Gut and Liver
https://doi.org/10.5009/gnl220268
pISSN 1976-2283eISSN 2005-1212

Original Article

Combinatorial Effect of Prophylactic Interventions for Post-ERCP Pancreatitis among Patients with Risk Factors: A Network Meta-Analysis

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Article Info
Received June 22, 2022
Revised September 19, 2022
Accepted October 18, 2022
Published online December 13, 2022

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Background/Aims: The combinatorial effects of prophylactic methods for postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) in patients with risk factors remain unclear. In this network meta-analysis, we compared the efficacy of various prophylactic strategies to decrease the risk of PEP among patients with risk factors.

Methods: A systematic review was performed to identify randomized controlled trials from PubMed, Embase, and the Cochrane Library through July 2021. We used frequentist network meta-analysis to compare the rates of PEP among patients who received prophylactic treatments as follows: class A, rectal nonsteroidal anti-inflammatory drugs; class B, prophylactic pancreatic stent; class C, aggressive hydration; or control, no prophylaxis or active control. We selected those studies that included patients with risk factors for PEP.

Results: We identified 19 trials, comprising 4,328 participants. Class ABC (odds ratio [OR], 0.08; 95% confidence interval [CI], 0.03 to 0.24), class AC (OR, 0.10; 95% CI, 0.02 to 0.47), class AB (OR, 0.12; 95% CI, 0.05 to 0.26), class BC (OR, 0.13; 95% CI, 0.04 to 0.41), class A (OR, 0.16; 95% CI, 0.05 to 0.50), and class B (OR, 0.26; 95% CI, 0.14 to 0.46), were associated with a reduced risk of PEP as compared to that of the control. The most effective prophylaxis was ABC (0.87), followed by AC (0.68), AB (0.65), BC (0.56), A (0.49), and B (0.24) according to P-score.

Conclusions: The results of this network meta-analysis suggest that the more prophylactic methods are employed, the better the outcomes. It appears that for patients with risk factors, we need to prevent PEP through the use of these well proven combination strategies. **(Gut Liver 2023;17:814-824)**

Key Words: Endoscopic retrograde cholangiopancreatography; Pancreatitis; Prophylaxis; Nonsteroidal anti-inflammatory agent; Stent

INTRODUCTION

Postendoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis (PEP) is one of the most burdensome adverse events for endoscopists. PEP occurs in about 2% to 15% of patients who have undergone various ERCP procedures, and it occurs in up to 19.1% of patients with risk factors for PEP.[1,2] Although most cases of PEP exhibit only mild or moderate severity, severe and/or necrotizing pancreatitis can cause considerable morbidity and mortality. It is difficult to define proper indications for PEP prophylaxis because its occurrence is difficult to predict, even when there are previously reported patient-related or procedure-related risk factors.[2,3]

Endoscopists have generally considered four major approaches to providing effective prophylaxis for PEP, and these include pharmacologic prevention, prophylactic pancreatic duct stent (PS) insertion, patient selection, and procedural techniques during ERCP. The efficacy of rectal nonsteroidal anti-inflammatory drugs (NSAIDs), PS insertion, and aggressive hydration have been demonstrated in previous studies with a high level of evidence.[4-7] Recently,

European Society of Gastrointestinal Endoscopy guidelines suggested a PEP prevention algorithm, using these well-proven methods that made decisions while considering key information before, during, and after the procedure.[2] There remains ongoing debate as to which method is the most appropriate for prevention of PEP, because there are few head-to-head trials among these preventive methods. Also, it is not well known whether more effective prevention can be achieved by using multiple methods simultaneously. In addition, previously reported meta-analyses including randomized controlled trials (RCTs) appear to be confounded by allowing arbitrary use of different prophylactic approaches such as prophylactic PS insertion at the discretion of endoscopists.[8-11] Therefore, despite the various meta-analyses, there is still no consensus on which of the prophylactic strategies are better than others. Rectal NSAIDs, PS, and aggressive hydration, are commonly recommended by the representative guidelines, particularly for patients with risk factors.[2,12,13]

The aim of this study was to compare the effectiveness of various prophylactic treatments including rectal NSAIDs, PS, and aggressive hydration as well as combinations of these, for the prevention of PEP in patients with risk factors.

MATERIALS AND METHODS

1. Search strategy and study selection

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analysis (NMA). We conducted a search of PubMed, Embase, and the Cochrane Library from January 1, 1990, to July 8, 2021. Supplementary Table 1 shows the detailed search strategies used for each database. We also included studies identified through manual search of systematic review bibliographies.

