Review Article

Nafamostat mesylate in the prevention of post-endoscopic retrograde cholangiography pancreatitis: A meta-analysis

Abstract:

Nafamostat mesylate was found to be effective in post-ERCP pancreatitis, however, well-controlled randomized studies with a sufficient number of patients are lacking. We aimed to assess full-text prospective studies on the role of NM in post-ERCP pancreatitis. We searched the PubMed, Medline, and Google Scholar databases for relevant articles during the period from 2009 to November 2020, no restriction regarding the language of publication. The keywords nafamostat mesylate, post-ERCP pancreatitis, prevention, and role were used. A total of 113 studies were identified through the database search, and eight studies (all were published in Asia) met the inclusion criteria for the systematic review. There were four control trials (three randomized and one comparative), three case-control studies, and an experimental study (32026 patients included. In the present meta-analysis, seven studies [9-11, 15, 18, 20] concluded the benefit of nafamostat mesylate in the prevention of post-ERCP pancreatitis, and one [19] showed no benefit. The overall effect was highly significant, odd ratio, 0.44, 95%*CI*=0.31-0.62, P-value=0.0001, heterogeneity=0.0%, P-value for heterogeneity=0.48, I^2=0%. Nafamostat mesylate might be effective in post-ERCP pancreatitis. Larger randomize multi-center studies investigating the effectiveness in combination with other preventive measures are needed.

Keywords: Nafamostat mesylate, post-ERCP pancreatitis, prevention

Background:

Endoscopic retrograde cholangiopancreatography (ERCP) is an effective common diagnostic and therapeutic procedure; post-ERCP pancreatitis may be an unavoidable complication of ERCP, various endoscopic and pharmacological approaches have been tried, but most have ineffective [1]. The European Society of Gastrointestinal Endoscopy recommended rectal NSAIDs for the prevention of PEP, however, the American Society of Gastrointestinal Endoscopy and the Japanese guidelines emphasized the lack of efficacy of certain pharmacological measures [2-4]. Nafamostat mesylate (NM) (a protease inhibitor) has been used for the treatment of influenza, pancreatitis, and disseminated intravascular coagulation; recently it has been shown to be useful in Covid-19 [5, 6]. Literature investigating the role of NM in the prevention of post-ERCP pancreatitis is lacking, thus we conducted this meta-analysis to assess the role of NM in the prevention of PEP.

Methodology:

Literature search:

We searched PubMed, Medline, and the first 100 articles in Google Scholar databases, no restriction to languages was adopted, all the articles published in the period 2009-November 2020 were eligible, bibliographies of relevant systematic reviews were searched manually for relevant articles.

Eligibility criteria:

Only randomized controlled and clinical trials that assessed the incidence reduction of PEP, conference abstracts, cohort studies, case reports, case-series, and animal studies were excluded. Conferences abstracts were not included because of the information to

measure the outcomes might be inadequate, trials reporting the hyperamylasaemia and not reporting on the PEP risk reduction were excluded.

Article review and data abstraction:

Two reviewers conducted a systematic literature search according to Cochrane guidelines [7], the reviewers independently screened the titles and including any title potentially related to ERCP, then any abstract evaluating the effects of nafamostat mesylate and pancreatitis in the setting of ERCP was included. During the full-text review, articles stating the incidence of PEP even if the number was zero. During the review, any conflict was resolved by consensus. The opinion of a biostatistician and endoscopist were thought when necessary. One reviewer abstracted the data that was confirmed by the second reviewer, the data were included in an extraction sheet including the author's name, year of publication, country of origin, the incidence of pancreatitis, the odd ratio/95%*CI*, P-values. The different phases of the systematic review were reported in Figure 1

The quality and risk of bias assessment:

