

A LESS INVASIVE METHOD OF REDUCING THE INCIDENCE OF POST-ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS: INTRAVENOUS DICLOFENAC SODIUM VERSUS PLACEBO

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ABSTRACT

Objective: The purpose of this study is to reduce the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) by the administration of intravenous (IV) diclofenac sodium.

Methods: This is a prospective, randomized, double-blinded control study. This study was performed in the hepatobiliary unit of general surgery department in University Kebangsaan Malaysia Medical Centre (UKMMC) from May 2015 to May 2016. A total of 128 patients were enrolled in this study. 59 patients were randomized into the treatment arm, while 63 were randomized into the control group. Patients were randomized by envelope system, and patients in the treatment arm received 75 mg of diclofenac sodium intravenously, within 30 min of ERCP commencement. Both groups were observed for PEP post-ERCP and their pain score recorded. Patients' demographic data were also observed.

Results: A total of 122 patients were included in the study, with 59 patients randomized into the treatment arm and 63 into the placebo arm. There was an increase of 7.6% PEP rates in the placebo group (12.7% vs. 5.1% in the treatment arm). However, this was not statistically significant ($p=0.142$).

Conclusion: This study shows that IV diclofenac sodium can decrease PEP but is not statistically significant.

Keywords: Anti-inflammatory agents, Nonsteroidal, Cholangiopancreatography, Endoscopic retrograde, Pain, Prospective studies.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important tool used for diagnostic and therapeutic purposes for both benign and malignant diseases.

There are a few complications from ERCP, but post-ERCP pancreatitis (PEP) is the most common, with the rate of incidence of post-ERCP PEP, is anywhere between 1 and 15% [1-6], but in higher risk patients, the risk may be more than 25% [7]. Severe PEP was only seen in 0.4% of patients, while there was only 0.11% mortality [5]. In two of the prospective studies published, the rate of severe PEP was only 0.32% of 7252 patients [1,2]. In our center of practice, Pusat Perubatan Universiti Kebangsaan Malaysia, the rate of PEP was 14.5% in 2012.

At current, multiple medications have been used in attempts to reduce the incidence of PEP, but only rectally administered nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have any efficacy [8,9]. There have been many meta-analyses that review the efficacy of NSAIDs in decreasing the risk of PEP overall. However, rectal NSAIDs (in particular, diclofenac and indomethacin) are most effective [8].

There are only a few studies that look at other routes of administration of NSAIDs in reducing PEP. A meta-analysis by Ding X [8] examines 10 randomized trials on NSAIDs in reduction of post-ERCP PEP, analyzing six trials on rectal NSAID, one oral NSAID, one intramuscular NSAID, and one intravenous (IV) NSAID. The result of this meta-analysis showed that rectal NSAID favored a lower incidence of post-ERCP PEP, while other forms were not favorable. Senol (2009) showed a lower risk ratio in using intramuscular diclofenac [10].

However, none of these papers examined the role of IV diclofenac in reducing post-ERCP PEP episodes, and they have been no proper study examining the effects of IV diclofenac in reduction of PEP rates. IV diclofenac is the choice for study as it is relatively cheap, easily attainable with less invasive delivery; hence, its use in reduction of PEP post-ERCP is beneficial.

METHODS

This study was done as a requirement for completion of Masters of Surgery program.

It is a double-blinded, randomized controlled clinical trial, which took patient samples from all patients undergoing ERCP under hepatobiliary unit University Kebangsaan Malaysia Medical Centre (UKMMC) from May 2015 to May 2016. All patients who are able to give consent were included into the study, whereas patients, who had contraindications or allergies to NSAIDs, or did not consent, had recent PEP in the past 5 days or already on NSAIDs were excluded from the study.

This study was done in a single center, in UKMMC, and patients were randomized through the envelope system and as per CONSORT protocol. The medical assistants in the procedure room randomize the patients to either treatment with IV diclofenac sodium 75 mg within 30 min commencement of procedure, or normal saline as a placebo. The surgeon who performs the ERCP and the assessor post-ERCP is unaware of the intervention administered. Post-procedure, patients are assessed 4 h post-ERCP clinically and biochemically to ascertain the development of PEP. Approval from the Faculty of Medicine and Ethics

committee of UKMMC was granted before commencement of the study with project code FF-2015- 239.