Eligible RCTs examined the effects of the various prophylactic management strategies to reduce the risk of PEP. We only considered those RCTs with human subjects with risk factors for PEP, written in English, and which compared at least one prophylactic strategy against another, or against control. Prophylactic management strategies (Fig. 1) were classified as follows: (1) class A: prophylaxis with rectal NSAIDs, (2) class B: prophylaxis with PS insertion or PS placement on demand based on the clinical judgment of endoscopists, (3) class C: prophylaxis with aggressive hydration of more than 1 L during the 8 hours following procedure, or (4) control: no prophylaxis or prophylaxis with sham drugs. Each combination of preventive methods are described in abbreviated form using the class letters. For example, class ABC means using all methods of the prophylactic strategy class A, B, and C. We excluded studies among found RCTs related to PEP as follows: studies including patients without risk factors; studies of comparisons between procedural techniques other than PS placement; studies of comparison between prevention methods of the same class; studies on topical agents; studies with insufficient data to analyses; studies difficult to find full text.

2. Data identification and extraction

Two investigators (J.H.C. and J.S.K.) independently screened articles by title, abstract, and full text according to the inclusion and exclusion criteria of data selection. We gathered the full text articles of potentially relevant studies, and J.H.C. and J.S.K. independently extracted the data on study characteristics, patient features, prophylactic strategies, and the results of all included studies. Any discrepancies between the two investigators were resolved after discussion with the corresponding author (S.H.L.). We accepted the study definitions of PEP and patients with risk factors in each study. Supplementary Table 2 shows the details of the included studies for inclusion criteria and treatment details. Each study applied the selection criteria for patients with risk factors based on patient characteristics, or risk factors identified during the procedure, according to the selection criteria in reference to existing studies. All of these criteria were applied together in several studies. The study outcome illustrated the incidence of PEP in patients with risk factors, according to prophylactic strategies and their combinations.

3. Statistical analysis

All statistical meta-analyses were performed using the

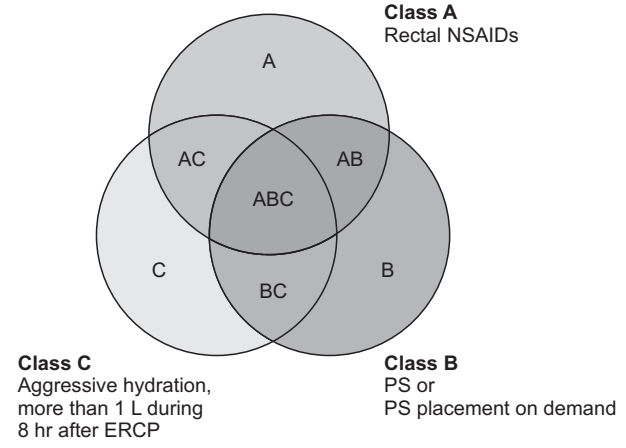

Fig. 1. A diagram of the classification of prophylaxis for post-ERCP pancreatitis in this study.
NSAIDs, nonsteroidal anti-inflammatory drugs; ERCP, endoscopic retrospective cholangiopancreatography; PS, pancreatic duct stent.

"netmeta" package R, version 3.5.2 (R Core Team, Vienna, Austria). All outcomes of interest were binary and the relative treatment effects were reported as being odds ratios (ORs) with 95% confidence intervals (95% CI). We performed a frequentist NMA, and the model framework used random effects to allow for apparent heterogeneity among studies in treatment comparison effects. We calculated a pairwise meta-analysis to generate direct estimates for outcomes by using a random effects model. Forest plots were presented to visualize the estimated effect sizes for all treatments compared to the control. We calculated P-scores by the "netrank" function to rank the intervention's hierarchy in the NMA, which has been shown to be equivalent to the surface under the cumulative ranking curve score, between 0 and 1.[14] P-score means the probabilities that each treatment is the best, and it was easily calculated on the basis of the point estimates and standard errors of the frequentist NMA and it measures the mean extent of certainty that an intervention is better than the competing interventions.[15,16]

Sensitivity analyses were performed on: (1) studies that were evaluated as having low level study specific risk of bias except for blinding-related categories, because bias for blinding was inevitable within comparison studies between prophylactic PS and control; and (2) with studies that included over 100 patients in each group.

We evaluated impacts on study outcomes by estimating 95% of the prediction intervals according to the previously suggested formula.[17] Global heterogeneity was evaluated by τ^2 and I^2. The consistency of the network was statistically assessed by separating indirect from direct evidence splitting,[18] and we assessed inconsistency by a network heat plot. Publication bias was evaluated by visual inspection of comparison-adjusted funnel plots and Egger regression tests.

We evaluated the feasibility of the transitivity assumption by comparing potential confounders as a level of comparison with a one-way analysis of variance test. The distribution of patient and study characteristics that might affect treatment outcomes across treatment comparisons were as follows: mean age, the proportion of female patients, the rate of sphincter of Oddi dysfunction, the rate of patients with a history of PEP, the rate of difficult cannulation, and the rate of precut endoscopic sphincterotomy.

