

## Review Article



# Comparison of the therapeutic methods (pharmacologic and nonpharmacologic) on prevention of post-ERCP pancreatitis: A systematic review and meta-analysis

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## Abstract

**Introduction:** Pancreatitis is considered as the well-known and serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Different approaches have been suggested to prevent or reduce this complication. Therefore we aim to investigate them in the current study.

**Methods:** This systematic review was performed in 2019 using Embase, google scholar, PubMed, and Cochrane library. The eligible investigations and outcomes of interest were selected and extracted by two reviewers. Meta-analysis was done using random or fixed-effect models. I-square statistic test was used for heterogeneity analysis.

**Results:** Totally, 2758 articles were searched. Thereafter duplicated and irrelevant articles were excluded, and six articles were entered into the present study. Six randomized controlled trials (RCTs) were considered eligible with a total participants of 1685. The relative risk of post-ERCP pancreatitis (PEP) was not significantly different in non-steroidal anti-inflammatory drug (NSAID) and hydration groups (pooled RR=1.19, 95% CI: 0.40 to 3.50, *P* value=0.74). The random effect model indicated no significant differences between NSAID and NSAID+hydration groups regarding the incidence of PEP (pooled risk ratio (RR)=2.19, 95% CI: 0.70 to 6.88, *P* value=0.17).

**Conclusion:** Using only NSAIDs or in part with hydration can decrease the PEP risk. Lack of studies comparing different approaches of prophylaxis in post-ERCP patients or the reporting of different parameters among the existing studies seriously limited the possibility and quality of meta-analysis.

## Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a designed procedure for diagnosis and treatment of pancreaticobiliary complications, including biliary tract disease, choledocholithiasis, pancreatobiliary neoplasms, cholangitis, obstructive jaundice, pancreaticobiliary disease, and suspicion for the pancreatitis of unknown source.<sup>1-4</sup>

Despite the well-documented beneficial effects of this procedure, ERCP is probably associated with some potential complications including post-ERCP pancreatitis (PEP).<sup>5,6</sup>

Until now, PEP is considered as one of the well-known complications of ERCP, occurred in up to 15% of patients.<sup>7</sup> Considering the high cost and morbidity rates associated with PEP, its prevention is utmost of importance. In this regard, different approaches have been suggested

to prevent or reduce these complications; however, no universally accepted method has been introduced.<sup>8</sup> For instance, administration of corticosteroids, somatostatin, gabexate, a high osmolality contrast medium are sorted among these approaches.<sup>9-11</sup> Moreover, the administration of non-steroidal anti-inflammatory drugs (NSAIDs) like indomethacin and diclofenac or hydration with lactated Ringer's solution (LR) or normal saline are recommended for preventing PEP.<sup>8,12-17</sup> In a concluding systematic review and meta-analysis, Elmunzer et al showed a lower risk of PEP with the administration of diclofenac and indomethacin.<sup>18</sup>

Additionally, pancreatic stent placement (PSP), was first introduced in the United States in the late 1990s, as a common clinical practice and extended as an effective preventing tool for PEP in high-risk cases.<sup>19,20</sup> While the pancreatic duct (PD) stent placement decreases risk<sup>21,22</sup>;

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it remains time-consuming, technically challenging, and also costly.<sup>23-26</sup>

Additionally, attempting to place a PD stent with subsequent failure elevates the PEP risk above baseline by injury to the pancreatic orifice inducing.<sup>27,28</sup>

According to our knowledge, there is no systematic review and meta-analysis to summarize the results of studies conducted on hydration therapy. Therefore, we aim to investigate the relevant literature to compare the effectiveness of NSAIDs and Hydration or the combination of both in the prevention of PEP in the current systematic review and meta-analysis.

## Methods

In the present study our PICO was as following: p= Patients undergoing ERCP; I= pharmacologic ; C=nonpharmacologic ; O= prevention of PEP.

### Study design

This investigation completely adhered to Preferred Reporting Items to Systematic reviews and Meta-Analyses (PRISMA) checklist.

The main objective of this review is a comparison of therapeutic methods (pharmacologic and nonpharmacologic) on the prevention of post ERCP pancreatitis.

### Literature searching strategy

Bibliographic databases including PubMed, Embase, and Cochrane library were searched independently only in English by two authors (A.Sa and M.Gh) using related keywords including “prevention”, “endoscopic retrograde cholangiopancreatography”, “pancreatitis”, “post ERCP pancreatitis”, “anti-inflammatory agents, non-steroidal”, “diclofenac”, “indomethacin”, “hydration”, “normal saline” and “lactated Ringer’s serum” in July 2019. The search strategy of each database is provided in Table S1. Medical Subject Headings (MeSH) and Emtree keywords were selected to search these databases Besides, the bibliographies of the identified articles were manually searched for finding additional investigations as well.

