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Non-Steroidal Anti-Inflammatory Drugs Role in the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Review of Reviews and Meta-Analysis

Hyder Osman Mirghani[1]; Abdolmohsen Alamri[2]; Moaz Alyasi[2]

[1]Department of Internal Medicine, Faculty of Medicine, University of Tabuk, Saudi Arabia.

[2]Faculty of Medicine, University of Tabuk, Saudi Arabia.

***Corresponding Author(s): Hyder Osman Mirghani**

Faculty of Medicine, University of Tabuk, PO Box 3378, Tabuk 51941, Saudi Arabia.

Email: s.hyder63@hotmail.com

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Abstract

Background: Endoscopic Retrograde Cholangiopancreatography (ERCP) is an effective diagnostic and therapeutic procedure in the field of endoscopy. Post-ERCP pancreatitis is a serious, morbid, and stressful consequence. The current review aimed to assess the role of Non-steroidal anti-inflammatory drugs as a preventive measure in post-ERCP pancreatitis.

Methods: A systematic electronic search for review articles in English published in the period 2007-2019 was conducted, updated in November 2020. There were 179 articles, the figure stands at 32 after applying the inclusion and exclusion criteria. The author names, the year of publication, country, and the number of articles included in the previous reviews were reported.

Results: There were 31 reviews and meta-analyses, 80482 patients were included. All the reviewed reviews (except one including six randomized controlled trials) concluded the effectiveness of rectal NSAID in the prevention of post-ERCP pancreatitis. However, patients risk stratification is recommended.

Conclusion: Peri-operative rectal NSAID is effective as a preventive intervention in post-ERCP pancreatitis. Further reviews investigating the dose, time, and route of administrations of NSAID are recommended.

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Introduction

Endoscopic Retrograde Cholangiopancreatography (ERCP) was developed about 50 years ago in 1968 as a diagnostic tool. In 1973 in Japan, the first biliary sphincterotomy was done, and it kept evolving ever since [1].

It is estimated that about 500,000 procedures were performed annually in the United States. It became almost only a therapeutic tool due to emerging sensitive non-invasive diagnostic tools (Endoscopic Ultrasonography (EUS) and Magnetic Resonance Cholangiopancreatography (MRCP) [2].

ERCP indications include biliary stones, strictures, and leaks.

The American Society of Gastrointestinal Endoscopy (ASGE) has issued guidelines for the rule of ERCP in biliary and pancreatic diseases including precautions and contraindications of ERCP [3].

Like any procedure, ERCP has complications including Pancreatitis, Cholangitis, perforation, and bleeding.

The high-risk criteria ASGE was suggested to minimize complications rates, it includes [4]:

- common bile duct (CBD) stone on ultrasonography or cross-sectional imaging.
- total bilirubin >4 mg/dL *and* dilated CBD on imaging (>6 mm with gallbladder in situ).
- ascending cholangitis.

Post ERCP pancreatitis is one of the serious complications and the most common one with an incidence ranging from 1% to 10% in average-risk patients, and up to 30% in high-risk patients. ASGE updated its guidelines in 2015 recommending Rectal Indomethacin for patients undergoing ERCP as prophylaxis against Post ERCP. Pancreatitis (PEP) in patients with suspected Sphincter of Oddi Dysfunction (SOD). Also, rectal indomethacin is recommended for high-risk patients [5].

Levenick et al. (2016) conducted a randomized controlled trial of 449 consecutive patients undergoing ERCP at Dartmouth Hitchcock Medical Center showed that rectal indomethacin did not prevent PEP [6]. Also in 2017, a review article by Feng Y et al, the article included six studies with a total of 2473 patients that showed that indomethacin did not significantly prevent the effect of PEP [7].

In the face of the above and the controversy regarding the use of Non-Steroidal Anti-Inflammatory Drugs (NSAID) in the prevention of PEP, we conducted this review to assess the role of NSAID in the prevention of PEP.

Selection criteria according to PICOS

The studies were included if they were review and meta-analyses published in English and assessing the role of NSAIDs on the prevention of PEP. Observational studies, randomized trials, and experimental studies were excluded. The route of the drug use was not specified.