Data collection table and statistical analysis

Data were summarized by descriptive statistics. Computer-assisted analysis was carried out at the end of the study. For categorical data, Pearson's Chi-square test was used. Statistical significance is taken at $p < 0.05$ (Fig. 1).

RESULTS

This study was carried out between the period of June 2015 and May 2016, and patients were selected from ERCP carried out in the Department of Hepatobiliary, UKMSC, Malaysia, under emergency or elective setting. There were a total of 276 patients during this period of time, but only 181 patients fulfilled the inclusion criteria. 35 patients did not consent for the study, and 146 were plan for randomization, but 18 did not proceed for the procedure. In total, 128 patients were randomized, 64 each to the treatment and placebo arm. In both arms, there was error in protocol, leaving 59 patients in the treatment arm and 63 patients in the placebo arm.

Patients randomized were evenly matched (not statistically significant) in age groups, gender or comorbidities. In the treatment arm, there were 26 males (44.1%) and 33 females (55.9%). There were 35 males (57.4%) and 28 females (44.4%) in the placebo arm. The mean age for the treatment group was 52.86 years (95% confidence interval [CI] 48.85–56.88) and 55.70 years (95% CI 51.48–59.92). The majority race of both treatment and placebo arms, respectively, were the Malays; 36 and 33, followed by the Chinese; 17 and 27, the Indians; 3 and 2, and other races; 3 and 1.

The majority of patients undergoing ERCP were for obstructive jaundice (60 or 49.1%), followed by patients who were reassessed

for residual stones with stent removal (28 or 23%), patients who were reassessed and reinserted with a new stent (15 or 12.3%), for cholangitis (9 or 7.4%), for assessment and insertion of stent (7 or 5.7%), and for patients who underwent pancreatic duct stenting (3 or 2.5%) (Table 1).

Post-ERCP results

Patients given diclofenac sodium within 30 minutes of procedure have less incidence of PEP post-ERCP, with 3 (5.1%) in the treatment arm in comparison to 8 (12.7%) in the placebo arm. Although there is a 7.6% difference, it is not statistically significant. It is noted, however, an increase in hyperamylesemia in the treatment arm, (9 patients or 15.3%) in comparison to the placebo arm (6 patients or 9.5%). This difference was also not statistically significant. There was no significant difference in epigastric pain between the treatment and placebo arm, with most of the patients, not having any epigastric pain after the ERCP procedure. One patient had developed allergic reaction to diclofenac sodium but was amenable to treatment (Tables 2 and 3).

Table 1: Distribution for treatment and placebo group

Patient characteristics	Diclofenac sodium (Voltaren)		p value
	Yes n (%)	No n (%)	
Race			
Malay	36 (61)	33 (52.4)	0.324
Chinese	17 (28.8)	27 (42.9)	
Indian	3 (5.1)	2 (3.2)	
Others	3 (5.1)	1 (1.6)	
Age			
18–30	4 (6.8)	4 (6.3%)	0.304
31–40	11 (18.6)	11 (17.5)	
41–50	7 (11.9)	7 (11.1)	
51–60	13 (22)	10 (15.9)	
61–70	18 (30.5)	14 (22.2)	
71–80	6 (10.2)	17 (27)	
Mean age (SD)	52.86 (15.4)	55.70 (16.76)	
Gender			
Male	26 (44.1)	35 (57.4)	0.205
Female	33 (55.9)	28 (44.4)	
Comorbid			
Yes	26 (44.1)	32 (50.8)	0.457
No	33 (55.9)	31 (49.2)	
Reason for ERCP			
Cholangitis	3 (5.1)	6 (9.5)	0.873
Obstructive jaundice	28 (47.5)	32 (50.8)	
Assessment/insertion of stent	4 (6.8)	3 (4.8)	
Reassessment/removal of stent	15 (25.4)	13 (20.6)	
Reassessment/change of stent	7 (11.9)	8 (12.7)	
Pancreatic duct stenting	2 (3.4)	1 (1.6)	