4. Quality assessment

We assessed the risk of bias in RCTs by using the Cochrane Collaboration tool for randomized trials for each outcome. The certainty of evidence was evaluated with the Confidence in Network Meta-Analysis approach,[19] which is based on the Grading of Recommendations Assessment, Development and Evaluation framework.[20] This evaluates the potential presence of within-study bias, reporting bias,

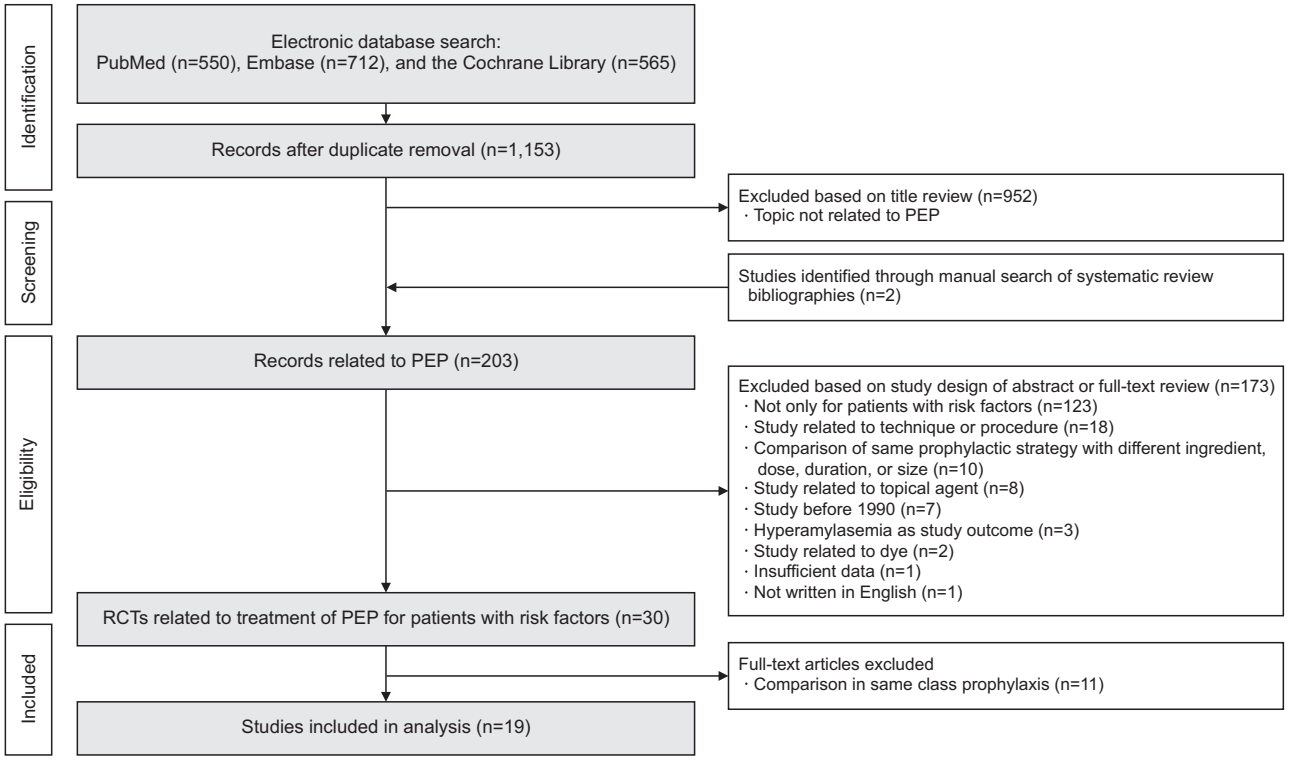

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search results in this study.
PEP, postendoscopic retrospective cholangiopancreatography pancreatitis; RCT, randomized controlled trial.

indirectness, imprecision, heterogeneity, and incoherence. Indirectness was assessed by the relevance of studies to the research question in this study. Imprecision was evaluated by the cross of CIs into clinically important effects, defined as a 10% increase or decrease in the incidence of the target outcome. Heterogeneity was judged by the 95% prediction intervals and incoherence, which represented the intransitivity in the statistical approach, and this was evaluated by the separating indirect from direct evidence splitting test.