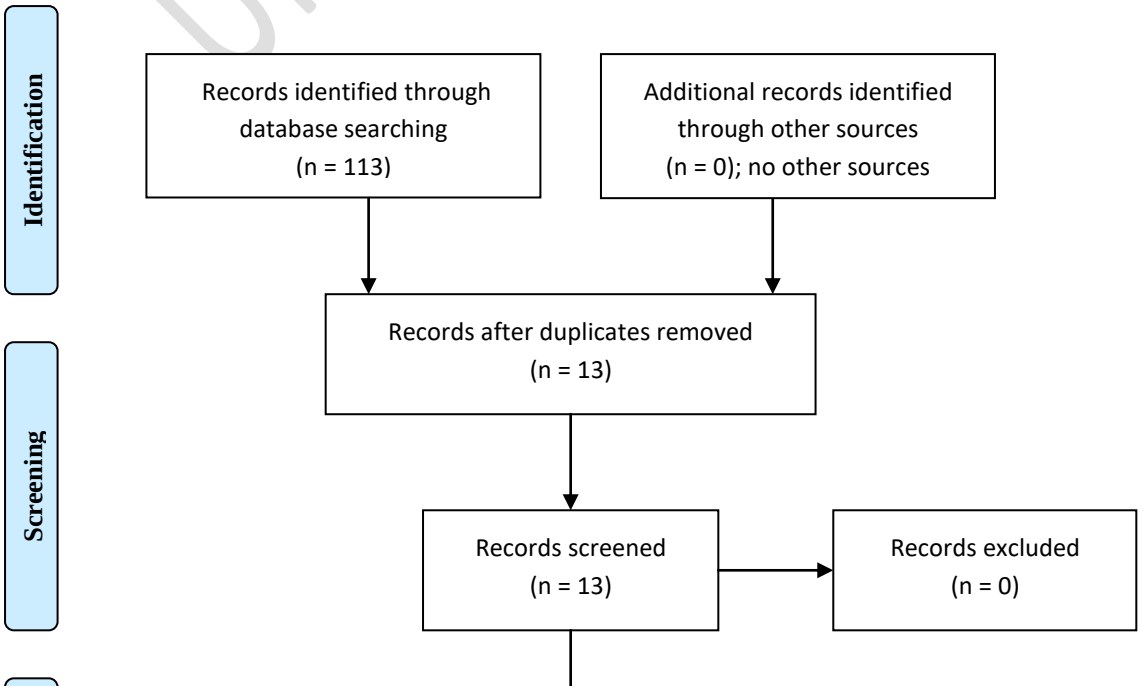
Cochrane risk of bias was used to assess the quality and risk bias of the randomized controlled studies [8].

Statistical analysis:

RevMan 54 software was used for the meta-analysis. For nafamostat mesylate (binary) risk ratios (RRs) with 95% confidence intervals (CIs) were combined across relevant studies, the fixed effects module was applied unless if substantial heterogeneity was found (A P value ≤ 0.10 for Cochran's Q test or an $I2 \geq 50\%$ was

suggestive). A two-tailed P < 0 05 was considered statistically significant for all analyses except heterogeneity tests.

Figure 1 - Flow diagram through the different phases of the systematic review (PRISMA flowchart).



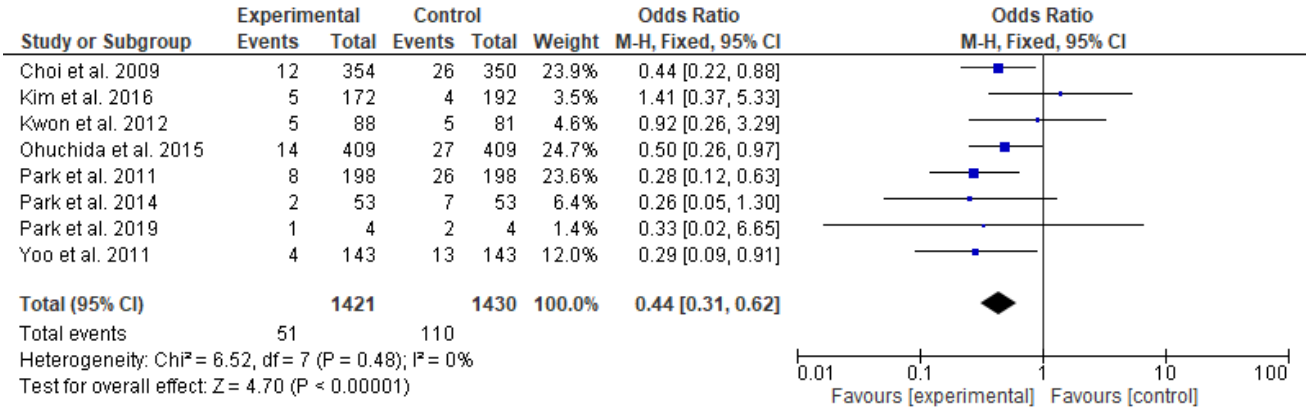
Results:

A total of 113 studies were identified through the database search. Among these 13 papers, thirteen full-text articles were assessed for eligibility: Eight studies (all were published in Asia) met the inclusion criteria for the systematic review. There were four control trials (three randomized and one comparative), three case-control studies, and an experimental study (32026 patients included. In the present meta-analysis, seven studies [9-12, 15, 18, and 20] concluded the benefit of nafamostat mesylate in the prevention of post-ERCP pancreatitis, and one [19] showed no benefit. The overall effect was highly significant, odd ratio, 0.44, 95%*CI*=0.31-0.62, P-value=0.0001, heterogeneity=0.0%, P-value for heterogeneity=0.48, I^2=0%. Figure 2 and 3 Table 1

Table 1. Nafamostat mesylate and prevention of post-ERCP pancreatitis

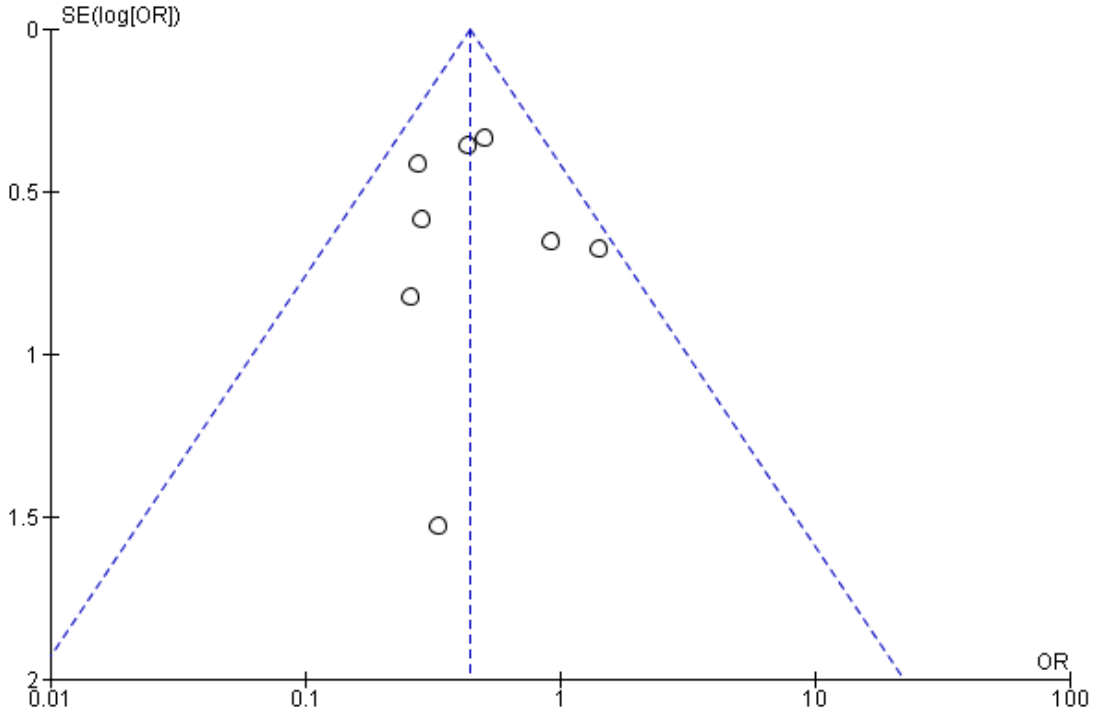
author	year	country	type	Patients/control	result
Choi et al. [9]	2009	South Korea	A randomized controlled trial	354 vs. 350	Reduction in pancreatitis
Kim et al.[10]	2016	South Korea	A randomized comparison trial	191 vs.191	No difference in 6 vs.24 hours infusion
Kwon et al.[11]	2012	Korea	A case-control study	88 vs. 81	No difference between placebo and nafamostat
Ohuchida et al. [12]	2015	Japan	A randomized controlled trial	409 vs. 409	Reduction in pancreatitis
Park et al. [13]	2011	South Korea	A case-control	203 vs. 203	No difference between 20mg and 50mg
Park et al. [14]	2014	South Korea	A case-control study	53 vs. 53	Both ulinastatin and nafamostat reduced pancreatitis
Park et al. [15]	2019	South Korea	Experimental study	4 vs. 4	Nafamostat injection into the intrapancreatic duct produced promising results
Yoo et al. [16]	2011	South Korea	A randomized controlled trial	143 vs. 143	Prophylactic intravenous nafamostat mesylate reduces the frequency of post-ERCP pancreatitis.