Search strategy

A systematic search in the Pub Med and Google Scholar was conducted. Only review articles and meta-analyses in the English language and conducted during the period 2007-2019 were approached. An update was done in November 2020. The terms post-ERCP pancreatitis, prevention, NSAID, indomethacin, and diclofenac sodium were used for the literature search. Articles other than reviews and meta-analysis were not included. Two reviewers screened the manuscripts for inclusion and exclusion criteria and removal of duplications. We used a data extraction sheet to report the author name, year of publication, country, type of study, and the number of patients. One hundred seventy-nine studies were identified through the database search. Ninety studied were included after duplicate removal, of them, 31 full texts were included in the final review. The different phases of the systematic review were reported in **Figure 1.**

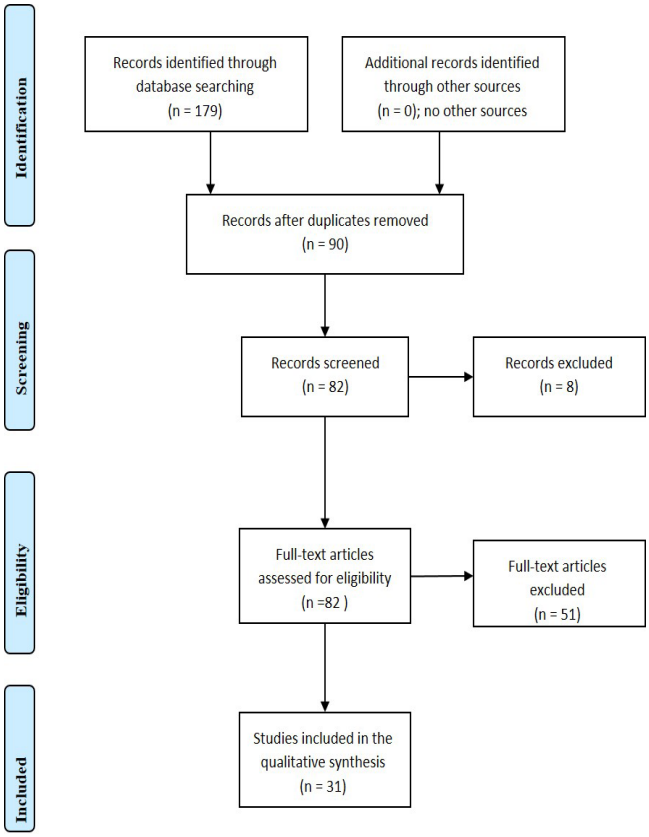

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart).

Results

Among these 179 papers, 90 full-text articles were assessed for eligibility: Only 31 reviews including 512 randomized controlled trial (11 from the USA, five from Europe, and sixteen were from Asia) met the inclusion criteria for the systematic review. The reviews included 80482 patients, all the reviews except two showed that NSAIDs were effective in reducing PEP. However careful patient stratification is needed (Table 1).

Table 1: NSAID and prevention of post-ERCP pancreatitis.