ERCP: Endoscopic retrograde cholangiopancreatography, SD: Standard deviation

Table 2: Post-ERCP pancreatitis rates in treatment and placebo group

Medication	Pancreatitis		Total	p value
	Yes	No		
Voltaren				
Yes				0.142
Count	3	56	59	
% within Voltaren	5.1%	94.9%	100.0%	
No				
Count	8	55	63	
% within Voltaren	12.7%	87.3%	100.0%	

ERCP: Endoscopic retrograde cholangiopancreatography

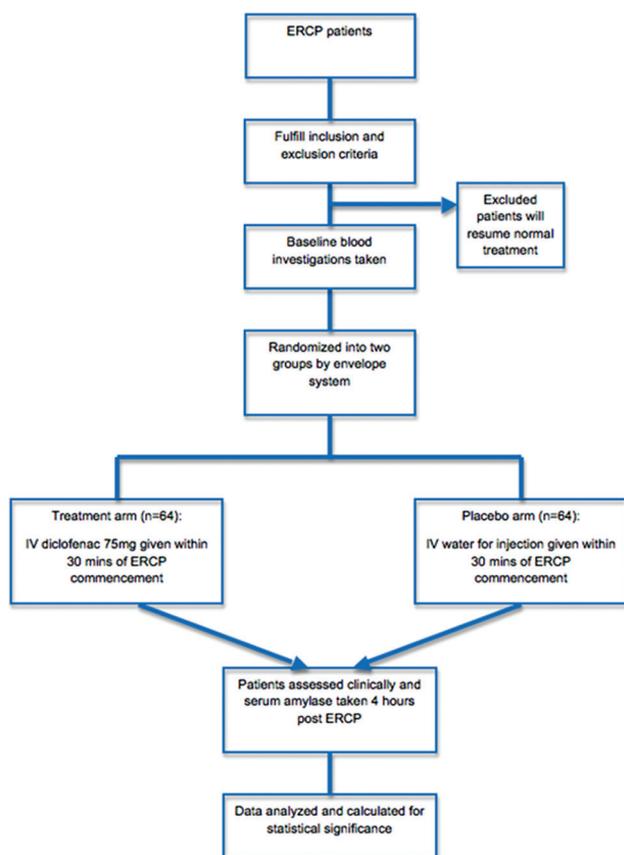


Fig. 1: Flowchart for methodology

DISCUSSION

ERCP is one of few common causes of acute PEP. ERCP may also cause hyperamylasemia and, hence, must be differentiated from acute PEP by fulfilling 2 out of 3 of the following criteria [11]:

1. Abdominal pain, which is usually acute in onset, and mainly in the epigastric region that mostly radiates to the back
2. Serum lipase/amylase activity that is 3 times the upper limit of normal
3. Characteristics of PEP, which is seen on imaging (either abdominal ultrasonography, computed tomography, or magnetic resonance imaging)

The pathophysiology of PEP post-ERCP is thought to be due to hydrostatic injury or from direct manipulation of the pancreatic duct [12]. Injury to the papilla or ampulla, either mechanical (from repeated manipulation or instrumentation of pancreatic duct) [13] or thermal (during electrocautery) [14] can cause pancreatic secretions to be impaired. During diagnostic ERCP or sphincter of Oddi manometry, over-injection of the pancreatic duct may lead to hydrostatic injury [15] - another important cause of pancreatic post-ERCP.

Factors that increase the risk of post-ERCP PEP can be divided into three factors: Operator-related, patient-related, or procedure-related factors [16-18] (Table 4).