Figure 2. Effects of nafamostat mesylate on post-ERCP pancreatitis



The present meta-analysis showed that out of the eight studies included, 7 reduced post-ERCP pancreatitis, while one showed no effect.

Figure 3. Figure plot of nafamostat mesylate and post-ERCP pancreatits



Discussion:

The role of nafamostat mesylate in the prevention of PEP is controversial, in the present meta-analysis, seven studies [9, 11-16] concluded the benefit of nafamostat mesylate in the prevention of post-ERCP pancreatitis, and one [10] showed no benefit. The overall effect was highly significant, odd ratio, 0.44, 95%*CI*=0.31-0.62, P-value=0.0001, heterogeneity=0.0%, P-value for heterogeneity=0.48, I^2=0%. Akshintala et al. [17] in their meta-analysis showed that nafamostat mesylate is the second most efficacious preventive measure only after topical ephedrine regarding PEP prevention in line with the current findings. Kubiliun et al. [18] found the NM is promising and warranted future confirmation supporting the present observation. Similar findings were reported by Yuhara et al. [19] who showed that NM is efficacious in PEP prevention (RR = 0.41; 95 %CI 0.28-0.59), Yu et al. [20] conducted a meta-analysis and observed the effectiveness of NM in the prevention of PEP (risk ratio [RR], 0.47; 95% confidence interval [CI], 0.34-0.63).

Mechanism of action of various pharmacological agents used in PEP prevention:

- Protease inhibitors (nafamostat, gabexate, and ulinastatin) had similar anti-secretory effects**,** but NM also showed higher potency and long duration of action [21, 22]. The need to administer intravenously for a prolonged time perioperative limited their use.
- Somatostatin (relaxation of the sphincter of Oddi) and octreotide (constriction of the sphincter of Oddi), otherwise similar for their anti-secretory properties [23, 24]
- Non-steroidal anti-inflammatory drugs (anti-inflammatory), rectal administration may be difficult in patients undergoing ERCP and may be expelled during insufflation [25, 26].
- Antibiotics are limited by microbial resistance, a global health challenge [27]
- Ephedrine (relax duodenal musculature and edema reduction). Ephedrine is superior due to its short window of action [28, 29]
- Stents are invasive, costly, and need reoperation to remove

The administration of rectal NSAIDs and ephedrine was found to be synergistic [30]

The limitations of this study are the small number of studies included and the fact that we included both case-control and randomized studies.

Conclusion: The present meta-analysis showed that NM might reduce the risk of PEP, but the reduction is not reaching statistical significance, the need for intravenous administration for a relatively long duration may further limit their use. The

availability of ephedrine and NSAIDs, their cost-effectiveness, easy administration, and their few side effects rank these drugs higher, the combination of NSAIDs and ephedrine may be more effective.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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