidence intervals (95% CIs) and multilevel model. The risk of bias was assessed using the Rob2 tool. Seven randomized controlled trials involving 2,962 patients were eligible for inclusion. Nafamostat reduced the overall incidence rate of PEP (20 mg, OR: 0.50, 95% CI: 0.30–0.82 and 50 mg, OR: 0.48, 95% CI: 0.24–0.96). However, the occurrence of mild PEP was significantly reduced only in the subgroup receiving 20 mg nafamostat (OR, 0.49, 95% CI: 0.31–0.77). Overall, nafamostat therapy reduced moderate PEP in high-risk patients (OR: 0.18, 95% CI: 0.0.4–0.84) and mild PEP in low-risk patients (OR: 0.32, 95% CI: 0.17–0.61). Nafamostat is an effective therapy in the prevention of mild post-ERCP pancreatitis. Further research is required to determine the cost-effectiveness of this therapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The leading complication of endoscopic retrograde cholangiopancreatography (ERCP) is post-ERCP pancreatitis (PEP). The pharmacological management of pancreatitis is limited; therefore, researches focus on the prevention of PEP.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated the efficacy of low and high dose nafamostat in the prevention of PEP compared with placebo.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We pooled the results from 7 randomized controlled trials involving 2,962 patients. Nafamostat reduced the overall incidence rate of PEP, however, the occurrence of mild PEP was significantly reduced only in the subgroup receiving 20 mg. Furthermore, nafamostat therapy significantly reduced moderate PEP in high-risk patients and mild PEP in low-risk patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Clinicians might use nafamostat in low-risk patients expected to develop mild PEP; however, cost-effectiveness studies are required.

Endoscopic retrograde cholangiopancreatography (ERCP) is used in the diagnosis and in the treatment of patients with pancreatobiliary diseases. The procedure is minimally invasive, but not without risks. Although the overall mortality rate of ERCP is around 1%, it is highly dependent on the underlying disease, particularly cancer.[1] The leading complications of ERCP are bleeding, perforation, and post-ERCP pancreatitis (PEP).[2,3]

[1]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary; [2]University Pharmacy, Department of Pharmacy Administration, Semmelweis University, Budapest, Hungary; [3]Heim Pál National Pediatric Institute, Budapest, Hungary; [4]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; [5]Department of Biostatistics, University of Veterinary Medicine, Budapest, Hungary; [6]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary; [7]Institute of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary. *Correspondence: Dezső Csupor (csupor.dezso@szte.hu)

Received June 27, 2023; accepted November 21, 2023. doi:10.1002/cpt.3118

A common definition for PEP is based on the consensus by Cotton *et al*.[4] and the revised Atlanta classification for acute pancreatitis (AP).[5] However, the latest European guideline suggests a definition of the condition as "new or worsened abdominal pain combined with > 3 times the normal value of amylase or lipase at more than 24 hours after ERCP and requirement of admission or prolongation of a planned admission."[6] PEP is comparable in severity to biliary pancreatitis, but less severe than hypertriglyceridemia-induced AP.[7] The overall incidence of PEP ranges from 3.5 to 9.7%,[6] with a mortality rate of around 0.7%. Of all ERCP cases, the incidences of mild, moderate, and severe PEP are 6.0%, 3.3%, and 0.7%, respectively.[8] The precise pathophysiology is not fully understood; however, several risk factors have been identified. Physical (mechanical, thermal, and hydrostatic), chemical (contrast agent and enzymatic), and patient-related (female sex, history of PEP, and sphincter of Oddi dysfunction) factors can contribute to the development of PEP.[9] Physical damage can occur during the procedure, for example, the prolonged manipulation of the papillary orifice, or difficult cannulation, causing papillary edema. This process inhibits the outflow of the pancreatic juice and thus leads to pancreatitis.[9] The type of contrast agent might cause osmolality-induced and ionic toxicity; however, a recent analysis found no significant difference between the types of agents.[10]

There is no recommended treatment for acute pancreatitis[11] and PEP; therefore, the focus shifted toward preventative measures, such as the use of appropriate techniques and patient selection based on risk factors, or consideration of prophylactic duct stent.[9] As chemoprophylaxis, only aggressive hydration and the combination of indomethacin and nonsteroidal anti-inflammatory drugs have been proven to be effective.[12] Protease inhibitors can inhibit several pancreatitis-related mediators and might show effectiveness as prophylactic agents, but the evidence is controversial or scarce.[13] Despite the lack of evidence, Seta *et al*.[14] reported a significant increase in the prescription of these drugs in Japan.