RESULTS

1. Study selection

Fig. 2 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of search results in this study. Our database searches identified 550 articles in PUBMED, 712 in Embase, and 565 in the Cochrane Library. After duplicate removal, we found 1,153 articles to be related to pancreatitis. We extracted 201 RCTs related to the treatment of PEP after reviewing the abstract and we identified two RCTs through manual searching of systematic review bibliographies. We further excluded studies that did not meet the inclusion criteria, and finally we included a total of 19 RCTs in this meta-analysis. Table 1 summarizes detailed information for each of the included studies. Study sample sizes varied between 40 and 813 (median, 155.5), with an overall number of 4,328 individuals included. Patient age ranged from a mean of 44.7 to 78.9 years (median, 57.5), and enrolled females ranged from 13.5% to 79.6% (median, 48.8%).

2. NMA assessing the efficacy of various prophylactic strategies for PEP

1) Summary of network structure

The result of nine RCTs were included for comparison of class B with a control,[5,6,21-27] four RCTs for comparison of class AB with class B,[7,28-30] two RCTs for comparison of class A with a control,[31,32] one RCT for class ABC with class BC,[33] one RCT for class ABC with class AC,[34] one RCT for class ABC with class AB,[35] and one RCT for class BC with class B.[4] There was there no RCT comparing class C and control or other methods (Fig. 3). According to prophylactic strategies, a total of 691 patients received prophylaxis with class ABC, 1,099 with class AB, 207 with class AC, 362 with class BC, 132 with class A, 1,262 with class B, and 575 patients served as controls.

2) Summary results from NMA in the prevention of PEP

The results from NMA of differing prophylaxes for PEP prevention among patients with risk factors as compared

Table 1. Summary Characteristics of Included Studies in This Study

Author (year)	Place	Total patients	Mean age, yr	Female sex, %	History of PEP, %	Biliary EST, %	Difficult cannulation, %	Inclusion criteria for patients	Study population	Compared prophylactic strategies*	Severity of PEP		
											Total	Moderate to severe	Mild
Smithline *et al.* (1993)[21]	USA	93	46.5	79.6	NA	100	NA	Patient- and procedure-related risk factors	High risk	Class B: prophylactic PS	3	0	3
										Control	8	4	4
Tarnasky *et al.* (1998)[22]	USA	80	46	73.8	NA	100	28.8	Patient- and procedure-related risk factors	High risk	Class B: prophylactic PS	1	1	0
										Control	10	5	5
Murray *et al.* (2003)[28]	Scotland	220	56.5	65	NA	72.3	19.5	Patient- and procedure-related risk factors	High risk	Class AB: prophylactic rectal diclofenac with PS on demand	7	NA	NA
										Class B: placebo with PS on demand	17	NA	NA
Fazel *et al.* (2003)[23]	USA	74	44.7	13.5	NA	21.6	54.1	Procedure-related risk factors	High risk	Class B: prophylactic PS	2	0	2
										Control	10	5	5
Khoshbaten *et al.* (2008)[31]	Iran	100	58.5	53	NA	49	66	Procedure-related risk factors	High risk	Class A: rectal indomethacin	2	NA	NA
										Control	13	NA	NA
Ito *et al.* (2010)[24]	Japan	70	69	44.3	0	51.4	100	Procedure-related risk factors	Average risk	Class B: prophylactic PS	0	NA	NA
										Control	9	NA	NA
Elmunzer *et al.* (2012)[7]	USA	602	45.2	20.9	15.9	57.0	25.9	Patient- and procedure-related risk factors	High risk	Class AB: prophylactic rectal indomethacin with PS on demand	27	13	14
										Class B: placebo with PS on demand	52	27	25

