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Post endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis: evaluation of two different NSAID regimens

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ABSTRACT – Background – Endoscopic retrograde cholangiopancreatography is a widely used therapeutic modality for the pancreaticobiliary tree. However, it is responsible for the highest rates of complications among the endoscopic procedures, especially post-endoscopic retrograde cholangiopancreatography pancreatitis. The preventive methods include mechanical and pharmacological approaches, such as the use of non-steroidal anti-inflammatory drugs. **Objective** – To compare the efficacy of two different strategies using non-steroidal anti-inflammatory drugs for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis, and to clarify the uncertainty about the route of administration of non-steroidal anti-inflammatory drugs in the prevention of this complication. **Methods** – This was a prospective trial. Two therapeutic groups were compared with a control group that was composed of patients who underwent endoscopic retrograde cholangiopancreatography, performed in the same service and by the same team in the period preceding the study (historical series), without the administration of any type of prophylaxis. The first group received 100 mg rectal diclofenac. The second group received 100 mg intravenous ketoprofen. Both groups were compared, separately and jointly, with the control group. **Results** – Post-endoscopic retrograde cholangiopancreatography pancreatitis occurred in 4.39% (12/273) of the participants. In the group without prophylaxis, the incidence was 6.89% (10/145). Among those who received intravenous ketoprofen, the incidence was 2.56% (2/78). No cases of acute post-procedural pancreatitis were observed in the group that received rectal diclofenac (0/52). Although there was no statistical difference between the therapeutic groups when they were separately analyzed, a statistical difference in the prevention of post-procedural pancreatitis was observed when they were analyzed together (P=0.037). **Conclusion** – This study provides evidence for the efficacy of non-steroidal anti-inflammatory drugs in the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Keywords – Diclofenac; ketoprofen; NSAID; prophylaxis; pancreatitis; ERCP.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic procedure that is widely accepted as the most important therapeutic modality for benign and malignant diseases of the pancreaticobiliary tree[1]. The therapeutic possibilities of this procedure range from the removal of stones to palliative biliary drainage with stents[2]. Of all gastrointestinal endoscopic procedures, ERCP is responsible for the highest rates of complications, including pancreatitis, bleeding, cholangitis, cholecystitis, and perforation[3,4]. Among these complications, post-ERCP pancreatitis (PEP) is the most frequent[5]. The incidence of PEP substantially varies across studies, and is reported to be approximately 1–10%; however, some studies reported an incidence of approximately 30% when only patients with a high risk for the development of pancreatitis were analyzed[3,6]. In 1991, Cotton et al. defined PEP as the presence of the characteristic abdominal pain of pancreatitis requiring new hospitalization or prolongation of hospital stay for at least 2–3 days and an amylase level of at least three times the reference limit, up to 24 h after the procedure[7].

The preventive methods include mechanical and pharmacological approaches, such as pancreatic duct stent placement, selective catheterization methods, hyperhydration, and the use of allopurinol, antibiotics, oral corticosteroids, interleukin-10, non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin, diclofenac), N-acetylcysteine, nifedipine, octreotide, secretin, and somatostatin[8].

The positive results in a meta-analysis of randomized clinical trials on rectal indomethacin led to the highest degree of recommendation (A) from the European Society of Gastrointestinal Endoscopy (ESGE) for the use of this medication in all patients, resulting in the increased acceptance of the administration of NSAIDs via the rectal route in clinical practice[3,9,10].

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However, the difficulty in using indomethacin in Brazil has resulted in the need for other options. Following the ESGE guidelines, 100 mg rectal diclofenac is used in Brazil to prevent PEP. Nevertheless, the appropriate timing and appropriate route of administration of NSAIDs still need to be clarified[11].

Aims

We aimed to clarify the uncertainty about the route of administration of NSAIDs in the prevention of PEP.

METHODS

This study was a prospective trial that investigated two groups of patients who received NSAIDs for PEP prophylaxis, and compared them with a historical sample. This study was approved by the local institutional review board.