The serine protease inhibitor nafamostat is an approved drug in South Korea and Japan for the treatment of AP and disseminated intravascular coagulation with a general dose of 10 mg once or twice a day. It had promising results in the past in the prevention of PEP.[15] However, a recent network meta-analysis showed no beneficial effect.[16] Since then, several trials had been published; therefore, we aimed to investigate the current evidence for nafamostat in the prevention of PEP in this systematic review and meta-analysis.

METHODS

Search and selection strategy

The recommendations of the Cochrane Collaboration[17] and the statements of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020)[18] were followed in reporting the findings of this systematic review and meta-analysis. We registered the review protocol in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022367988).

The Population, Intervention, Comparator, Outcomes (PICO) process was used to define our clinical question. The patient population consisted of adult patients who underwent the ERCP procedure. We investigated the effects of nafamostat as a preventive treatment compared with placebo. The primary outcome was the incidence of PEP. Secondary outcomes were PEP severity, complication rates, adverse reactions, and laboratory parameters. Only randomized clinical trials were eligible for inclusion.

The systematic search was conducted on September 26, 2022 in 5 databases (Cochrane Central Register of Controlled Trials, Embase, PubMed, Scopus, and Web of Science) without any restrictions or filters, using the following search key: *pancreatitis AND nafamostat AND random**. We checked the reference lists of the included studies for additional reports. The detailed inclusion and exclusion criteria, and the reasons for exclusions are in the Supplementary Material.

We processed the exported database search results in a reference manager software (EndNote X9; Clarivate Analytics, Philadelphia, PA). Duplicate records were removed using an automation tool and manually (author I.L.H.). The title-abstract and the full-text selection were performed by two independent authors (I.L.H. and D.K.) according to eligible criteria. We calculated the Cohen's Kappa coefficient to evaluate the level of agreement between the two authors at each major step. Non-English articles were translated using Google Translate (Google LLC, Mountain View, CA).

Microsoft Excel (Microsoft Office 365; Microsoft, Redmond, WA) was used to manage the extracted data. Two independent authors retrieved the following information for each eligible trial: author, publication year, the origin of the trial, number of centers, sample sizes, gender, mean age, applied medications (dosage and duration), and procedure-related data.

Statistics

We used multilevel random effect models[19] with dosage and post-ERCP severity as predictors. Multilevel modeling was necessary to account for the clustered data structure (multiple effect sizes reported per study) while also allowed to simultaneously test for moderator effects. Initially, we tested for nafamostat dosage effect on our outcome effects (PEP and hyperamylasemia odds). We also tested the interaction of dosage and risk categories and severity in separate models. Small study bias was controlled for visually with funnel plots. We used R version 4.2.1[20] using the metafor package.[21]

We were able to perform a subgroup analysis according to the risk stratification of the patients. Generally, patients were categorized as "high" risk, if they had any of the following characteristics: history of PEP, suspected sphincter of Oddi dysfunction, difficult cannulation, and young age. The detailed definitions are summarized in **Table S1**.

Risk of bias and certainty of evidence assessment

The risk of bias was independently assessed by two authors (I.L.H. and D.K.) using the Cochrane risk-of-bias tool (RoB 2)[22] for randomized clinical trials. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[23] was used to appraise the evidence level of the included trials, and to formulate recommendations for clinicians. In case of a disagreement, a third author (D.C.) made the final conclusion.

RESULTS

Systematic search

After a systematic search in the databases, we found 133 articles. The manual and automatic duplication removal discarded 80 records. After title-abstract selection (Cohen's coefficient 1.00) and full-text selection (Cohen's coefficient 1.00), six reports from the database searches were found suitable for inclusion in the systematic review. We also screened the references of the included articles and found one additional study. Both independent authors agreed to include it in the review, resulting in a final article pool of seven articles (**Figure 1**). The characteristics of the included studies are summarized in **Table 1**.