Patients are placed into the high-risk category when the following occur during ERCP:

1. Suspected sphincter of Oddi dysfunction
2. Difficult cannulation
3. Previous post-ERCP PEP

In previous studies, suppository Voltaren was shown to have a role in reducing the incidence of post-ERCP PEP, although mostly not statistically significant. In two meta-analysis, overall benefit is seen in

Table 3: Post-ERCP hyperamylasemia rates in treatment and placebo group

Medication	Hyperamylasemia		Total	p value
	Yes	No		
Voltaren				0.142
Yes				
Count	9	50	59	
% within Voltaren	15.3%	84.7%	100.0%	
No				
Count	6	57	63	
% within Voltaren	9.5%	90.5%	100.0%	

ERCP: Endoscopic retrograde cholangiopancreatography

Table 4: Risk factors for post-ERCP

Operator-related	Patient-related	Procedure-related
Inadequate training	Younger age	Difficult cannulation
Lack of experience	Female sex	Pancreatic duct injection
	Normal serum bilirubin	Sphincter of Oddi manometry
	Recurrent pancreatitis	Precut sphincterotomy
	Prior ERCP-induced pancreatitis	Pancreatic sphincterotomy
	Sphincter of Oddi dysfunction	Minor papilla sphincterotomy
		Biliary balloon sphincteroplasty
		Ampullectomy

ERCP: Endoscopic retrograde cholangiopancreatography

its forest plot, favoring rectal NSAIDs in the reduction of PEP [8,9,19,20]. In previous studies, NSAIDs were given through a different route or patients were given a different form of IV NSAID. Up to the conception and design of this study, there were no studies that involved the usage of IV diclofenac sodium.

There was an improvement in the incidence of PEP with IV diclofenac. Numbers may not have been significant due to overall number of patients recruited into the study, and an overall low rate of PEP in this center. Previously, our center's rate of PEP was 15% in 2012, showing an improvement most likely due to physician improvement in performing procedure and increased experience in handling ERCP. PEP in the placebo group was only 12.7%. Although pancreatitis rates are acceptable up to 10%, most reported studies have a PEP rate up to 26% [21], and in this study, rectal diclofenac was shown to be beneficial.

Another limitation of this study is patients who are at high risk for PEP was not screened initially and noted during collection of data. In previous studies [22], factors that increased risk for PEP were studied, and hence, a more in-depth look at the usage of diclofenac can be looked at in decreasing PEP incidence. A further study can be conducted to correlate the efficacy of IV diclofenac in patients who are high risk of PEP. There was no incidence of severe PEP in both arms; hence, no conclusion can be made regarding reducing the severity of PEP in this study.

IV diclofenac has not been used before this, as its efficacy is uncertain due to rapid decrease in bioavailability after administration. Willis *et al.* [23] had shown the two concentrations of IV diclofenac 50 mg versus oral diclofenac 50 mg in bloodstream after administration in human candidates (Figs. 2-4). In another study by Morimoto *et al.* [24], it can be seen that plasma concentration levels are higher and stay longer in the blood after suppository diclofenac sodium. Even though plasma levels decline quickly after administration, it may not be a clear indicator of its efficacy. For example, the oral diclofenac produces a quick drop after the 3rd h but has continuous analgesic effect even after its plasma levels are on the decline. Hence, its full efficacy is unable to be quantified. For this reason, IV diclofenac sodium was served within 30 min of ERCP, but perhaps more specifically; it should be administered around the time of cannulation of the bile ducts and cholangiography. The effects of diclofenac would be most important during this period to prevent PEP as sequelae of ERCP. To further clarify this issue, a direct comparison study between IV versus rectal diclofenac sodium should be performed.

Theoretically, reduction in the incidence of PEP should occur as NSAIDs are thought to reduce inflammation. If bioavailability was to be considered as a factor, previous study using oral diclofenac

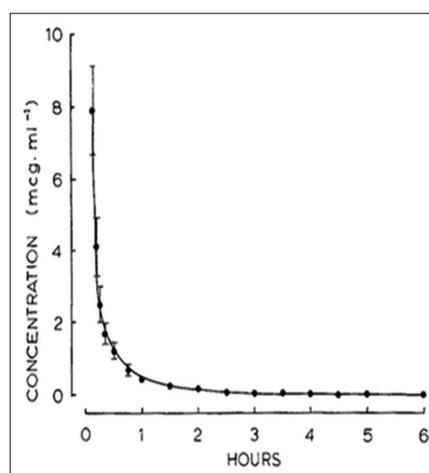


Fig. 2: Mean plasma concentration of diclofenac in seven healthy female volunteers following an intravenous injection of 50 mg diclofenac sodium [23]

