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Research Article

Role of NSAIDs in the Prevention of Post-ERCP Pancreatitis: A Narrative Review

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Abstract

Acute pancreatitis is the most common complication after Endoscopic Retrograde Cholangio-Pancreatography (ERCP), occurring in about 3.5% of the procedures. NSAIDs have been shown to play a vital role in the prevention of post-endoscopic retrograde cholangio-pancreatography pancreatitis (PEP). However, not much is known about the most effective drug in preventing this complication. Furthermore, there is a lot of conflict regarding the correct dose, route, and timing of the drug administration.

The current study aims to investigate the role of NSAIDs in the prevention of PEP. The literature search was performed using PubMed, and after applying the inclusion and exclusion criteria, 9 published papers were found. All relevant articles on the topic have been included. Our review article has demonstrated that NSAIDs are quite effective in reducing the chances of PEP. It is best to administer drugs per-rectally and pre-procedurally for it to be more effective. However, more Randomized Controlled Trials (RCTs) need to be done to fully understand NSAIDs' role in PEP prophylaxis.

Keywords: Acute Pancreatitis; ERCP; NSAIDs

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has become an integral procedure in modern gastroenterology practice. It is a combined endoscopic and fluoroscopic procedure where an endoscope is led into the second part of the duodenum to do a minimally invasive procedure in biliary and pancreatic ducts. It is a diagnostic as well as a therapeutic tool [1] and has become an substantial procedure to diagnose ampullary carcinomas and also for stent placement in patients with strictures, fistulae, leaks, or as a therapeutic tool for people who can't undergo surgery i.e patients with ampullary carcinomas. From a mere removal of stone to stenting, all this could be done through ERCP. Having said that, there are some complications associated with it as well. The most frequent complication being post-ERCP pancreatitis (PEP), occurs in about 3.5% of cases and can be fatal at times [2].

Several trials are going on to look out for the best medication that can be used prophylactically to prevent PEP. Drugs currently being studied are nitroglycerin, NSAIDs (indomethacin, naproxen, diclofenac), ceftazidime, octreotide, somatostatin, and anti-protease drugs [3]. NSAIDs have proven to be quite beneficial in this regard. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit enzymes, phospholipase A2, and cyclooxygenase, as well as neutrophil-endothelial interactions, which are known to be involved in the pathogenesis of acute pancreatitis [4]. Many studies have demonstrated NSAIDs to be a very effective drug category in the prevention of PEP. But there is a lot of heterogeneity involving route of administration, timings (before or after the procedure), and dose.

So, in this review article, we not only explore NSAID as a prophylactic drug for PEP but also try to resolve the conflict regarding dosage, route of administration, and timing.

2. Methods

A search of PubMed was performed to identify potentially relevant publications. Mesh keywords used included "Anti-Inflammatory agents, Non-Steroidal" AND "Cholangiopancreatography, Endoscopic Retrograde") AND "Pancreatitis". The search was restricted to human studies, and those done in the last 5 years. Only articles written in the English language were included. The pediatric population was not included, and a filter of >18 years was applied. The exclusion criteria were: 1). non-english literature, and 2). animal studies.

3. Results

The total number of studies retrieved was 37 initially. After the primary and secondary screening, a total of 9 studies were included in our review, with the total number of subjects being 4870. All studies were prospective and randomized. Most of the studies were double-blinded except Katoh T and Luo H, which were single-blinded. All studies demonstrated the effect of NSAIDs before ERCP except for one by Luo H et al.

4. Discussion

ERCP is an invasive procedure. Despite its countless advantages, it does have some downsides. After the procedure, some patients can develop post-ERCP pancreatitis. The patient is said to have post-ERCP pancreatitis if the patient develops signs and symptoms of acute pancreatitis (i.e. abdominal pain) with the elevation of pancreatic enzymes. But it is very important to consider other causes of post-procedural abdominal discomfort, such as air insufflation. After ERCP, serum amylase levels may be elevated in up to 75% of patients, regardless of symptoms.