Table 1. Continued

Author (year)	Place	Total patients	Mean age, yr	Female sex, %	History of PEP, %	Biliary EST, %	Difficult cannulation, %	Inclusion criteria for patients	Study population	Compared prophylactic strategies*	Severity of PEP		
											Total	Moderate to severe	Mild
Lee *et al.* (2012)[5]	South Korea	101	57.6	37.6	0	56.4	57.4	Procedure-related risk factors	Average risk	Class B: prophylactic PS	6	1	5
										Control	15	3	12
Kawaguchi *et al.* (2012)[6]	Japan	120	67	56.7	8.3	NA	16.7	Patient- and procedure-related risk factors	High risk	Class B: prophylactic PS	1	0	1
										Control	8	0	8
Conigliaro *et al.* (2013)[25]	Italy	40	78.9	47.5	NA	NA	NA	Procedure-related risk factors	Average risk	Class B: prophylactic PS	0	0	0
										Control	6	4	2
Cha *et al.* (2013)[26]	USA	151	56.7	41.1	NA	NA	100	Procedure-related risk factors	High risk	Class B: prophylactic PS	2	0	2
										Control	10	6	4
Andrade-Davila *et al.* (2015)[32]	Mexico	166	52.8	33.7	1.8	58.4	47.0	Patient- and procedure-related risk factors	High risk	Class A: rectal indomethacin	4	1	3
										Control	17	3	14
Lua *et al.* (2015)[29]	Malaysia	144	49.9	41.0	2.8	NA	62.5	Patient- and procedure-related risk factors	High risk	Class AB: prophylactic rectal diclofenac with PS on demand	7	3	4
										Class B: placebo with PS on demand	4	0	4
Patil *et al.* (2016)[30]	India	400	69.4	62.8	2.8	NA	31.8	Patient- and procedure-related risk factors	High risk	Class AB: prophylactic rectal diclofenac with PS on demand	6	0	6
										Class B: placebo with PS on demand	23	9	14
Yin *et al.* (2016)[27]	China	206	57.3	55.3	NA	99.0	87.9	Patient- and procedure-related risk factors	High risk	Class B: prophylactic PS	8	NA	NA
										Control	18	NA	NA
Mok *et al.* (2017)[33]	USA	192	60.3	62.5	3.6	80.7	13.0	Patient- and procedure-related risk factors	High risk	Class ABC: prophylactic rectal indomethacin and aggressive hydration with PS on demand	9	1	8
										Class BC: placebo and aggressive hydration with PS on demand	19	NA	19
Park *et al.* (2018)[4]	South Korea	395	58.7	54.7	NA	NA	32.9	Patient- and procedure-related risk factors	Average to high risk	Class BC: aggressive hydration with PS on demand	13	NA	NA
										Class B: control with PS on demand	15	NA	NA
Sotoudehmanesh *et al.* (2019)[34]	Iran	414	55.35	39.4	0.7	NA	68.6	Patient- and procedure-related risk factors	High risk	Class ABC: prophylactic rectal indomethacin, prophylactic PS and aggressive hydration	26	4	22
										Class AC: prophylactic rectal indomethacin and aggressive hydration	33	6	27
Sperna Weiland *et al.* (2021)[35]	Netherland	813	59	59	NA	NA	4.9	Patient- and procedure-related risk factors	Average to high risk	Class ABC : prophylactic rectal NSAIDs and aggressive hydration with PS on demand	30	3	27
										Class AB : prophylactic rectal NSAIDs with PS on demand	39	10	29

PEP, postendoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; PS, pancreatic duct stent; NSAIDs, nonsteroidal anti-inflammatory drugs; NA, not applicable.
*Classification of prophylactic methods are as follows: class A, prophylaxis with rectal NSAIDs; class B, prophylaxis with PS or prophylactic PS placement on demand based on the clinical judgement of performing endoscopist; class C, prophylaxis with aggressive hydration; each classified preventive strategies were compared as single or combination.

to the control were as follows: class ABC (OR with NMA, 0.08; 95% CI, 0.03 to 0.24), class AC (OR with NMA, 0.10; 95% CI, 0.02 to 0.47), class AB (OR with NMA, 0.12; 95% CI, 0.05 to 0.26), class BC (OR with NMA, 0.13; 95% CI, 0.04 to 0.41), class A (OR with NMA, 0.16; 95% CI, 0.05 to 0.50), class B (OR with NMA, 0.26; 95% CI, 0.14 to 0.46), and Fig. 4 shows a forest plot of these comparison results in a NMA as compared to the control group. According to the P-score, the most effective prophylaxis for PEP reduction was ABC (0.87), followed by AC (0.68), AB (0.65), BC (0.56), A (0.49) and B (0.24) (Fig. 4). All prophylactic strategies showed better effects for PEP prevention compared to the control, and classes ABC (OR, 0.30; 95% CI, 0.11 to 0.79) and AB (OR, 0.45; 95% CI, 0.25 to 0.81) were superior to class B according to NMA (Fig. 5).

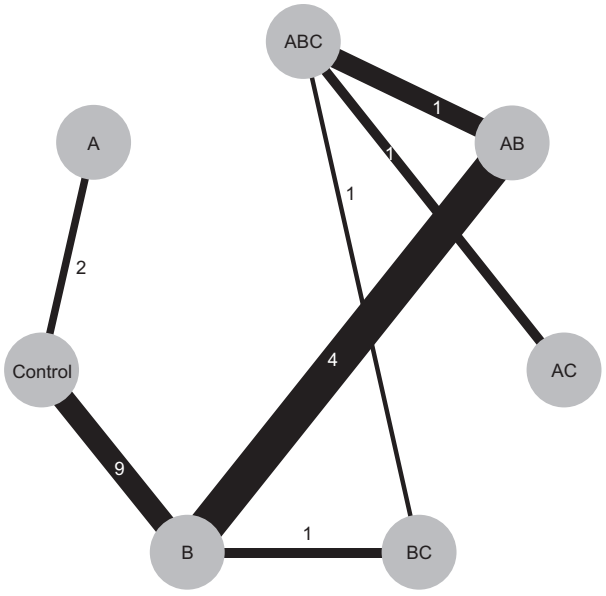

Fig. 3. Network meta-analysis design for the included studies of different prophylaxis strategies for preventing postendoscopic retrospective cholangiopancreatography pancreatitis among patients with risk factors. The width of each line denotes the sample size and the number on each line indicates the included studies for each comparison.
NSAIDs, nonsteroidal anti-inflammatory drugs; PS, pancreatic duct stent.