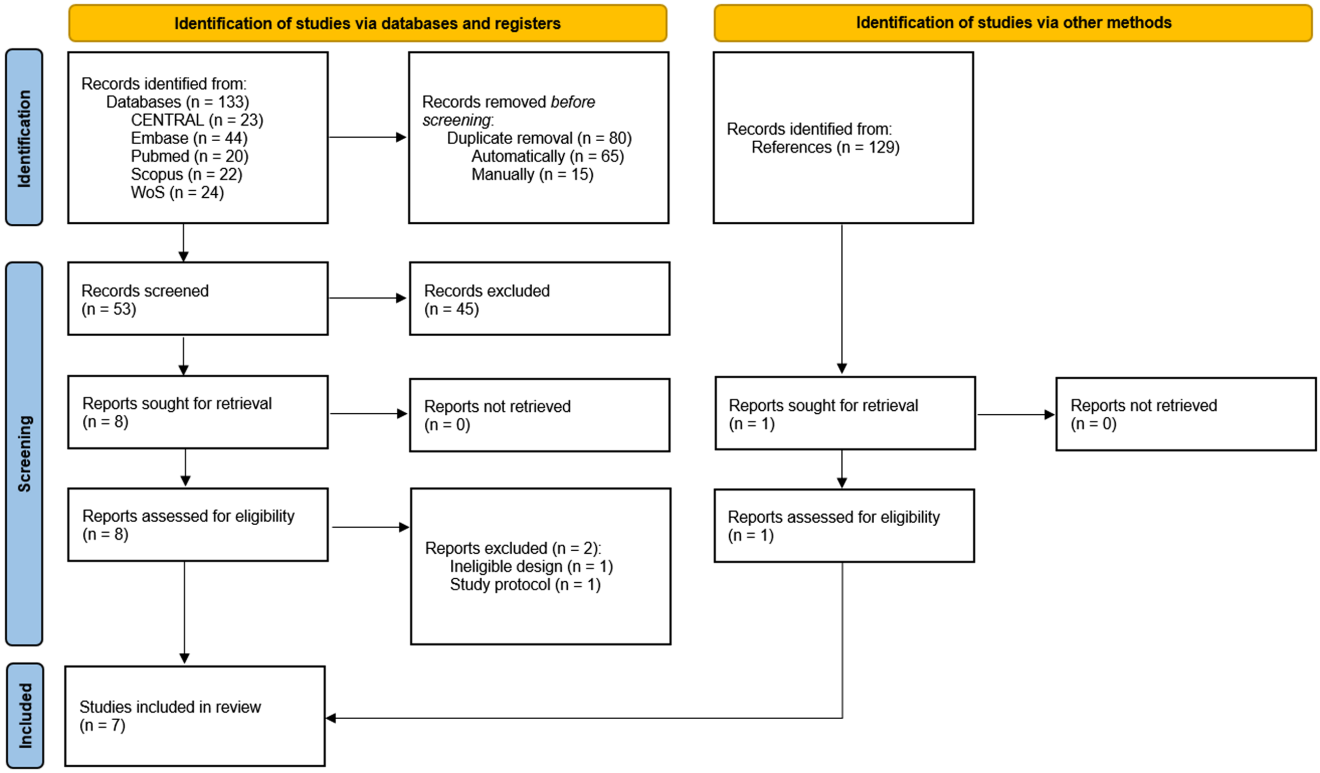

Figure 1 PRISMA flowchart. CENTRAL, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; WoS, Web of Science.

Post-ERCP pancreatitis

Seven studies reported on PEP using 20 mg[24–28] and 50 mg[25,29,30] of nafamostat. The overall incidence of PEP was lower in both nafamostat groups compared with the standard of care (20 mg, odds ratio (OR): 0.50, 95% confidence interval (CI) 0.30–0.82 and 50 mg, OR: 0.48, 95% CI: 0.24–0.96; **Figure 2**). However, in the subgroup analysis, we found statistically significant prevention of mild PEP only in the 20 mg subgroup (OR: 0.49, 95% CI: 0.31–0.77). We found no statistical differences in other severity groups (mild, moderate, and severe) investigating 20 mg and 50 mg doses of nafamostat compared with the standard of care (**Figure 3**).

We analyzed PEP severity in high- and low-risk patients. The overall use of nafamostat therapy could reduce moderate PEP in high-risk patients (OR: 0.18, 95% CI: 0.0.4–0.84); and mild PEP in low-risk patients (OR: 0.32, 95% CI: 0.17–0.61; **Figure 4**.). There were insufficient reports of severe PEP in high- and low-risk patients.

The pooled results of the five studies[24,25,27,29,31] showed no statistical difference in the ability of nafamostat to reduce post-ERCP hyperamylasemia compared with placebo. The results of the multilevel analysis are shown in **Figure 5**.

Risk of bias analysis and GRADE

Overall, the trials included had a low risk of bias. In some cases, due to the inaccessible study protocols, we were unable to compare the intended interventions with the published results and therefore marked them with "some concerns." On the basis of the GRADE assessment, the certainty of evidence is "low." The detailed risk of bias and GRADE assessments can be found in the **Figures S1** and **S2** and **Table S2**.

Ethical approval

No ethical approval was required for this systematic review with meta-analysis, as all data had already been published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our study. The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

DISCUSSION

PEP is the leading adverse event of ERCP procedure.[6] Ulinastatin in combination with somatostatin shows promising results[32] in the treatment of AP; however, only supportive therapies are widely available. For this reason, clinical trials mainly focus on the prevention of PEP with limited success. In this systematic review and meta-analysis, we investigated nafamostat as a prophylactic agent in the prevention of PEP.

