

A randomized trial comparing the efficacy of single-dose and double-dose administration of rectal indomethacin in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Background and Aims: The before-procedure or after-procedure rectal indomethacin administration was shown to be useful in preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. We designed this prospective randomized study to compare the efficacy of single-dose and double-dose rectal indomethacin administration in preventing post-ERCP pancreatitis (PEP).

Methods: We enrolled patients who underwent the ERCP in Taipei Mackay Memorial Hospital from 2016 June to 2017 November. Patients were randomly assigned to 2 groups: single and double-dose groups. The primary endpoint was the frequency of post-ERCP pancreatitis.

Results: A total 162 patients participated in this study, and there were 87 patients randomly assigned to the single-dose group, and 75 patients were assigned to the double-dose group. In the high-risk patients, the incidence of PEP was lower in double-dose patients (4.8%) than the single-dose patients (9.5%), but there was no significant difference ($P = .24$). Difficult cannulation was the only 1 risk factor for PEP after rectal indomethacin treatment.

Conclusions: Single-dose rectal indomethacin administration immediately after ERCP in general population is good enough to prevent PEP, but difficult cannulation could induce the PEP frequency up to 15.4% even under rectal indomethacin use.

Abbreviations: CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography, SOD = sphincter of Oddi dysfunction.

Keywords: ERCP, indomethacin, pancreatitis, PEP

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the major procedure performed for the management of pancreatobiliary disease. However, post-procedure adverse events, including post-ERCP pancreatitis (PEP), may cause high morbidity or even mortality after the procedure. Many studies have been

performed to identify the methods for preventing PEP, but only prophylactic pancreatic stent and rectal indomethacin administration were shown to be effective in preventing PEP.^[1] The before-procedure or after-procedure rectal indomethacin administration was shown to be useful in preventing PEP, but its pathophysiology is still unknown.^[2] According to previous literatures, it has not been well studied whether the number of rectal indomethacin administration influences PEP prevention, so we designed this prospective randomized study to compare the efficacy of single-dose and double-dose rectal indomethacin administration in preventing PEP.

2. Methods

The Institutional Review Board of Mackay Memorial Hospital, Taipei, Taiwan, approved the protocol of this double-blind controlled randomized clinical trial (15MMHIS074) on December 15 in 2015. This study was conducted on 162 consecutive patients who underwent ERCP at Mackay Memorial Hospital between June 2016 and November 2017. All patients signed an informed consent form before inclusion in this study and were admitted to the hospital for pre- and post-study evaluation and care.

The inclusion criteria were ERCP for standard clinical indications such as choledocholithiasis, benign or malignant biliary stricture/obstruction, and sphincter of Oddi dysfunction

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(SOD). Patients with chronic or acute pancreatitis, pancreatic stent placement for any purpose, allergy to nonsteroidal anti-inflammatory drug (NSAID), and severe heart and renal diseases, as well as those who were pregnant, were excluded from the study.

Patients were randomly assigned to 2 groups: single-dose and double-dose groups. We put 5 black chess pieces and 5 white chess pieces into a bag to represent 2 study groups, and 1 study nurse draw 1 chess piece before ERCP procedure to decide which group the patient was assigned. The patients in the single-dose group received 100 mg rectal indomethacin immediately after ERCP. The patients in the double-dose group received 100 mg rectal indomethacin about 4~5 hours before ERCP (due to the elimination half-life is 4.5 hour) and immediately after ERCP. Six experienced endoscopists performed the ERCP. The patients and ERCP endoscopists were blinded with regards to the methods of intervention.

The ERCP procedures were carried out with side-viewing duodenoscopes (JF-260 V; TJF-260 V, Olympus, Japan). Biliary cannulation was attempted with a standard cannula catheter or sphincterotome. ERCP endoscopists chose the cannulation methods, such as wire cannulation or contrast injection, based on the clinical condition. The guidewire cannulation method uses a 0.025-in (VisiGlide 2 guidewire, Olympus, Japan) or 0.035-in (Dreamwire, Boston Scientific) guidewire. The contrast injection method uses a diluted contrast (7 mL Urografin from Bayer Company, Spain, with 3 mL normal saline). If bile duct cannulation was unsuccessful, double-wire or pre-cut access cannulation was considered. When cannulation of the bile duct was achieved, additional procedures such as sphincterotomy or biliary stent placement were performed as necessary.

Patients continued fasting after the procedure for a minimum of 24 hours with drip infusion of 5% dextrose in normal saline/water (D5S/D5W). Serum hematologic and biochemical tests were performed before the procedure and 12 and 36 hours after the procedure. Patients' symptoms and physical findings were evaluated by attending doctors and student nurses during the hospital stay. None of the patients withdrew from the study. The primary endpoint was acute PEP based on a serum amylase level of more than 3 times the upper limit of normal associated with upper abdominal or back pain.