3) Results from NMA in the prevention of PEP for high-risk patients

Fourteen studies reported the efficacy of PEP prophylaxis for high-risk patients among the included studies (Table 1).[6,7,21-23,26-34] To avoid two separated subnets formation, we defined class AB and AC as class A based combinatorial methods. The results from NMA were shown in Supplementary Fig. 1, and the most effective prophylaxis for PEP reduction was ABC (0.90), followed by A based combinatorial methods (0.72), A (0.68), BC (0.40), and B (0.30) according to P-score. All prophylactic strategies showed better effects for PEP prevention compared to the control.

4) Results from NMA in the prevention of moderate to severe PEP

Fourteen studies reported the severity of PEP among the included studies were further analyzed to evaluate the efficacy to prevent moderate to severe PEP (Table 1).[5-7,21-23,25,26,29,30,32-35] The results from NMA were shown in Supplementary Fig. 2, and the most effective prophylaxis for moderate to severe PEP was ABC (0.94), followed by AC (0.79), AB (0.64), B (0.39), and A (0.21) according to P-score. All prophylactic strategies showed better effects for preventing moderate to severe PEP compared to the control, except class A.

3. Sensitivity analyses

When we conducted sensitivity analyses with 10 studies having low level study specific risk of bias except for blinding-related categories,[4,5,7,24,28,31-35] and with seven studies that included over 100 patients in each group,[4,7,27,28,30,34,35] the estimated effects of each of the prophylactic strategies were not greatly changed. As well, the order of effectiveness when comparing the rank according to P-score,

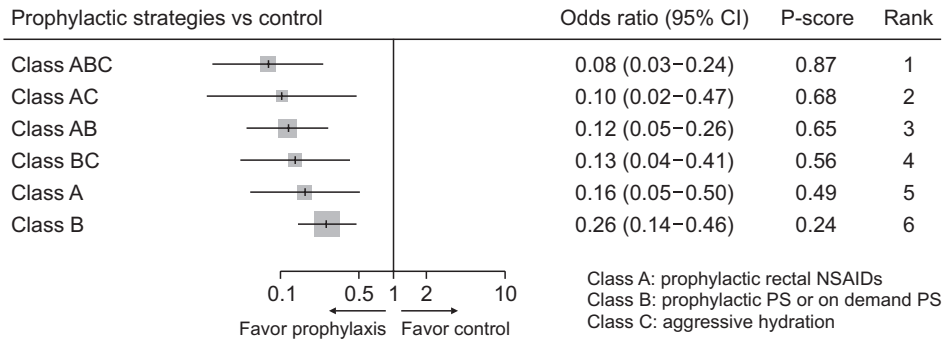

Fig. 4. Forest plot of the network meta-analysis estimates of effects for the comparison of different prophylaxis strategies for preventing postendoscopic retrospective cholangiopancreatography pancreatitis among patients with risk factors.
CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; PS, pancreatic duct stent.

Class A	-	-	-	-	-	0.16 (0.05–0.50)*
1.41 (0.35–5.66)	Class AB	1.21 (0.44–3.28)	-	0.49 (0.26–0.90)*	-	-
2.11 (0.43–10.30)	1.49 (0.62–3.58)	Class ABC	0.76 (0.27–2.12)	-	0.42 (0.12–1.41)	-
1.60 (0.24–10.60)	1.13 (0.29–4.38)	0.76 (0.27–2.12)	Class AC	-	-	-
0.63 (0.18–2.23)	0.45 (0.25–0.81)*	0.30 (0.11–0.79)*	0.40 (0.10–1.63)	Class B	2.56 (0.80–8.21)	0.26 (0.14–0.46)
1.21 (0.25–5.91)	0.86 (0.31–2.36)	0.58 (0.22–1.53)	0.76 (0.18–3.15)	1.92 (0.73–5.00)	Class BC	-
0.16 (0.05–0.50)*	0.12 (0.05–0.26)*	0.80 (0.03–0.24)*	0.10 (0.02–0.47)*	0.26 (0.14–0.46)*	0.13 (0.04–0.41)*	Control

Fig. 5. League table for all comparisons of possible prophylactic strategies against postendoscopic retrograde cholangiopancreatography pancreatitis in patients with risk factors. The estimated preventive effects with network meta-analysis are presented as odds ratios (95% confidence intervals). *Statistically significant comparisons with a p-value of less than 0.05.

showed class ABC was still the best, with merging of two prophylactic methods next, and methods used alone having the worst results (Supplementary Table 3). As a result, we concluded that the main outcome of our study was well maintained in sensitivity analyses.