### Selection criteria

Designed clinical trials to compare two or more prophylactic methods (hydration therapy and NSAIDs) for preventing PEP that were published in English were involved in the current systematic review and meta-analysis. Letters to editor, case reports, or article abstracts were excluded from this study.

Two authors independently (A.Sa and M.Gh) extracted the data using an extraction table. T items included authors’ names, date of publication, the population of each study group, demographic features, and outcomes. In the case of missing data, like incomplete reporting or not reporting data, we contacted the original authors via Email.

The abstracts of the identified articles were reviewed by two independent reviewers (A.Sa and M.Gh). Then the full-text review was performed to rule out studies that did not meet the inclusion criteria. The reviewers’ disagreement was resolved by referring to a third reviewer (F.T).

### Assessing the methodological quality

Assessing the methodological quality and the risk of bias for the selected randomized controlled trials was performed by two reviewers independently and based on *the Cochrane Handbook for Systematic Reviews of Interventions* V.5.1.0, and the following domains were investigated: randomization sequence, blinding of participants or outcome assessors, allocation concealment, and evidence of selective reporting or other notable biases. Subsequently, Studies were sorted into three groups: 1. Low risk of bias; 2. High risk of bias, and 3. Unclear risk of bias.

### Statistical analysis

Statistical analysis was conducted employing Comprehensive Meta-Analysis (CMA) v.0.3 software. The first data analysis was standardized into equivalent units. The significant heterogeneity was defined as  $I^2 > 50\%$  and also a  $P$  value of  $< 0.05$ . The model of the random-effects or fixed-effects was selected for meta-analysis according to the heterogeneity results.

## Results

As depicted in [Figure 1](#), 2615 articles were searched. After excluding duplicated and irrelevant cases, finally, six articles were included into our study ([Table 1](#)).

Five RCTs were considered eligible with a total of 1083 participants. A total of 322 patients used NSAIDs, 250 hydration therapy, 296 both NSAIDs and hydration, and 215 did not use any drug before ERCP (control group).

About the type of drugs, diclofenac (hajikhani, senol)<sup>29,30</sup>, and rectal indometacin (masjedizadeh, hosseini, elmuzar, MOK)<sup>31-34</sup> were used as NSAIDs in five studies.

In the term of hydration therapy, normal saline serum or LR serum were used as a hydration therapy. The patients in the control group received rectal glycerin,<sup>32</sup> normal saline alone,<sup>30</sup> or no treatment at all.<sup>33</sup>

In three studies, patients received the treatment 30 minutes to two hours before the ERCP procedure.<sup>29,32,34</sup> In the other three studies, the intervention was done in the timespan of immediately after the procedure to two hours.<sup>30,33,35</sup>

### Quality of studies

All studies had one or more domains characterized as a high risk of bias ([Table 2](#)). Four studies enjoyed a better quality in terms of having more low-risk domains than high-risk ones out of 7 domains.<sup>31-34</sup>

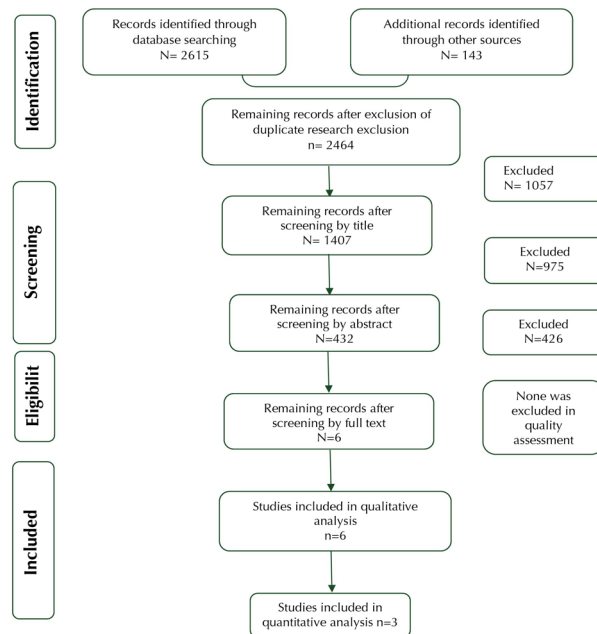


Figure 1. Prisma Flow diagram of studies for inclusion in the systematic review.