Patients' personal and clinical demographics were recorded, including age, gender, hematologic and biochemical blood tests results, and history of gallstone and cholecystectomy. ERCP findings, including juxtapapillary diverticula (JPD), common bile duct (CBD) diameter, and number of CBD stones, cannulation attempts, pancreatic sphincterotomy, trainee involved, and procedure time were also recorded for each patient. Cannulation attempts exceeding 8 times were considered to indicate difficult cannulation.^[3]

We further analyzed PEP in high-risk patients. The definition of high-risk group was patients who were females aged less than 50 years, underwent difficult cannulation, pancreatic sphincterotomy, pre-cut access sphincterotomy, and had SOD.^[4]

2.1. Statistical analysis

According the real world ERCP databases in our hospital, we have a PEP incidence in a retrospective series of 15.8%. We calculated the sample size based on settings of alpha, power, group 1 and 2 incidences as 0.05, 80%, 15.8%, and 3%, respectively. Statistical analysis was performed using the SPSS

21.0 statistical package (SPSS, Chicago, IL). A 2-sided *P* value of .05 was considered statistically significant. The distributional properties of continuous variables were expressed as mean \pm standard deviation, whereas categorical variables were expressed as frequency and percentage. Independent sample *t* test, chi-square test, and crosstabs statistics were conducted to compare the clinical characteristics between the 2 groups. Multivariate analysis was conducted to compare the clinical characteristics between the groups of patients with and without PEP.

3. Results

A total of 162 subjects were enrolled and underwent simple randomization before the ERCP procedure. There were 87 patients being assigned to single-dose group, and 75 patients were assigned to the double-dose group. There was no patient dropout during the study. The characteristics, as well as laboratory data at presentation and ERCP indications, were not different in both groups (Tables 1 and 2). The overall PEP incidence is 5.6%. However, the cannulation attempts and procedure time had differed significantly between the 2 groups. The double-dose group had more patients ($n=17$, 23%) who underwent difficult cannulation in ERCP compared to the single-dose group ($n=9$, 10.3%). Thus, we divided all 162 patients into 2 groups based on cannulation attempts and then analyzed the difference in PEP incidence (Table 3). There are 26 patients (16%) in the difficult cannulation group and 136 patients in the non-difficult cannulation group. The average PEP incidence of the difficult (4/26) and non-difficult (5/136) groups are 15.4% and 3.7%, respectively. There was no patient who developed an adverse effect to indomethacin, even with double doses.

In these patients who were administered rectal indomethacin; only difficult cannulation was a risk factor for PEP (Table 4). Other ERCP procedures, such as biliary sphincterotomy, dilatation, pancreatic sphincterotomy, and biliary stent placement had no significant effect on PEP incidence.

We also selected high-risk patients with PEP for further analysis (Table 5). A total of 42 patients were in the high-risk group, and 120 patients were in the average-risk group. The average PEP incidences in high-risk and average-risk groups were 7.1% ($n=3$) and 5% ($n=6$), respectively. There were 21 high-risk patients each in the single-dose and double-dose groups. The

Table 1
Comparisons of patient related baseline parameters between single-dose and double-dose groups.

	Single-dose group (n=87)	Double-dose group (n=75)	<i>P</i> value
Female, n (%)	33 (37.9%)	28 (37.3%)	.938
Age, yr	60.5 \pm 16.9	59.3 \pm 15.7	.642
DM, n (%)	13 (14.9%)	14 (18.7%)	.535
Hypertension, n (%)	33 (37.9%)	27 (36.0%)	.739
Hyperlipidemia, n (%)	17 (19.5%)	9 (12.0%)	.342
Gallstone, n (%)	34 (39.1%)	27 (36%)	.741
Post Cholecystectomy, n (%)	13 (14.9%)	10 (13.3%)	.824
ERCP indication			
Cholelithiasis	75 (86%)	69 (92%)	.242
Malignant obstructive jaundice	6 (6.9%)	4 (5.3%)	.680
Benign biliary stricture	5 (5.7%)	1 (1.3%)	.138
Sphincter of Oddi dysfunction	1 (1.1%)	1 (1.3%)	.916

Table 2**Comparisons of ERCP related parameters between single-dose and double-dose groups.**

	Single-dose group (n=87)	Double-dose group (n=75)	P value
Periampullary diverticulum, n (%)	26 (29.9%)	27 (36%)	.408
CBD diameter, mm	10.9±6.8	11.0±5.0	.987
Stone size, mm	10.7±11.4	10.0±5.8	.709
Stone number	1.4±0.5	1.5±0.5	.361
Difficult cannulation	9 (10.3%)	17 (23.0%)	.033
Cannulation methods			.531
Contrast	20	17	
Guide-wire	70	56	
Double-wire	5	6	
Pre-cut	1	6	
Biliary sphincterotomy	50 (57.5%)	60 (80%)	.001
P-EST	3 (3.4%)	1 (1.3%)	.394
Papillary balloon dilatation	24 (27.6%)	14 (18.7%)	.182
Biliary stent placement	19 (21.8%)	11 (14.7%)	.241
Contrast volume, mL	12.3±9.3	12.3±7.2	.751
SOD	3 (3.4%)	2 (2.7%)	.754
Trainee involve, n (%)	15 (17.2%)	14 (18.9%)	.809
Mean procedure time, min	20.2±11.1	28.3±16.1	.001

P-EST=pancreatic sphincterotomy, SOD=Sphincter of Oddi dysfunction.