4. Quality assessments and network assumptions

1) Quality assessment

Supplementary Table 4 presents the results of risk bias assessment for each of the RCTs. Overall, we judged that eight RCTs seemed to have a low risk of bias,[4,7,28,31-35] and the other 11 RCTs had a high risk of bias.[5,6,21-27,29,30] Studies of prophylaxis with PS mostly showed bias in blinding, as they had adopted an open-label design or had not adequately described a blinding process. Supplementary Table 5 presents the results of the certainty of evidence assessment of each comparison by Confidence in Network Meta-Analysis. Among 21 comparisons of PEP prophylaxis, two "major concerns" of within-study bias were affected by the risk of bias in each of the studies. There is no need to downgrade the certainty of evidence on account of the domain of indirectness, because the majority of these studies were designed in accordance with the research question of this study. Two comparisons showed some concerns in reporting bias because they did not report detailed information on dropouts or follow-up of patients, even though each reported study outcomes properly. We had major concerns about imprecision in four of the comparisons which contains direct portion. None were considered to rate the final certainty of evidence for each comparison, because there had been no need to rate the indirect evidence when the certainty of the direct evidence was high, and the contribution of the direct evidence to the network estimate was at least as great as that of the indirect evidence.[20] The effects of heterogeneity were significant for two comparisons, whereas major concerns about incoherence were not raised in any comparisons. Finally, seven comparisons of a high level, one of a moderate level, 12 of low a level, and one of a very low level were judged as a final rating of certainty of evidence for each of the comparisons by Confidence in Network Meta-Analysis (Supplementary Table 5).

2) Inconsistency assessment and network assumptions

No threats to the transitivity assumption were identified because there were no significant differences in the distributions of potential confounding factors (Supplementary Fig. 3). For the global assessment, we observed a moderate degree of heterogeneity (τ^2=0.197, I^2=38.0%). The separating indirect from direct evidence test did not identify any significant differences between the direct and indirect treatment effect estimates for the prophylactic strategies comparison (Supplementary Table 6). Construction of comparison-adjusted funnel plots demonstrated that there was no potential presence of small-study effects, in this meta-analysis (Supplementary Fig. 4). The network heat plot revealed no hotspots of potential inconsistency (Supplementary Fig. 5).

DISCUSSION

PEP has not been completely overcome, despite advances in PEP prevention.[36-38] For endoscopists who perform ERCP, the real world concern may be whether to select the best effort-to-effectiveness strategy for PEP prevention or to reduce PEP with a maximal prevention strategy by applying all available key methods. We planned this study to determine whether well-proven prophylactic methods including rectal NSAIDs, PS insertion, and aggressive hydration, act in complementary fashion, or as alternatives to

each other.

We found that class ABC was most effective for preventing PEP in patients with risk factors, followed by combination strategies with two prophylactic methods. Prevention strategies with any of the combinations showed better efficacy for reducing PEP, while single use of each prophylactic class was better than control. According to subgroup analyses, we found that class ABC could also be a more appropriate method for patients with high risk for PEP, and for preventing moderate to severe PEP. As well, it would be more effect to include rectal NSAIDs in the prevention strategy for PEP.

Although these prophylactic methods appear to have additive effects, it seems a little much to accept results that support either the superiority or the synergistic effects of the combination, because the differences between prophylactic effects were minimal and were not statistically significant. Also, it should be interpreted cautiously considering that the class B category in this study included patients who did not have actual PS placement. The recent guidelines have neutral stance on combinatorial prophylaxis for PEP.[2,12,13] European Society of Gastrointestinal Endoscopy recommended that all patients take prophylactic rectal NSAIDs in the pre-interventional period. Also, high-volume hydration with lactated Ringer's solution in patients with contraindication for NSAIDs is recommended, and provision of sublingual glyceryl nitrate to patients who are contraindicated with high-volume hydration is recommended in the pre-interventional period. In the peri-interventional period, they recommended to continue hydration for cases of standard cannulation or difficult cannulation without easy pancreatic stenting, and consider prophylactic pancreatic stent in the case of prophylactic with sublingual glyceryl nitrate in pre-interventional period. In case of difficult cannulation with easy pancreatic stenting, insertion of p-stent and cessation of hydration were recommended. In post-interventional period, aggressive hydration was recommended if no pancreatic stent is placed. We basically agree with the step-wise algorithm by European Society of Gastrointestinal Endoscopy, and believe that maximally combining prophylactic methods has obvious benefits for patients with risk factors. Further, it seems reasonable to adopt a strategy with regard to a decision on PS, at the discretion of the endoscopist, when combined with other methods that ensure sufficient prophylactic effects. PS should be conducted for at risk patients under situations that are favorable to PS and in patients prone to PEP, such as with inadvertent guidewire insertion or opacification of pancreatic duct, double guidewire cannulation, and difficult biliary cannulation.[2,12,13]