The excessive Ca^{2+} signal is the main driver of AP, which also promotes the activation of trypsin and kallikrein. This, in combination with reduced ATP generation, causes necrosis, which further releases these mediators, causing an inflammatory cascade.[33] Nafamostat mesylate is a serine protease inhibitor that suppresses trypsin and kallikrein in experimental models of pancreatitis.[34,35] In theory, the effects of nafamostat reduce circulating mediators of AP, thus preventing the escalation of the inflammation. However,

Table 1 Baseline characteristics of included articles in the meta-analysis

Author, publication year	Origin	Sample size	Intervention	Intervention group, sample size	Intervention group, female (%)	Intervention group, mean age SD ± (years)	Control	Control group, sample size	Control group, female (%)	Control group, mean age ± SD (years)	Outcome
Choi 2009	South Korea	704	Nafamostat 20 mg i.v. for 24 hours; starting 1 hour before ERCP	354	171 (48.3)	64.4 ± 12.6	5% dextrose	350	168 (48.0)	65.6 ± 12.1	PEP, HA
Kwon 2012	South Korea	169	Nafamostat 50 mg i.v. for 12 hours; starting 0.5 hours before ERCP	88	49 (55.7)	66.6 ± 12.8	5% dextrose	81	50 (61.7)	64.4 ± 13.8	PEP
Matsumoto 2020	Japan	293	Nafamostat 20 mg for 6 hours; starting 0.5–2 hours before ERCP	144	50 (34.7)	75[a]	5% dextrose	149	48 (32.2)	71[a]	PEP
Ohuchida 2015	Japan	809	Nafamostat 20 mg i.v. for 2 hours; starting with ERCP	405	147 (36.3)	68.4 ± 12.1	5% dextrose	404	160 (39.6)	69.3 ± 11.2	PEP, HA
Park 2011 20 mg	South Korea	398	Nafamostat 20 mg for 24 hours; starting 1 hour before ERCP	198	94 (47.5)	64.1 ± 10.6	5% dextrose	200	91 (45.5)	62.7 ± 12.4	PEP, HA
Park 2011 50 mg	South Korea	397	Nafamostat 50 mg for 24 hours; starting 1 hour before ERCP	197	91 (46.2)	63.3 13.8	5% dextrose	200	91 (45.5)	62.7 ± 12.4	PEP, HA
Park 2014	South Korea	106	Nafamostat 10 mg i.v.; starting 2–4 hours before ERCP + Nafamostat 10 mg i.v.; starting 6–8 hours after ERCP	53	24 (45.3)	58.6 ± 17.1	5% dextrose	53	24 (45.3)	60.5 ± 16.2	PEP, HA
Yoo 2011	South Korea	286	Nafamostat 50 mg i.v. for 6 hours; starting 1 hour before ERCP	143	74 (51.7)	61.9 ± 15.7	5% dextrose	143	69 (48.3)	63.2 ± 15.4	PEP, HA

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; HA, hyperamylasemia; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; SD, standard deviation.
[a]SD was not reported.

the exact mechanism of nafamostat in the prevention of PEP is not known yet. Several reports investigated the intra-arterial or intravenous administration of nafamostat; however, there are inconsistencies in the results.[36–41] Nafamostat also inhibits other proteolytic enzymes, for example, thrombin and plasmin,[34] which can be used as an anticoagulant in the treatment of disseminated intravascular coagulopathy (DIC),[42] cardiopulmonary bypass[43–45] or during continuous renal replacement therapy.[26,46] It also emerged in the treatment of coronavirus disease 2019 (COVID-19) because it inhibits viral and human cell fusion.[47,48] The drug is only available in Far Eastern countries (e.g., South Korea and Japan) for the treatment of pancreatitis or DIC.

Previous meta-analyses showed controversial results about the effectiveness of nafamostat in the prevention of PEP. Yu *et al.*[15] showed a significant reduction in overall PEP, including mild and moderate PEP prevention. Their analysis also showed significant prevention of PEP in both low- and high-risk patients. A later network meta-analysis by Lyu *et al.*,[16] which included four published RCT trials, showed no statistical differences compared with placebo. Since then, a new trial had been published that we were able to include in our analysis. Our results suggest that nafamostat can reduce the overall incidence of PEP using 20 and 50 mg doses; however, we found a statistically significant difference only in the 20 mg nafamostat subgroup only for mild PEP. This might suggest that there is no dose