The ESGE defines PEP as the presence of a new or aggravated abdominal pain in combination with an amylase or lipase level of more than three times the reference value at >24 h after ERCP, leading to the requirement for admission or prolongation of a planned admission. Clinical evaluation and symptom score calculation were performed, in addition to the determination of the levels of pancreatic enzymes before and 24 h after the procedure. In this study, the severity of pancreatitis was classified according to the ESGE classification, depending on the hospitalization duration and complications. The inclusion criteria were as follows: age >21 years, absence of a history of active or previous pancreatitis, and absence of comorbidities that can increase the risk of pancreatitis (such as suspicion of Oddi's sphincter dysfunction).

The exclusion criteria were failure to meet the inclusion criteria, lack of follow-up, and refusal to participate in the study. For the control group, the inclusion criterion was the availability of medical records and examination reports that had the necessary information for the study. Patients without measurements of serum pancreatic enzymes before and after the procedure, without pain assessment after the ERCP, and who presented with an increased risk for pancreatitis (such as Oddi's sphincter dysfunction and previous similar events or other comorbidities) were excluded.

The control group was composed of patients who underwent ERCP, performed in the same center and by the same team involved in the prospective study, before the implementation of the prophylactic protocols in August 2015. These control patients did not receive any prophylactic treatment, and were analyzed through a review of the medical records and examination reports.

All patients who fulfilled the inclusion criteria and were referred for ERCP were invited to participate in the study. Those who consented to participate received one of the two prophylactic options. The serum levels of pancreatic enzymes were analyzed before and after ERCP.

For the prevention of PEP, 100 mg rectal diclofenac or 100 mg intravenous ketoprofen was administered to the patients following the ESGE guidelines.

In the period from August 2015 to June 2016, all patients who were referred for ERCP and agreed to participate received 100 mg rectal diclofenac, and were assigned to the diclofenac group (TABLE 1). Diclofenac was administered immediately before the procedure or up to 2 h after the procedure.

From July 2016 to December 2017 (TABLE 1), all patients who were referred for ERCP and agreed to participate received 100 mg intravenous ketoprofen, and were included in the ketoprofen group. Both experimental groups were compared with the historical control group.

TABLE 1. Collection period and total patients for each experimental group.

Period	Group	Total procedures	Completed the study
2015–2016	Control	223	145
2016	Diclofenac	70	52
2017	Ketoprofen	87	78

Data were collected using a form that documented sociodemographic data, comorbidities, patient's status before the procedure (whether in the course of antibiotic therapy or using agents with a different pathway of anti-inflammatory effect), presence of acute pancreatitis, previous ERCP, and elapsed time. Factors that led to the indication for ERCP and the main signs and symptoms that necessitated the examinations were also recorded.

Moreover, the values of biochemical parameters implicated in biliary tract diseases, especially the amylase level before the procedure, were compared with the post-procedural values to determine the diagnosis of PEP, along with signs and symptoms recorded after the examination. Other information about the ERCP procedure was analyzed, and the variables implicated in the higher risk for complications were difficulty in catheterization of the duodenal papilla, sphincterotomy, dilatation of the biliary tract, presence of calculi, and use of prosthesis.

For the historical control group, data were obtained from the electronic medical records system of the hospital.

The comparison between the different drug prophylaxis treatments with respect to the age of the patients was performed using a non-parametric test. The evaluation of the association between prophylaxis with non-steroidal drugs and the variables age, sex, presence of comorbidities, duration of pancreatitis, previous ERCP, papillotomy, papilla condition (preserved vs altered anatomy, difficulty in examinations, and development of pancreatitis was performed using the chi-square test. The other results of this study are presented in the form of descriptive statistics, tables, and graphs. Statistical analysis was performed using the statistical program SigmaPlot version 12.0, considering a significance level of 5% (P<0.05).

RESULTS

A total of 275 participants completed the study, and the measurements in this sample were normally distributed. The data of the control group were collected between 2015 and 2017. The data of the ketoprofen group were collected in 2017, and those of the diclofenac group were collected in 2016 (TABLE 1).

The control group presented a significantly older age than the prophylactic treatment groups (Dunn's post-test, P<0.05). Moreover, there was a significant difference between the drug prophylaxis treatments with respect to patient age (Kruskal-Wallis test, P=0.010), with the ketoprofen group showing an older mean age (44.5 years).