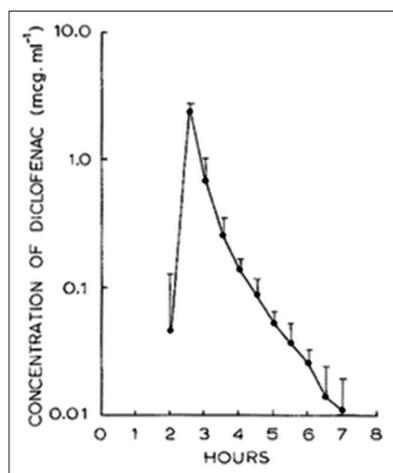


Fig. 3: Mean plasma levels of diclofenac following single oral 50 mg doses. Drug level curves are normalized around time of peak drug levels [23]

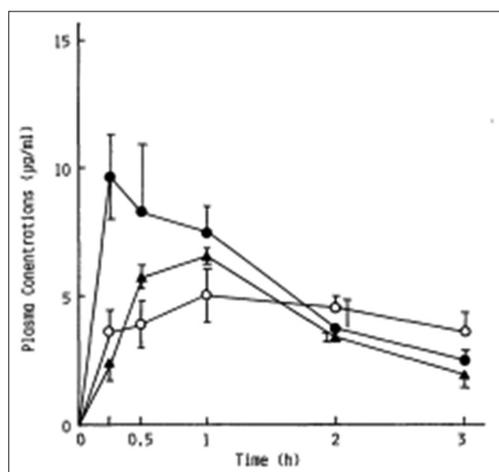


Fig. 4: Plasma concentration of diclofenac following rectal administrations of diclofenac sodium gel preparation and a commercial suppository in a man [24]

sodium [25] showed that there was improvement, but no difference statistically. Studying mean plasma levels of oral diclofenac sodium, one may postulate that timing of administration may change outcome for patients. It is clear that among the three options of administration that rectal form gives a more steady state and likely the reason of better prevention. It is important to produce a steady state of plasma levels, especially when cannulation of the bile duct may be difficult and may take longer than anticipated. This, in turn, reduces its bioavailability if timing of cannulation and injection of contrast is prolonged. As mentioned previously, plasma mean levels may be low in the blood, but its effects whether due to direct effect or from its metabolites are not well known.

As PEP is defined by fulfillment of 2 out of 3 criteria [11], additional imaging should be done to confirm the presence of PEP. Diclofenac sodium being also an analgesic could blunt the perception of pain in the patient and hence under-reported as PEP, but instead labeled as hyperamylasemia. The cause of increased amylase can actually be further tested by simple agarose gel electrophoresis [26] to differentiate possible causes and further pinpoint as due to PEP.

Diclofenac sodium is a relatively safe and cheap drug to be used, in most cases for its analgesic purposes, but will need further studies to determine if IV diclofenac sodium is beneficial in improving the rates of

PEP. It should, however, be used with caution as it may develop allergic reactions; skin rashes, angioedema, pneumonitis, and also anaphylactic reaction, leading to death [27].

CONCLUSION

In this study, IV diclofenac sodium decreases the rate of post-ERCP PEP. However, it is not statistically significant and further study with a larger sample size can be performed to check if IV diclofenac is beneficial.

AUTHOR'S CONTRIBUTIONS

Chik Ian - data collection and processing and writing of manuscript. Razman Jarmin - conception of idea and contribution to discussion of manuscript. Affirul Ariffin - conception of idea and contribution to discussion of manuscript. Hairol Othman - performed ERCP for the collection of data and data processing. Zamri Zuhdi - performed ERCP for the collection of data and data processing. Azlanudin Azman - performed ERCP for the collection of data and contribution to discussion of manuscript. Nik Ritza Kosai Nik Mahmood - proof reading of manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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