Over the years, many attempts have been made to prevent post-ERCP pancreatitis. Several strategies have been introduced to decrease its risk. The most studied being pharmacological interventions that provide effective medical prophylaxis against pancreatitis. NSAIDs are a hot topic of interest in this regard [5].

In this current review, we analyzed data from 9 randomized control trials with 4870 subjects. These trials used NSAIDs (Indomethacin, naproxen, diclofenac, celecoxib, and Ketoprofen) as a prophylaxis to prevent post-ERCP pancreatitis (PEP). The review article has looked closely at the route of administration, dosage, and timings. A summary of studies included in our review is given in Table 1.

4.1 Main outcome

In this review, we have found out that any form and any route of NSAID is generally more effective than placebo to prevent PEP in patients undergoing ERCP. 6 out of 9 studies have shown that NSAID use causes a significant reduction in pancreatitis. In the remainder of the studies, either the percentage differences are small, or the PEP percentage was slightly more than in the control group, as seen in study 1. Table 2 summarize our study in an elaborative way.

4.2 Route of administration

Several routes are being studied for the effective prophylactic administration of NSAID for PEP. These routes include IM (Intramuscular), IV (intravenous), rectal and oral. Most of the studies are done on the PR (Per-rectal) route. A total of 6 out of 9 studies have used the per-rectal route. 5 studies have demonstrated that per-rectal is an effective mode of administration. A meta-analysis has also supported this finding that PR diclofenac is the most effective route of administration [15]. 3 RCTs have used the per-oral route.

Only one study showed it to be effective. Geraci G et al. aimed to evaluate the efficacy of intramuscular, intravenous, oral, and rectal diclofenac sodium for prophylaxis of PEP and found the overall incidence of PEP to be 15%, 5%, 15%, and 0% in the intramuscular, intravenous, oral and rectal groups respectively, and 20% in the control group [7]. This study also showed the per-rectal route to be a better option. Table 2 demonstrates the route of administration and the percentage of PEP compared with placebo.

4.3 Time of administration

ESGE (European Society of Gastrointestinal Endoscopy) has suggested that NSAIDs can be used before or after the procedure, but theoretically speaking, the time of administration does play a huge role for

prophylaxis to be effective against PEP [16]. In our review, there was only one RCT with post-ERCP NSAID administration [12]. All eight studies have used pre-ERCP prophylaxis. Results have demonstrated pre-ERCP prophylaxis to be most effective.

Previous research on per-rectal indomethacin has shown that the peak plasma concentration of indomethacin is reached 30 min after rectal administration when bioavailability is complete [2]. When the drug was used before ERCP, the peak level was achieved at the desirable time. A meta-analysis by Rustagi et al. [16] in 2014 found that NSAID administration before ERCP had a greater benefit than administration after the procedure. Recently, Luo et al. found that the strategy of prophylactic pre-ERCP administration of rectal indomethacin for all patients was superior to the rectal indomethacin after ERCP in only high-risk patients [17]. Hence, the timing of administration of rectal indomethacin should be before rather than after ERCP.

Reference	**Study Design**	**NSAID used**	**Subject/ N**
Katoh T 2020 [6]	Prospective, single-center, single-blinded, two-arm parallel-group	Diclofenac	297
Geraci G 2019 [7]	Prospective, randomized, double-blinded, study	Diclofenac	100
Li L 2019 [8]	Randomized	Indomethacin	100
Kato K 2017 [9]	Prospective, randomized controlled study	Celecoxib	170
Mohammad Alizadeh AH 2017 [10]	Double-blind, randomized study	Indomethacin/ Diclofenac/ Naproxen	372
de Quadros Onófrio F 2016 [11]	Randomized, double-blind clinical trial	Ketoprofen	477
Ishiwatari H 2016 [12]	A multicenter, randomized, prospective, placebo-controlled, double-blind trial.	Diclofenac	430
Mansour-Ghanaei F 2016 [13]	Double-blind, randomized control trial	Naproxen	324
Luo H 2016 [14]	Multicentre, single-blinded, randomized controlled trial	Indomethacin	2600

Table 1: Baseline characteristics of the trials used in the review article.