Author	Year	Country	Type	Studied included	Number of patients	Results
Wagh et al. [8]	2007		Review			Promising, but proper patient selection
Elmunzer et al. [9]	2008	USA	A meta-analysis	4 RCTs	912	NSAID was effective
Dai et al. [10]	2009	China	Ameta-analysis of	6 RCTs		NSAID was effective
Dumonceau et al. [11]	2011	Switzerland	Review	narrative		NSAID was recommended
Ding et al. [12]	2012	China	A meta-analysis	10 RCTs	2269	NSAIDs were effective
Akbar et al. [13]	2013	USA	A meta-analysis of 29 studies	Seven studies on NSAIDs		Rectal NSAIDs are effective
Yaghoobi et al. [14]	2013	USA	A meta-analysis Of 67 studies	61 on NSAIDs trials	1470	Rectal indomethacin used before or after ERCP was effective
Akshintala et al. [15]	2013	USA	A meta-analysis	99 trials	25313	Rectal indomethacin efficacious
Yuhara et al. [16]	2014	Japan	A meta-analysis of 26 RCTs	7 studies on NSAIDs		NSAIDs were effective
Sun et al. [17]	2014	China	A meta-analysis	7 RCTs	1846	Rectal NSAIDs reduced both the incidence and severity of PEP
Sethi et al. [18]	2014	India	A meta-analysis	7 RCTs	2133	rectal NSAIDs decreased the overall incidence of PEP
Ahmad et al. [19]	2014	USA	A meta-analysis	4 RCTs	1422	Rectal indomethacin significantly reduced the incidence of PEP
Puig et al. [20]	2014	Spain	A meta-analysis	9 RCTs	2133	Rectal NSAIDs before or immediately after prevents PEP
Li et al. [21]	2014	China	A meta-analysis	8 RCTs and 18 observational studies		NSAIDs reduce mild pancreatitis
Thaker et al. [22]	2015	USA	Narrative review			NSAIDs effective in high-risk patients
Kubiliun et al. [23]	2015	USA	A meta-analysis	85 RCTs and 28 meta-analyses		NSAIDs appropriate
Shi et al. [24]	2015	China	A meta-analysis	3 studies		Rectal indomethacin can reduce the overall incidence and the severity of PEP
Patai et al. [25]	2015	Hungary	A narrative review			Patients stratification and NSAIDs are important
Rustagi et al. [26]	2015	USA	A meta-analysis	11 trials	2497	NSAIDs were effective
Vadalà di Prampero et al. [27]	2016	Serbia	A meta-analysis	30 RCTs	10251	Rectal diclofenac is effective
Inamdar et al. [28]	2017	USA	A meta-analysis	8 RCTs	3778	Rectal indomethacin is effective in high but not moderate risk patients
Yang et al. [29]	2017	China	A meta-analysis	12 RCTs	3998	Rectal indomethacin was effective
Feng et al. [7]	2017	China	A meta-analysis	6 Blind randomized controlled trials		Rectal indomethacin was not effective
Chen et al. [30]	2017	China	A meta-analysis	9 trials		Rectal NSAIDs were effective
Patai et al. [31]	2017	Hungary	A meta-analysis	17 trials	4741	Diclofenac and indomethacin were effective
Wan et al. [32]	2017	China	A meta-analysis	7 RCTs	3031	Rectal indomethacin is effective in high-risk patients
Li et al. [33]	2017	China	A meta-analysis	8 RCTs	1883	NSAIDs effective
Lyu et al. [34]	2018	China	A meta-analysis	19 RCTs	6134	NSAIDs effective
Grag et al. (35)	2018	USA	A meta-analysis	6 RCTs	2229	Indomethacin is effective in unselected patients
Serrano et al. (36)	2019	Brazil	Meta-analysis	21 RCTs	3427	Rectal administration of diclofenac and indomethacin significantly reduced the risk of developing mild PEP
Liu et al. (37)	2019	China	Meta-analysis	19 RCTs	5031	Moderate to a severe reduction

Discussion

In the current review, Wagh et al. [8] reviewed the literature in 2007 and concluded that NSAIDs are promising but proper patient selection is needed. Elmunzer et al. [9] and Dai et al. [10] reviewed six RCTs and found that NSAIDs are effective in post-ERCP pancreatitis. A review from Switzerland [11] concluded that NSAIDs are recommended. The above findings were supported by further reviews of RCTs [12-16]. In the present review, Sun et al. [17] analyzed seven RCTs and observed the effectiveness of NSAID in reducing the incidence and severity of post-ERCP pancreatitis, meta-analyses from India, USA, and Spain [18-20] showed the effectiveness of rectal NSAID before or after ERCP in reducing pancreatitis. In the present review, while Li et al. [21] analyzed 8 RCTs and found that NSAIDs reduce only mild pancreatitis, however the review was less powered by including both RCTs and observational studies. Thaker et al. [22] in their review concluded that NSAIDs are effective, and Kubiliun et al. [23] included 851 patients in their meta-analysis of RCTs and found that NSAID is appropriate. A meta-analysis of three studies [24] found rectal indomethacin can reduce the overall incidence and the severity of PEP, an observation that was supported by other studies [25,26], but proper patients selection was recommended. In the current review, Vadalà di Prampero et al [27] analyzed 12 RCTs and observed that rectal diclofenac is effective, while Inamdar et al. [28] in their meta-analysis of 8RCTs showed that rectal indomethacin is effective in high but not moderate-risk patients. Yang et al. [29], Chen et al. [30], Patai et al. [31], and Wan et al. [32] analyzed the literature and concluded the benefit of rectal NSAID, on the other hands Feng et al. [7] showed that rectal indomethacin not effective. It is important to note that Feng and colleagues included only six studies in their meta-analysis and only assessed rectal indomethacin, the findings of the effectiveness of NSAD in PEP prevention were supported by Li et al., liu et al., Lyu et al., and Grag et al. [33-36]. A recent meta-analysis from Brazil [37] showed that rectal administration of diclofenac and indomethacin significantly reduced the risk of developing mild PEP.

Conclusion

The current review found that NSAIDs were effective in reducing post-ERCP pancreatitis, however the patient's stratification was recommended by some authors. Also, some studies pointed out that, NSAIDs were effective only in reducing mild pancreatitis.

Ethical consideration: This review did not include any study on humans or animals published by the authors.

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