Table 1. Characteristics and information of the included studies

Author (date)	Country	Sample Size					Results
		NSAID (Indomethacin or Diclofenac)	Hydration	Stent	NSAID + Hydration	NSAID + Stent	
Hosseini et al (2016)	Iran	100	100	-	101	-	105 (Rectal glycerin) The incidence of PEP was 21% in rectal indomethacin group, 10% in intravenous saline perfusion group, 0% in indomethacin plus saline group and 16% in control group. The differences indomethacin plus saline group and control group was significant ( $P<0.001$ ).
Mok et al (2016)	USA	48	48	-	48	-	48 (Normal saline +placebo) The incidence of PEP was 21% in normal saline+placebo group, 13% in normal saline+indomethacin group, 19% in lactated Ringer's solution+placebo group and 6% in lactated Ringer's solution+indomethacin group. The difference between normal saline+placebo group and lactated Ringer's solution+indomethacin group was significant ( $P=0.04$ )
Hajalikhani et al (2018)	Iran	112		-	107	-	The incidence of PEP was 2.7% in the diclofenac only group and 0.9% diclofenac + hydration group with no significant difference (2.7% vs. 0.9%, $P = 0.622$ )
Masjedizadeh et al (2016)	Iran	62	62	-		-	62 (no treatment) The incidence of PEP was 12.9% in intravenous fluid resuscitation group, 25.8% in rectal indomethacin group and 32.3% in control group. There were significant differences in the incidence of pancreatitis between the groups ( $P = 0.036$ )
Senol et al (2009)	Turkey		40	-	40	-	The incidence of PEP was 7.5% in the diclofenac group and 17.5% in the placebo group. There were no significant differences in the incidence of pancreatitis between the two groups.
Elmunzer et al (2013)	USA	48	-	249	-	247	58 (no treatment) After adjusting for risk using two different logistic regression models, rectal indomethacin alone appeared to be more effective for preventing PEP than no prophylaxis, PSP alone, and the combination of indomethacin and PSP.

**Table 2.** Quality assessment of the included studies

Author	Random sequence	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Hosseini et al (2016)	L	U	L	L	L	L	L
Mok et al (2016)	L	L	L	L	L	L	L
Hajalikhani et al (2018)	U	U	U	U	L	L	L
Masjedizadeh et al (2016)	L	U	L	L	L	L	L
Senol et al (2009)	U	U	U	U	L	L	L
Elmunzer et al. (2013)	U	U	U	L	L	L	L

U, Unclear; H, High risk of bias; L, Low risk of bias.

**Meta-analysis**

**Comparison of the incidence of PEP in NSAID and hydration groups**

Two studies compared the incidence of PEP in NSAID (110 patients) and hydration (110 patients) groups. Considering the presence of heterogeneity (Q-value=3.08, P value=0.08, I<sup>2</sup>=67.58), random effect model was used. According to the results of the random effect model analysis, there was no significant difference between the two groups (Pooled risk ratio (RR)=1.19, 95% CI: 0.40 to 3.50, P value=0.74) (Figure 2).

**Comparison of the incidence of PEP in NSAID and NSAID+hydration groups**

The effect of NSAID (160 patients) or NSAID+hydration (155 patients) in the prevention of PEP was compared in two studies. The results of the heterogeneity analysis showed no significant heterogeneity among studies. (Q-value=0.07, P value=0.79. I<sup>2</sup>=0.00). According to the results of the random effect model analysis, there was no significant difference between the two groups (pooled RR=2.19, 95% : 0.70 to 6.88, P value=0.17) (Figure 3).

**Comparison of the incidence of PEP in hydration and NSAID+hydration groups**

In two studies that compared the incidence of PEP in hydration (88 patients) and NSAID+hydration (n=88) groups, no significant heterogeneity between the trials was observed. According to the results of the fixed effect model analysis, the relative risk of PEP was 2.65 times higher in the hydration group compared with the NSAID+hydration group (pooled RR=2.65, 95% CI: 1.08 to 4.47, P value=0.03) (Figure 4).

**Discussion**

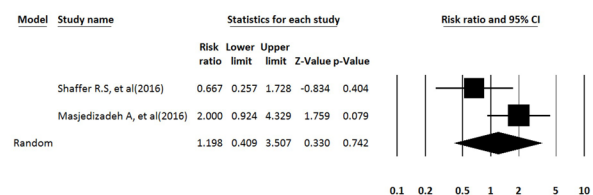
This systematic review and meta-analysis was carried out for comparing the effects of different approaches of hydration and hydration+NSAID administration on the management of PEP for the first time.