Reference	NSAID/ placebo used	Subjects number	Timing	Route	Dose/mg	Percentage of PEP(%)	Conclusion
Katoh T 2020 [6]	Diclofenac	147	3o minutes before ERCP	Rectal	50mg	5.4	Not significant
	Placebo	150				3.3	
Geraci G 2019 [7]	Diclofenac	20	30 to 90 minutes before ERCP	Oral	50mg	15	Single rectal administration of diclofenac is an effica-cious and safe measure. (Significant)
		20		Rectal	100mg	0	
		20		IM	75 mg/3 ml	15	
		20		IV	75 mg/3 ml	5	
	Placebo	20		Oral	--	20	
Li L 2019 [8]	Indomethacin	50	15-20 min before ERCP	Rectal	100mg	12	Significant
	Placebo	50			--	32	
Kato K 2017 [9]	Celecoxib	85	1 hour before ERCP	Oral	400mg	11.7	Significant
	Celecoxib			Infusion	--		
	Placebo	85		Infusion	--	15.3	
Mohammad Alizadeh AH 2017 [10]	Indomethacin	122	30 min before undergoing ERCP	Rectal	100	7	Significant for diclofenac and indomethacin patient groups
	Diclofenac	124			100	4	
	Naproxen	126			500	20	
de Quadros Onófrio F 2016 [11]	Ketoprofen	224	Immediately before the procedure	Infusion	--	2.2	Not significant
	Placebo(saline)	253				2	
Ishiwatari H 2016 [12]	Diclofenac	216	After ERCP	Oral	50	9.8	Not significant
	Placebo	214			--	9.4	
Mansour-Ghanaei F 2016 [13]	Naproxen	162	Immediately before ERCP	Rectal	500	7.4	Suppository naproxen significantly reduces the incidence of PEP.
	Placebo	162				17	
Luo H 2016 [14]	Indomethacin	1297	30 min before ERCP	Rectal	100	4	Rectal indomethacin reduces the occurrence of post-ERCP pancreatitis (significant)
		1303	Immediately after ERCP			8	

Table 2: Main findings of RCTs included in the review article.

Reference	NSAID/placebo used	Route	Percentage of PEP(%)	Effective
Katoh T 2020 [6]	Diclofenac	Rectal	5.4	No
	Placebo		3.3	
Geraci G 2019 [7]	Diclofenac	Oral	15	Yes
		Rectal	0	
		IM	15	
		IV	5	
	Placebo	Oral	20	
Li L 2019 [8]	Indomethacin	Rectal	12	Yes
	Placebo		32	
Kato K 2017 [9]	Celecoxib	Oral	11.7	Yes
	Celecoxib	Infusion		
	Placebo	Infusion	15.3	
Mohammad Alizadeh AH 2017 [10]	Indomethacin	Rectal	7	--
	Diclofenac		4	
	Naproxen		20	
de Quadros Onófrio F 2016 [11]	Ketoprofen	Infusion	2.2	No
	Placebo(saline)		2	
Ishiwatari H 2016 [12]	Diclofenac	Oral	9.8	No
	Placebo		9.4	
Mansour-Ghanaei F 2016 [13]	Naproxen	Rectal	7.4	yes
	Placebo		17	
Luo H 2016 [14]	Indomethacin	Rectal	4	Yes
			8	

Table 3: Table illustrating the route of NSAID administration use by RCTs used in the review article.

5. Conclusion

NSAID use should be recommended for preventing PEP in patients before ERCP. Furthermore, the per-rectal route should be preferred as it has shown to be most effective. Besides, larger multi-center RCTs are still needed to determine NSAIDs' role in PEP and if there any significant adverse effects associated with its use.

Limitations

The present review article provides a comprehensive overview on the use of NSAIDs for possible prophylaxis of PEP. It also discusses in detail the route and timing of the administration of NSAIDs. However, there are some limitations to it.

First, randomized control trials done in the last five years were only included. Secondly, the data was obtained from one search engine (PubMed).

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