The data presented in TABLE 2 show the association between prophylaxis with non-steroidal drugs and age, sex, presence of comorbidities, duration of pancreatitis, previous ERCP, papillotomy, papilla condition, and difficulty in examinations among the patients evaluated in this study.

TABLE 2. Results referring to the evaluation of the relationship between prophylaxis with non-steroidal drugs and the variables age, gender, presence of comorbidities, duration of pancreatitis, previous ERCP, papillotomy, preserved anatomy papilla condition and difficulty on the exam.

Variables	Group			*P*-value
	Control group (n=145)	Diclofenac100 mg PR (n=52)	Ketoprofen 100 mg IV (n=78)	
Age – $\bar{x}$ – (min-max)	57 (9 to 106)	43.5 (10 to 81)	44.5 (17 to 87)	0.010
Female n (%)	86 (59.3)	36 (69.2)	49 (62.8)	0.445
Comorbidities n (%)	73 (50.3)	16 (30.8)	13 (16.7)	<0.001
Current pancreatitis n (%)	28 (19.3)	10 (19.2)	12 (15.4)	0.751
Previous ERCP n (%)	27 (18.6)	5 (9.6)	18 (23.1)	0.147
Papilotomy n (%)	98 (67.6)	42 (80.8)	47 (60.3)	0.048
Preserved anatomy papilla n (%)	113(77.9)	43 (82.7)	62 (79.5)	0.767
Exam difficulty n (%)	32 (22.1)	11 (21.2)	17 (21.8)	0.991

ERCP: endoscopic retrograde cholangiopancreatography; PR: per rectum; IV: intravenously.

No association was observed between drug prophylaxis treatment and the variables sex (chi-square test, *P*=0.445), current pancreatitis (*P*=0.751), previous ERCP (*P*=0.147), preserved anatomy of the papilla (*P*=0.767), and difficulty in examinations (*P*=0.991).

The control group showed more comorbidities (50.3% [n=73]; chi-square test, *P*<0.001) than patients who received treatment with diclofenac (30.8%, n=16) and ketoprofen (16.7%, n=13) (chi-square test with Bonferroni correction, *P*<0.05).

In addition, there was an association between both therapeutic groups and papillotomy, when the therapeutic groups were analyzed together (chi-square test, *P*=0.048; TABLE 2). However, in the comparison between treatments (ketoprofen vs diclofenac), there was no significant difference in the frequency of papillotomies (chi-square test with Bonferroni correction, *P*>0.05). TABLE 3 presents the results concerning the association between prophylaxis with non-steroidal drugs and the development of pancreatitis in the patients evaluated in this study. Despite the difference in absolute numbers, no significant association was observed between these variables (chi-square test, *P*=0.164).

Although TABLE 3 shows differences in the incidence of pancreatitis between the control group and the diclofenac group, and between the control group and the ketoprofen group, statistical significance was not reached (*P*=0.151 and *P*=0.218, respectively); however, when the control group was compared with the combination of the two therapeutic groups, the difference was statistically significant (*P*=0.037) (TABLE 4). was statistically significant (*P*=0.037) (TABLE 4).

PEP occurred in 10 of the 145 patients in the group without prophylaxis for PEP, in none of the patients in the group that received prophylaxis with diclofenac, and in 2 of the 78 patients in the group with ketoprofen prophylaxis. Patients with PEP also showed prolonged hospitalization and amylase levels three times higher than the reference value after the procedure.

TABLE 4. Results comparing the two groups undergoing prophylaxis with NSAIDs with the group without prophylaxis for post-ERCP pancreatitis.

Pancreatitis	Group		*P*-value
	Control group (n=145)	NSAIDs prophylaxis (n=130)	
PEP	10 (6.89%)	2 (1.53%)	0.037
Absence of PEP	134 (92.4%)	128 (98.4%)	

P-value in the Fisher (*P*=0.037). ERCP: endoscopic retrograde cholangiopancreatography; PEP: post-endoscopic retrograde cholangiopancreatography pancreatitis; NSAIDs: nonsteroidal anti-inflammatory drugs.