Different studies investigated the probable effects of hydration or NSAID or the combination of them as a prophylactic approach to prevent port-ERCP pancreatitis.<sup>36,37</sup>

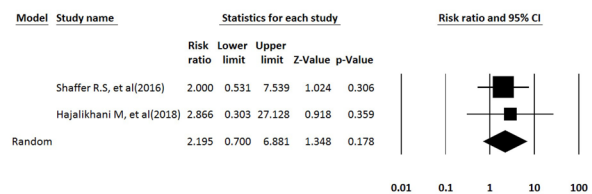
The results of our study demonstrated that the risk of PEP

when using NSAIDs+hydration compared to hydration therapy alone was significantly reduced. According to the results by Buxbaum et al, aggressive intravenous hydration with LR solution probably has the potency to decrease the PEP development as well and is not related to the overload volume.<sup>38</sup> An Iranian investigation revealed that rectal indomethacin in part with intravenous normal saline before ERCP remarkably suppresses PEP as well. These results express clearly the advantageous effects of using intervention method.<sup>32</sup>

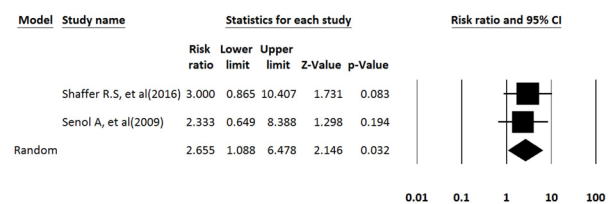
In a systematic review and meta-analysis, Yaghoobi et al studied the rectal indomethacin effect for the PEP prevention and displayed that rectal indomethacin has applied immediately pre or post-ERCP significantly decreases the PEP risk to half in both low- and high-risk



**Figure 2.** Forest plot for comparison of the incidence of PEP in NSAID and hydration groups.



**Figure 3.** Forest plot for comparison of the incidence of PEP in NSAID and NSAID+hydration groups.



**Figure 4.** Forest plot for comparison of the incidence of PEP in hydration and NSAID+hydration groups.



patients, with both statistically and clinically significance.<sup>39</sup> Two systematic reviews concentrated on the efficacy of aggressive hydration with LR solution in order to post-ERCP prevention. They revealed the positive impacts of this therapy in PEP prevention as well.<sup>40,41</sup> Reversed bile flow is not the only side effect of ERCP; however, exposure to the radiocontrast agents elevates the hydrostatic pressure in the PD.<sup>42</sup> Radiocontrast agents that have been injected into pancreaticobiliary trees are able to activate signaling of calcium ion and NF- $\kappa$ B-mediated inflammatory cascades in the pancreas. Additionally, in clinical settings, depletion of fluid is very common because of the pre-ERCP preparation with fasting and underlying disorders. It is confirmed that pancreatic microcirculation hypoperfusion is able to precipitate the PEP development. Inadequate fluid resuscitation is shown to be pertinent to the occurrence of organ failure in acute pancreatitis. Therefore, resuscitation of fluid is recommended by American College of Gastroenterology to be the mainstay for the acute pancreatitis treatment.<sup>43</sup> On the other hand, the mechanism of action for NSAIDs is phospholipase A2 inhibition, which reduces the inflammatory cascade and downregulates the pro-inflammatory factors, like the prostaglandins, leukotrienes, and platelet-activating agent. It also reduces the inflammatory lesions and organ necrosis. As can be inferred, NSAIDs and hydration therapy act at various stages of PEP development; hydration preserves pancreatic microcirculation, and NSAIDs inhibit the inflammatory response. Therefore, a synergistic effect of hydration and rectal NSAIDs is plausible.<sup>33</sup>

Our study faced several limitations. As it was mentioned previously, our investigation was restricted to the English language articles. Besides, a lack of studies comparing different approaches of prophylaxis in post-ERCP patients or the reporting of different parameters among the existing studies seriously limited the possibility and quality of meta-analysis and subgroup analysis. Moreover, most of the studies included in the present systematic review and meta-analysis did not exactly report how they prevented certain biases like allocation concealment or blinding across the study.

### Conclusion

The results of the current investigation displayed that using NSAIDs in part with hydration is able to decrease the risk of PEP. It is noteworthy to mention that further well-designed studies with accurate reporting of data need to be done to provide a more reliable conclusion.

### Conflict of interest

None to declare.

### Ethical Approval

This study was approved by the Ethics Committee of the Tabriz University of Medical Sciences IR.TBZ.REC.1398.4.5

### Authors' Contribution

All authors contributed to the preparation of data collection, writing, and editing processes completely.

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We would like to thank all colleagues for their expert guidance. All authors had contributed to prepare this manuscript.

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### Supplementary Files

Supplementary file 1 contains Table S1.

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