PEP incidences were 9.5% (n=2) and 4.8% (n=1) in the single-dose and double-dose groups, respectively. There was no significant difference between the 2 groups ($P=.24$).

4. Discussion

Although the pathophysiology of PEP has not yet been clarified, most clinicians consider its etiology as multifactorial.^[5] Patients' physiological condition, ERCP procedural techniques, and post-ERCP care influence the pathogenesis of PEP. The PEP incidence is reported to be between 2.1% and 24.4% in most studies.^[5-7] As PEP is a common adverse event of ERCP, many studies tried to find a way to decrease its incidence. Moreover, rectal indomethacin is the safest and most cost-effective prophylactic method.^[8]

Some studies report that rectal indomethacin had a protective effect against PEP only in high-risk patients but not in average-risk patients,^[9] but some authors suggested it should be used routinely in all patients.^[10-12] Hence, all patients received rectal indomethacin in our study.

Our results of PEP incidence rates (under rectal indomethacin prevention) are 5.6% and 7.1% in overall and high-risk patients, respectively. It was comparable with the results from other studies.^[13,14]

The results showed double-dose (before and after ERCP) rectal indomethacin administration did not have more significant effect in preventing PEP than single dose group. Hence, single-dose

Table 4**Risk factor for PEP after rectal indomethacin.**

	PEP (n=9)	No-PEP (n=153)	P value	OR (95% CI)
Female	5	96	.819	1.207 (0.242-6.021)
Post Cholecystectomy	1	22	.631	0.55 (0.048-6.316)
Periampullary diverticulum	3	50	.788	0.797 (0.153-4.162)
Difficult cannulation	4	22	.013	7.817 (1.536-39.79)
Biliary sphincterotomy	7	103	.183	0.174 (0.013-2.284)
Papillary balloon dilatation	3	35	.252	0.382 (0.074-1.982)
Biliary stent placement	2	28	.521	0.438 (0.035-5.435)

OR = odds ratio, PEP = post-ERCP pancreatitis.

Table 5**PEP in "high-risk" patients.**

	Single-dose group (n=21)	Double-dose group (n=21)	P value
PEP	2 (9.5%)	1 (4.8%)	.24

PEP = post-ERCP pancreatitis.

rectal indomethacin administration immediately after ERCP in general population is enough. It seemed not necessary to administer another dose of indomethacin to patients before ERCP. It is compared with other study results that low-dose nonsteroidal anti-inflammatory drug (NSAID) administration also could achieve preventive effect of PEP.^[15]

The reason why the double-dose did not have more effect may be due to the timing of the 2 doses. Indomethacin rectal suppository can achieve maximum concentration earlier but has a slower absorption rate compared with oral administration.^[16,17] Hence, the interval duration of the 2 doses administered should be a concern to avoid possible high dose-related adverse effects.^[18] In this study, the first dose administered timing was approximately 4~5 hours (same as half-life of indomethacin) before ERCP which may be too long to prevent PEP, but this needs further study to prove it.

In our study, two-thirds of patients with PEP had no obvious risk factors for PEP. Thus, ERCP endoscopists should keep in mind that absence of high-risk factors might not mean that the patient will not develop PEP.

This was a prospective randomized study that divided enrolled patients into 2 groups by baseline parameters (Table 1). However, it was difficult to control the ERCP related parameters beforehand, such as difficult cannulation, biliary sphincterotomy and procedure time (Table 2), thus, we divided all patients into 2 groups including difficult cannulation and non-difficult cannulation groups to avoid bias, and both groups were found no difference between single dose and double dose in PEP (Table 3). The study was performed in a single medical center, and this is a limitation of our study. The retrospective real-world ERCP database showed a higher PEP incidence of 15.8% than this

Table 3**PEP incidence in difficult and non-difficult cannulation patients.**

	Difficult cannulation (n=26)			Non-difficult cannulation (n=136)		
	Single-dose group (n=9)	Double-dose group (n=17)	P value	Single-dose group (n=78)	Double-dose group (n=58)	P value
PEP	1 (11.1%)	3 (17.6%)	.676	2 (2.6%)	3 (5.2%)	.428

PEP = post-ERCP pancreatitis.

prospective study, it might be due to retrospective poor chart record integrity and rigorous attitude for PEP prevention in this prospective study that made our sample size calculation had a bias. Those patients who had previous sphincterotomy were not excluded in this study, and it also might be a variation.

In conclusion, double-dose rectal indomethacin administration did not show a greater effect in preventing PEP in general population. Difficult cannulation is a risk factor for PEP in patients who are administered rectal indomethacin, and how to overcome which need further evaluation.

Author contributions

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