According to the consensus criteria, the severity of the 10 PEP cases in the group without prophylaxis was considered mild in one case, moderate in six cases, and severe in three cases (including two deaths). Of the two cases of PEP in the group treated with ketoprofen, one case was classified as mild and one case was severe, in which the patient presented with other associated complications such as duodenal perforation and progressed to death as the final outcome. Both NSAIDs (100 mg rectal diclofenac and 100 mg intravenous ketoprofen) were well tolerated in all patients, with no adverse effects.

DISCUSSION

In this study, we evaluated the pharmacological prevention of PEP by comparing two therapeutic groups with a historical control group. Despite the non-significant difference when the two therapeutic groups were separately analyzed, the joint analysis

TABLE 3. Results of the development of pancreatitis in each experimental group and the control group.

Pancreatitis	Group			*P*-value
	Control group (n=145)	Diclofenac 100 mg PR (n=52)	Ketoprofen 100 mg IV (n=78)	
Not presented n (%)	135 (93.1)	52 (100.0)	76 (97.4)	
Mild n (%)	1 (0.7)	0 (0.0)	1 (1.3)	0.155
Moderate/severe n (%)	9 (6.2)	0 (0.0)	1 (1.3)	

PR: per rectum; IV: intravenously

revealed that patients receiving prophylaxis had decreased incidence of PEP when compared with the control group. The incidence of PEP decreased from 10% to 1.3% with the use of intravenous ketoprofen and from 10% to 0% with the use of rectal diclofenac. When the two therapeutic groups (ketoprofen and diclofenac) were jointly compared with the control group, a statistically significant difference was obtained (P=0.037). We also observed a decrease in the severity of pancreatitis, in which moderate to severe pancreatitis was observed in nine patients in the control group and in two patients in the group with ketoprofen prophylaxis. The group that received prophylaxis with diclofenac did not develop pancreatitis after ERCP.

Patients who did not receive prophylactic treatment were older, in average, than patients who received ketoprofen and diclofenac treatments. Age should be taken into account as an additive risk factor for pancreatitis after ERCP[6,12]. Although lower age by itself should not increase the probability of PEP, in association with other factors it does influence the possibility of developing pancreatitis as an outcome. This fact could lead the control group to a lower risk of PEP.

The currently accepted hypotheses for the mechanism and pathophysiology of PEP are as follows: (i) trauma or thermal injury to the papilla, causing spasm and edema of Oddi's sphincter and leading to transient obstruction to pancreatic secretion; (ii) hydrostatic pressure due to contrast or saline injection into the pancreatic conduit; and (iii) infection caused by the introduction of intestinal microbiota together with bacteria transmitted by the endoscope in the pancreatic approach[13]. Any of these mechanisms or even a combination of them can trigger the activation of intraductal proteolytic enzymes that cause pancreatic self-digestion and inflammatory activation[13].

However, the exact mechanism of PEP remains to be elucidated. PEP is known to be a process that develops from a proinflammatory cascade originating from a pancreatic acinar lesion. The activation of phospholipase A2 (PLA2) by trypsin results from the initial lesion. PLA2 is responsible for cleaving cell-membrane phospholipids into fatty acids and lysophospholipids, subsequently promoting the formation of arachidonic acid, a precursor of several inflammatory mediators such as prostaglandins, leukotrienes, and thromboxanes[14]. Thus, PLA2 is a key modulator of the inflammatory signaling cascade in pancreatitis. NSAIDs are known to be potent inhibitors of the PLA2 enzyme (elevated in pancreatitis), thus interrupting the inflammatory cascade in pancreatitis[14].

Our study provides new evidence that the use of NSAIDs reduces the severity or even the number of PEP events described in other studies.

The largest clinical trials used indomethacin as a prophylactic drug for PEP. However, although the trials showed broadly positive results in terms of the prevention of PEP, a common criticism was that these effects do not apply to the general population but rather offer greater benefits to high-risk patients, such as those with Oddi's sphincter dysfunction. In a 2016 clinical trial by Levenick et al.[15], indomethacin did not prevent PEP in consecutive patients undergoing examinations. Further studies comparing the effectiveness of the administration pathways of NSAIDs in the prevention of PEP after ERCP are relevant and necessary.