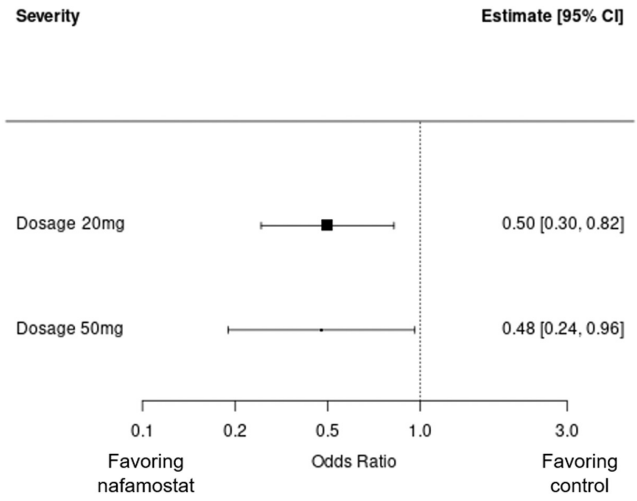

Figure 2 Multilevel model results on the overall effect of nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP). CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography.

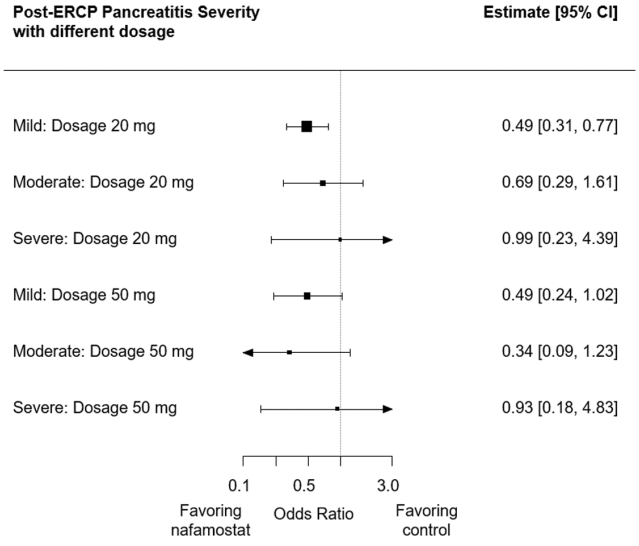

Figure 3 Multilevel model results on the nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP). CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography.

dependent effect of nafamostat on the prevention of PEP, and a lower dose regime is sufficient for the prevention. Side effects also did not appear to be dose dependent: only Matsumoto reported hyperkalemia; Choi and Park (2011), Park (2014), and Yoo did not report any side effects associated with the administration of nafamostat (Kwon did not report any side effect related information).

Although most PEP cases are mild, they can cause excessive distress for patients. By using nafamostat, mild PEP could be prevented, helping the patient to recover faster. Furthermore, nafamostat could decrease mild PEP in low-risk patients and moderate PEP in high-risk patients. Regarding the post-ERCP hyperamylasemia, Yu *et al*. found no statistically significant difference between the nafamostat and the placebo group.

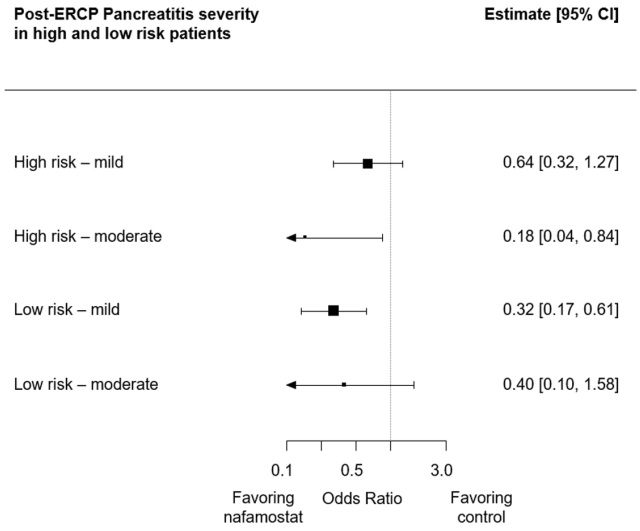

Figure 4 Multilevel model results on the nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP) in low- and high-risk patients. There was an overall a reduction of moderate PEP in high-risk patients and of mild PEP in low-risk patients. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography.