The results of this study were consistent with previous pivotal studies and meta-analyses. Recently, several studies reported NMA results for proper prophylactic PEP with different study designs, classifications and definitions.[8-11,39-43] Two studies conducted comparison between rectal NSAIDs and PS, both showed equivalent efficacy to prevent PEP,[10] but the other study showed superior efficacy of PS to prevent moderate to severe PEP in average and high-risk patients.[41] Several previous studies reported that PS appears to be the most effective preventive strategy for PEP in high-risk patients.[8,11,41] These findings for each single methods are consist with the result of the current study. We anticipate that a high level of evidence will be obtained through a future non-inferiority RCT of comparing stent and indomethacin for preventing PEP to determine whether PS will remain necessary in the era of NSAID pharmacoprevention (NCT 02476279).[44] The other five studies reported the greatest efficacy with the pharmacologic combination of rectal NSAIDs with hydration,[8,9,39,40,42] and those results are in line with findings in the current study that suggest the need for maximal support with combinatorial methods. Three studies were designed as comparison of each numerous detailed regimen instead of grouping them.[39,42] One study evaluated 18 regimens[39] and the other study evaluated 20 different regimens,[42] and they suggested rectal NSAIDs-based combination might be more effective than single agents alone. These studies provided evidence to make delicate decision, but in our opinion, it may cause confusion from the ranking of too many different methods in the same category.

This study has several strengths. First, we focused on three cornerstone prophylactic methods among numerous preventive therapies for PEP. These methods can be applied sequentially or together during procedural or periprocedural periods. The result of this study suggests that when endoscopists perform ERCP for patients with risk factors, it is necessary to keep all possible prophylactic methods in mind, rather than focusing on making specific choices for one above others. Second, this study classified prophylactic strategies for PEP including additive management by physicians, according to the description in the methods section in detail. This was not considered in any of the other meta-analysis studies. These efforts may play a major role in making the efficacy of each method for the prevention of PEP more clear and more accurate, by reducing the confounding effects of factors which may affect outcomes.

This study has several limitations. First, the level of each comparison-based certainty of evidence is generally low. The evidence level of RCTs involving PS tends to be especially low because double blinding in them is inherently difficult. This leads to a reduced certainty of evidence

of the comparative arm included in all of these studies. Second, it was difficult to review all of the possible confounding factors, because not all studies reported the same factors, and some were described at the study level or were only partially described. Instead, we confirmed the validity of the transitivity assumption between studies through a statistical analysis of several factors of a few missing values. Third, some may disagree with our classification of prophylactic methods. It may be difficult to accurately assess the true efficacy of PS alone or in combination with other preventive methods, because we classified those studies in which PS insertion had been done as mandatory or on demand as class B, including some patients who had not actually undergone PS insertion. Also, we classified aggressive hydration as more than 1 L in 8 hours after ERCP, which might be a slightly loose definition. Nevertheless, we believe that it likely reflects real world situations for endoscopists. Lastly, the effect size is recommended for comparison of two treatments, but it is difficult to make clear decision within multiple treatments.[14] Instead, the probabilities by P-score might facilitate decision making through intuitive comparison, despite of its own limitations, and strength of evidence.[45] Current study suggested the rationale of maximal support with feasible combinatorial methods based on P-score when compared with any single methods.

In conclusion, the results of this NMA suggest a combinatorial effect of prophylactic interventions for post-ERCP pancreatitis among patients with risk factors but direct evidences are inconclusive and further researches are required in future. These findings suggest that for patients with risk factors, we need to perform ERCP with maximal support, through use of these well proven combination strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

We thank to Medical Statistician Ban Seok Lee (MD, MPH, Kangil Hospital, Gimhae, Korea) for providing statistical review and advice for this study. The authors express sincere gratitude to Mr. Hwang Han and Mr. Park Jung Jin for their support to this study.

AUTHOR CONTRIBUTIONS

Study concept and design: J.H.C. Data acquisition: J.H.C., J.S.K. Data analysis and interpretation: J.H.C. Drafting of the manuscript: J.H.C. Critical revision of the manuscript for important intellectual content: S.H.L., N.P., M.H.L., M.W.L. Statistical analysis: J.H.C. Administrative, technical, or material support; study supervision: S.H.L., I.R.C., W.H.P., J.K.R., Y.T.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220268.

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