Indomethacin promoted a 90% reduction in PLA2 activity in vitro (at lower concentrations than NSAIDs)[14]. However, its use in Brazil is restricted to large health service centers, and the need to formulate the drug in compounding pharmacies makes its standardized use impossible. Thus, exploring new prophylactic possibilities is fundamental for safe advances in this area, including the adjustments of doses, timing of administration, and route of drug administration.

Diclofenac is a non-selective cyclooxygenase 1 (COX1) and COX2 inhibitor with a safe profile, mainly in terms of gastrointestinal complications and toxicity[16]. In an in vitro experiment, diclofenac was shown to reduce the activity of PLA2 by 93%, if used at high concentrations[14]. Previous studies performed in India and England showed that diclofenac administered via the rectal route decreased the incidence and severity of PEP[17,18]. Conversely, another study performed in Indiana, USA, failed to demonstrate similar results with respect to the use of oral diclofenac in high-risk patients[19]. Concerning the intravenous route, the performance of diclofenac depends on aspects such as its bioavailability and its ideal concentration and absorption[20]. Thus, pre-procedure intravenous administration with adjusted doses may promote early suppression of the inflammatory responses in pancreatitis. This is suggested by the positive results of reduced PEP incidence and severity in two studies in which prophylactic administration of diclofenac was performed 60 and 30–90 min before ERCP[21,22]. The routes of administration differ across studies, with some studies using the rectal and intramuscular routes. Routine administration of rectal diclofenac before or after ERCP has been recommended by European and Japanese society guidelines to minimize the risk of PEP.

Intravenous medicines are easier to administer and are more accessible than rectal NSAIDs. In Brazil, ketoprofen is widely available and is a low-cost drug that is widely used for osteoarticular and muscular inflammatory and pain disorders. It is a derivative of propionic acid, has a short half-life, is a COX1 and COX2 inhibitor, and can reach the plasma peak in minutes when intravenously administered, whereas NSAIDs such as diclofenac and indomethacin reach the peak concentration in plasma within 2–3 h when administered via the rectal or oral route[23]. The use of ketoprofen in vitro has been shown to reduce PLA2 activity by 90% at high concentrations[14].

Besides presenting good bioavailability, low cost, and pharmacological security, ketoprofen is more advantageous than other NSAIDs because of the ease and comfort of its intravenous administration. Highly stable concentrations of the drug can be obtained in tissues in a short time[24].

In our study, intravenous ketoprofen was administered during the procedure. Similarly, in the study by de Quadros et al., 100 mg intravenous ketoprofen was administered for 20 min, immediately before the procedure[22]. Both approaches might have led to less favorable results when the characteristics of intravenous administration were considered; that is, as the intravenous route allows a shorter time for the drug to be absorbed and take effect, ketoprofen was not administered in advance. It is important to highlight that the safety and efficacy of doses vary among different regimens.

In addition, two meta-analyses, showed the efficacy of anti-inflammatory drugs as prophylaxis of PEP, as well as their safety when administered via different routes (rectal, intravenous, and intramuscular), suggesting an effective combination of administration pathways[25,26]. Although technical improvements are a fundamental constant, the associated complications are not related to the endoscopist's learning curve and fewer complications were observed in the third collected group (treated with ketoprofen between 2016 and 2017), considering the participation of the same professionals throughout the study.

Other forms of prevention have been described, and the combination of different methods may be ideal. Pancreatic stents have proven benefits in the prevention of PEP; however, they are difficult to use in routine practice because of the risk of pancreatic ductal lesions during insertion, which requires the operator's expertise, in addition to the difficult availability of this material[5,25]. All of these factors need to be considered before choosing this method.

The main limitation of this study was the comparison of two non-randomized populations from different periods, both compared with a historical series. However, the methodology and the selection of participants were the same for both populations, and the two groups were collected immediately consecutive to each other. The participating medical team was the same for both populations. Moreover, studies conducted with a small number of patients can lead to false-negative findings, as the results may be influenced by the variability in sampling, although the team responsible for this study attempted to ensure proper planning and execution. The efficacy of the use of NSAIDs has been proven in a major meta-analysis study on prophylaxis of PEP events[25].