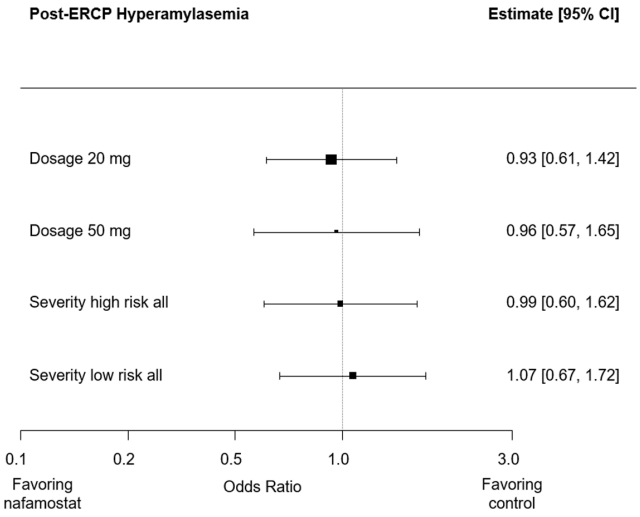

Figure 5 Multilevel model results on the nafamostat therapy regarding the post-ERCP hyperamylasemia. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography.

The ERCP procedure is generally associated with hyperamylasemia, which is present in 11.2–39% of the cases.[49–51] The development of hyperamylasemia can be due to patient-related (prior diabetes) and procedure-related factors (difficult cannulation, biliary duct stent placement, and nasobiliary drainage).[50] The underlying disease may also affect the procedure: cases of acute biliary pancreatitis appear to be more difficult than those of acute cholangitis, due to the increased use of advanced cannulation methods and inadvertent pancreatic cannulation, as well as longer cannulation time.[52] A retrospective analysis of 1,291 patients showed no correlation between hyperamylasemia and the severity of PEP.[53]

Strengths and limitations

This systematic review of nafamostat in the prevention of PEP is the most recent analysis of the current evidence for nafamostat based on randomized controlled trials. We followed the recommendations of international guidelines. The definition of PEP was the same across the studies. The main contributor to the identified limitations was the low number of studies. The efficacy in the prevention of PEP was separately investigated according to different dosages, and there were differences in the timing of the medications. Furthermore, because of this reason, data heterogeneity was moderate in some cases. There were only single-center studies located only in Far Eastern countries.

Implications for practice

Translational science is essential to the interpretation of clinical results in daily practice.[54,55] The use of nafamostat as a preventive medication after ERCP showed an overall reduction in PEP. The incidence of mild PEP was significantly reduced in the 20 mg subgroup. In addition, it reduced mild PEP in low-risk and moderate PEP in high-risk patients.

Implications for research

Considering the limited efficacy, researchers should focus on the cost-effectiveness of the therapy. Nafamostat therapy should also be investigated compared with available preventive therapies.

CONCLUSION

Nafamostat can reduce the overall incidence of PEP compared with placebo and should be considered for use in low-risk patients with mild PEP. Cost-effectiveness studies are required.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

No funding was received for this work.

CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

I.L.H., D.K., N.R., H.B., P.H., and D.C. wrote the manuscript. I.L.H., N.R., P.H., and D.C. designed the research. I.L.H. and D.K. performed the research. P.F. analyzed the data.

DATA AVAILABILITY STATEMENT

Data used for the analysis are available on reasonable request from the corresponding author.