The present study was able to reproduce data proving the efficacy of NSAIDs, with emphasis on reducing the incidence rate of pancreatitis after ERCP and the greater reduction in moderate cases (from six cases to one case), compared with the group without prophylaxis. This finding has great clinical relevance for the safety of both patients and medical professionals. Further, the costs of health services must be taken into account, as decreased hospitalization and treatment durations result in fewer required resources. However, further randomized prospective studies should be conducted on the use of prophylactic agents in paired and identical populations with larger sizes. Finally, and no less relevant, our results suggest the possibility of using intravenous administration when no other routes are available. We maintain that there is still room for experimentation with respect to the various routes of administration of NSAIDs and their combinations, including dose and dosage adjustments, assuming that this issue has not been exhaustively discussed in this work given the controversial state of the current literature.

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Authors' contribution

Paez LF: writing of the text, interpretation of the results, and development of the theoretical formalism and framework. Cury MS: planning and supervision of the work, development of the theoretical framework, survey execution, data collection, statistical analysis, and supervision of the text. Mello MPM: development of the theoretical formalism, and contribution to the implementation of research discussion, analysis of results, and writing of the text. Campos DN: survey execution, data collection, and contribution to manuscript writing. Rodrigues BER: survey execution, data collection, and contribution to manuscript writing.

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RESUMO – **Contexto** – A colangiopancreatografia retrógrada endoscópica (CPRE) é uma modalidade terapêutica amplamente utilizada para vias biliopancreáticas, responsável pelas taxas mais elevadas de complicações entre os procedimentos endoscópicos, especialmente a pancreatite pós-CPRE (PPC). Os métodos preventivos incluem abordagens mecânicas e farmacológicas, entre elas, a utilização de antinflamatórios não esteroidais (AINEs). **Objetivo** – Comparar a eficácia de duas estratégias diferentes utilizando AINEs para a prevenção de PPC. Elucidar o cenário incerto sobre a via de administração do AINEs na prevenção da PPC. **Métodos** – Ensaio clínico prospectivo. Duas estratégias terapêuticas foram comparadas a um grupo controle, composto por pacientes submetidos a CPRE no mesmo serviço e com a mesma equipe no período anterior ao estudo (série histórica), que não recebeu qualquer tipo de profilaxia. O primeiro grupo experimental recebeu 100 mg de diclofenaco via retal, o segundo grupo recebeu 100 mg de cetoprofeno endovenoso. Ambos os grupos foram comparados separadamente e em associação com o grupo de controle. **Resultados** – A PPC ocorreu em 4,39% (12/273) dos participantes. No grupo sem profilaxia, esta incidência foi de 6,89% (10/145); entre os que receberam cetoprofeno endovenoso foi de 2,56% (2/78). Não houve casos de pancreatite aguda após o procedimento no grupo que recebeu diclofenaco via retal (0/52). Apesar de não haver diferença estatística entre estes grupos analisados separadamente, quando os dois grupos terapêuticos são analisados em conjunto estes apresentam diferenças estatísticas na prevenção da PPC (P=0,037). **Conclusão** – Este estudo foi capaz de corroborar a eficácia da utilização de AINEs para a profilaxia de pancreatite pós-CPRE.

Keywords – Diclofenaco; cetoprofeno; via retal; endovenoso; profilaxia; pancreatite; colangiopancreatografia retrógrada endoscópica.