1. Kalaitzakis, E. All-cause mortality after ERCP. *Endoscopy* **48**, 987–994 (2016).
2. Siiki, A., Tamminen, A., Tomminen, T. & Kuusanmäki, P. ERCP procedures in a Finnish community hospital: a retrospective analysis of 1207 cases. *Scand. J. Surg.* **101**, 45–50 (2012).
3. Glomsaker, T. *et al*. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. *Br. J. Surg.* **100**, 373–380 (2013).
4. Cotton, P.B. *et al*. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest. Endosc.* **37**, 383–393 (1991).
5. Banks, P.A. *et al*. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* **62**, 102–111 (2013).
6. Dumonceau, J.M. *et al*. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* **52**, 127–149 (2020).
7. Balint, E.R. *et al*. Assessment of the course of acute pancreatitis in the light of aetiology: a systematic review and meta-analysis. *Sci. Rep.* **10**, 17936 (2020).
8. Kochar, B. *et al*. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. *Gastrointest. Endosc.* **81**, 143 e9–149 e9 (2015).
9. Parekh, P.J., Majithia, R., Sikka, S.K. & Baron, T.H. The "scope" of post-ERCP pancreatitis. *Mayo Clin. Proc.* **92**, 434–448 (2017).
10. Nagashima, K. *et al*. Does the use of low osmolality contrast medium reduce the frequency of post-endoscopic retrograde Cholangiopancreatography pancreatitis: a comparative study between use of low and high osmolality contrast media. *Digestion* **102**, 283–288 (2021).
11. Moggia, E. *et al*. Pharmacological interventions for acute pancreatitis. *Cochrane Database Syst. Rev.* **4**, CD011384 (2017).
12. Marta, K. *et al*. Combined use of indomethacin and hydration is the best conservative approach for post-ERCP pancreatitis prevention: a network meta-analysis. *Pancreatology* **21**, 1247–1255 (2021).
13. Boskoski, I. & Costamagna, G. How to prevent post-endoscopic retrograde Cholangiopancreatography pancreatitis. *Gastroenterology* **158**, 2037–2040 (2020).
14. Seta, T., Takahashi, Y., Yamashita, Y. & Nakayama, T. Status of use of protease inhibitors for the prevention and treatment of pancreatitis after endoscopic retrograde cholangiopancreatography: an epidemiologic analysis of the evidence-practice gap using a health insurance claims database. *Drug Discov. Ther.* **13**, 137–144 (2019).
15. Yu, G., Li, S., Wan, R., Wang, X. & Hu, G. Nafamostat mesilate for prevention of post-ERCP pancreatitis: a meta-analysis of prospective, randomized, controlled trials. *Pancreas* **44**, 561–569 (2015).
16. Lyu, Y., Wang, B., Cheng, Y., Xu, Y. & du, W. Comparative efficacy of 9 major drugs for Postendoscopic retrograde Cholangiopancreatography pancreatitis: a network meta-analysis. *Surg. Laparosc. Endosc. Percutan. Tech.* **29**, 426–432 (2019).
17. Higgins, T.J., Chandler, J., Cumpston, M., Li, T., Page, M.J. & Welch, V.A. *Cochrane Handbook for Systematic Reviews of Interventions*. version 6.3 (updated February 2022). 2022 (Cochrane, 2022). https://training.cochrane.org/handbook#how-to-cite
18. Page, M.J. *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021).
19. Harrer, M., Cuijpers, P., Furukawa, T. & Ebert, D. *Doing Meta-Analysis with R: A Hands-on Guide* 1st edn. (Chapman and Hall/CRC, New York, 2021).
20. Team, R.C. *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, Vienna, 2022).
21. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* **36**, 1–48 (2010).
22. Sterne, J.A.C. *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* **366**, l4898 (2019).
23. GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, Available from gradepro.org (2022).