REFERENCES

1. Freeman ML. Complications of Endoscopic Retrograde Cholangiopancreatography. Avoidance and Management. Gastrointest Endosc Clin N Am. 2012;22:567-86. DOI.org/10.1016/j.giec.2012.05.001
2. Ferreira F. Colangiopancreatografia. In: Averbach M. Endoscopia digestiva - diagnóstico e tratamento. Rio de Janeiro: Revinter; 2013. Cap.21
3. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2014;46:799-815. DOI: 10.1055/s-0034-1377875
4. Silviera ML, Seamon MJ, Porshinsky B, Prosciak MP, Doraiswamy VA, Wang CF, et al. Complications related to endoscopic retrograde cholangiopancreatography: A comprehensive clinical review. J Gastrointest Liver Dis. 2009;18:73-82.
5. Anderson MA., Fisher L, Jain R, Evans JA, Appalaneni V, Ben-Menachem T, et al. ASGE guideline: Complications of ERCP. Gastrointest Endosc. 2012;75: 467-73.
6. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: A comprehensive review. Gastrointest Endosc. 2004;59:845-64.
7. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RCG, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37:383-93.
8. Akshintala VS, Hutfless SM, Colantuoni E, Kim KJ, Khashab MA, Li T, et al. Systematic review with network meta-analysis: Pharmacological prophylaxis against post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013;38:1325-37.
9. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366:1414-22.
10. Hanna MS, Portal AJ, Dhanda AD, Przemioslo R. UK wide survey on the prevention of post-ERCP pancreatitis. Frontline Gastroenterol. 2014;5:103-10.
11. Onófrio FQ, Lima JCP, Watte G, Lehmen RL, Oba D, Camargo G, et al. Prophylaxis of pancreatitis with intravenous ketoprofen in a consecutive population of ERCP patients: a randomized double-blind placebo-controlled trial. Surg Endosc. 2017;31:2317-24.
12. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ercp pancreatitis: A prospective, multicenter study. Gastrointest Endosc. 2001;54:425-34.
13. El Zouhairi M. Post-ERCP Pancreatitis: Mechanisms, Risk Factors, and Prevention. Pancreat Disord Ther. 2013;03:2-5.
14. Mäkelä A, Kuusi T, Schröder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest. 1997;57:401-7.
15. Levenick JM, Gordon SR, Fadden LL, Levy LC, Matthew J, Hyder SM, et al. Rectal Indomethacin Does Not Prevent Post-ERCP Pancreatitis in Consecutive Patients. Gastroenterology. 2016;150:911-7.
16. Peloso PM. Strategies and practice for use of nonsteroidal anti-inflammatory drugs. Scand J Rheumatol. 1996;25 (Suppl 105):29-46.
17. Patil S, Pandey V, Pandav N, Ingle M, Phadke A, Sawant P. Role of Rectal Diclofenac Suppository for Prevention and Its Impact on Severity of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in High-Risk Patients. Gastroenterol Res. 2016;9:47-52.
18. Sheiybani G, Brydon P, Toolan M, Linehan J, Farrant M, Colleypriest B. Does rectal diclofenac reduce post- ERCP pancreatitis? A district general hospital experience. Frontline Gastroenterol. 2018;9:73-7.
19. Cheon YK, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, et al. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc. 2007;66:1126-32.
20. Lyu Y, Cheng Y, Wang B, Xu Y, Du W. What is impact of nonsteroidal anti-inflammatory drugs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: A meta-analysis of randomized controlled trials. BMC Gastroenterol. BMC Gastroenterology; 2018;18:1-16.
21. Otsuka T, Kawazoe S, Nakashita S, Kamachi S, Oeda S, Sumida C, et al. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: A randomized controlled trial. J Gastroenterol. 2012;47:912-7.
22. Uçar R, Biyik M, Uçar E, Polat İ, Çifçi S, Ataseven H, et al. Rectal or intramuscular diclofenac reduces the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography. Turkish J Med Sci. 2016;46:1059-63.
23. Hernandez C. Desenvolvimento e avaliação in vitro de matrizes de cetoprofeno para liberação prolongada. 2004. Available from: https://repositorio.usp.br/item/001427838
24. Hirahara JT, Bliacheriene S, Yamaguchi ET, Rosa MCR, Cardoso MMSC. Post-cesarean section analgesia with low spinal morphine doses and systemic nonsteroidal anti-inflammatory drug: diclofenac versus ketoprofen. Rev. Bras. Anestesiol. 2003;53:737-42.
25. Yuhara H, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T, Mine T. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: Protease inhibitors and NSAIDs in a meta-analysis. J Gastroenterol. 2014;49:388-99.
26. Ding, Xiwei, Min Chen, Shuling Huang, Song Zhang, and Xiaoping Zou, Nonsteroidal Anti-Inflammatory Drugs for Prevention of Post-ERCP Pancreatitis: A Meta-Analysis. Gastrointestinal Endoscopy. 2012;76:1152-9.