24. Park, J.Y. *et al*. Comparison between ulinastatin and nafamostat for prevention of post-endoscopic retrograde cholangiopancreatography complications: a prospective, randomized trial. *Pancreatology* **14**, 263–267 (2014).
25. Park, K.T. *et al*. Is high-dose nafamostat mesilate effective for the prevention of post-ERCP pancreatitis, especially in high-risk patients? *Pancreas* **40**, 1215–1219 (2011).
26. Choi, J.Y. *et al*. Nafamostat Mesilate as an anticoagulant during continuous renal replacement therapy in patients with high bleeding risk: a randomized clinical trial. *Medicine (Baltimore)* **94**, e2392 (2015).
27. Ohuchida, J., Chijiiwa, K., Imamura, N., Nagano, M. & Hiyoshi, M. Randomized controlled trial for efficacy of nafamostat mesilate in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* **44**, 415–421 (2015).
28. Matsumoto, T. *et al*. Nafamostat Mesylate is not effective in preventing post-endoscopic retrograde Cholangiopancreatography pancreatitis. *Dig. Dis. Sci.* **66**, 4475–4484 (2021).
29. Yoo, K.S. *et al*. Nafamostat mesilate for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized, double-blind, controlled trial. *Pancreas* **40**, 181–186 (2011).
30. Kwon, Y.H. *et al*. Could nafamostat or gabexate prevent the post endoscopic retrograde cholangiopancreatography pancreatitis? *Korean J. Gastroenterol.* **59**, 232–238 (2012).
31. Choi, C.W. *et al*. Nafamostat mesylate in the prevention of post-ERCP pancreatitis and risk factors for post-ERCP pancreatitis. *Gastrointest. Endosc.* **69**, e11–e18 (2009).
32. Horvath, I.L. *et al*. The combination of ulinastatin and somatostatin reduces complication rates in acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. *Sci. Rep.* **12**, 17979 (2022).
33. Petersen, O.H., Gerasimenko, J.V., Gerasimenko, O.V., Gryshchenko, O. & Peng, S. The roles of calcium and ATP in the physiology and pathology of the exocrine pancreas. *Physiol. Rev.* **101**, 1691–1744 (2021).
34. Iwaki, M. *et al*. Pharmacological studies of FUT-175, nafamostat mesilate. V. Effects on the pancreatic enzymes and experimental acute pancreatitis in rats. *Jpn. J. Pharmacol.* **41**, 155–162 (1986).
35. Fujii, S. & Hitomi, Y. New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kallikrein and trypsin. *Biochim. Biophys. Acta* **661**, 342–345 (1981).
36. Keck, T., Balcom, J.H., Antoniu, B.A., Lewandrowski, K., Warshaw, A.L. & Castillo, C.F.D. Regional effects of nafamostat, a novel potent protease and complement inhibitor, on severe necrotizing pancreatitis. *Surgery* **130**, 175–181 (2001).
37. Horibe, M. *et al*. Continuous regional arterial infusion of protease inhibitors has No efficacy in the treatment of severe acute pancreatitis: a retrospective multicenter cohort study. *Pancreas* **46**, 510–517 (2017).
38. Imaizumi, H. *et al*. Efficacy of continuous regional arterial infusion of a protease inhibitor and antibiotic for severe acute pancreatitis in patients admitted to an intensive care unit. *Pancreas* **28**, 369–373 (2004).
39. Ke, L., Ni, H.B., Tong, Z.H., Li, W.Q., Li, N. & Li, J.S. Efficacy of continuous regional arterial infusion with low-molecular-weight heparin for severe acute pancreatitis in a porcine model. *Shock* **41**, 443–448 (2014).
40. Yamamoto, T., Yamamura, H., Yamamoto, H. & Mizobata, Y. Comparison of the efficacy of continuous i.v. infusion versus continuous regional arterial infusion of nafamostat mesylate for severe acute pancreatitis. *Acute Med. Surg.* **3**, 237–243 (2016).
41. Hirota, M. *et al*. Continuous regional arterial infusion versus intravenous administration of the protease inhibitor nafamostat mesilate for predicted severe acute pancreatitis: a multicenter, randomized, open-label, phase 2 trial. *J. Gastroenterol.* **55**, 342–352 (2020).
42. Asakura, H. Classifying types of disseminated intravascular coagulation: clinical and animal models. *J. Intensive Care* **2**, 20 (2014).
43. Sato, T. *et al*. Nafamostat mesilate administration during cardiopulmonary bypass decreases postoperative bleeding after cardiac surgery. *ASAIO Trans.* **37**, M194–M195 (1991).
44. Sakamoto, T. *et al*. Efficacy of nafamostat mesilate as anticoagulation during cardiopulmonary bypass for early surgery in patients with active infective endocarditis complicated by stroke. *J. Heart Valve Dis.* **23**, 744–751 (2014).
45. Kikura, M., Tanaka, K., Hiraiwa, T. & Tanaka, K. Nafamostat mesilate, as a treatment for heparin resistance, is not associated with perioperative ischemic stroke in patients undergoing cardiac surgery with cardiopulmonary bypass. *J. Cardiothorac. Vasc. Anesth.* **26**, 239–244 (2012).
46. Lee, Y.K., Lee, H.W., Choi, K.H. & Kim, B.S. Ability of nafamostat mesilate to prolong filter patency during continuous renal replacement therapy in patients at high risk of bleeding: a randomized controlled study. *PloS One* **9**, e108737 (2014).
47. Yamamoto, M. *et al*. The anticoagulant Nafamostat potently inhibits SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system and viral infection in vitro in a cell-type-dependent manner. *Viruses* **12**, 629 (2020).
48. Hoffmann, M. *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **181**, 271 e8–280 e8 (2020).
49. Andriulli, A. *et al*. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. *Gastrointest. Endosc.* **56**, 488–495 (2002).
50. He, Q.B., Xu, T., Wang, J., Li, Y.H., Wang, L. & Zou, X.P. Risk factors for post-ERCP pancreatitis and hyperamylasemia: a retrospective single-center study. *J. Dig. Dis.* **16**, 471–478 (2015).
51. Hernandez Garces, H.R. *et al*. Risk factors associated with the development of hyperamylasemia and post-ERCP pancreatitis in the Cuban National Institute. *Rev. Gastroenterol. Peru* **34**, 127–132 (2014).
52. Pécsi, D. *et al*. ERCP is more challenging in cases of acute biliary pancreatitis than in acute cholangitis – analysis of the Hungarian ERCP registry data. *Pancreatology* **21**, 59–63 (2021).
53. Ito, K. *et al*. Relationship between post-ERCP pancreatitis and the change of serum amylase level after the procedure. *World J. Gastroenterol.* **13**, 3855–3860 (2007).
54. Hegyi, P., Erőss, B., Izbéki, F., Párniczky, A. & Szentesi, A. Accelerating the translational medicine cycle: the academia Europaea pilot. *Nat. Med.* **27**, 1317–1319 (2021).
55. Hegyi, P. *et al*. Academia Europaea position paper on translational medicine: the cycle model for translating scientific results into community benefits. *J. Clin. Med.* **9**, 1532 (2020).