

Role of Intravenous Indomethacin in Prevention of Post endoscopic Retrograde Cholangiopancreatography Sphincterotomy and Sphincteroplasty Pancreatitis

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ABSTRACT

Aim: To see role of post procedure parenteral indomethacin for prevention of Post-ERC Sphincterotomy and large balloon Sphincteroplasty related Pancreatitis.

Methods: 90 participants with large stones in common bile duct (CBD), underwent large balloon sphincteroplasty (LBS) were randomly assigned (using lottery method) Indomethacin group and control group at Department of Gastroenterology, Lahore General Hospital/AMC/PGMI; Lahore during August 2015 to July 2016. A total of 45 subjects were included in drug arm and were given 100 mg Indomethacin in 1000ml N/Saline over 4-6 hours. Control group (45 subjects) received 1000 ml N/Saline only. Stone size more than 15mm considered to be large stone and selection of balloon diameter was based on the diameter of distal common bile duct but minimum of 15mm diameter of balloon considered to be LBS. CBD stone/ stones were removed with the help of stone extraction balloon. All patients were observed for post procedure abdominal pain and rise in Serum amylase for 4-6 hours and persistence of abdominal pain longer than 24 hrs. Rise in serum amylase levels more than three times was considered significant and less than that as insignificant. Data was analyzed by using SPSS.

Results: In experimental group post procedure pancreatitis was developed in 7(15.6%) while in placebo it was seen in 10(22.2%) patients, although the rate of pancreatitis was higher in placebo but was statically insignificant when compared with experimental group, p-value > 0.05.

Conclusion: Incidence of pancreatitis in patients with large stone in common bile duct undergoing endoscopic sphincterotomy and large balloon Sphincteroplasty does not reduce with indomethacin infusion. It has been observed that Indomethacin infusion did not have any advantage on the standard post procedure care. Further larger multicenter studies are required to confirm role of intravenous Indomethacin in prevention of pancreatitis after endoscopic sphincterotomy and Sphincteroplasty.

Keywords: Large common bile duct stone, Indomethacin, Pancreatitis

INTRODUCTION

Presence of common bile duct stone is about 10-18% among patients who are going for cholecystectomy¹. Recommended treatment for removing large stones in common bile duct (CBD) is Endoscopic sphincterotomy (EST) and endoscopic large balloon sphincteroplasty (ELBS)². Post endoscopic retrograde cholangiopancreatography (ERC) related pancreatitis (PEP) is one of the potentially serious complications of ERC with its frequency approaching 30% in patients with high risk conditions³ and with mortality rate at least 3%-5% of all procedures⁴. There are multiple identified factors which increase risk for post-ERC pancreatitis. These factors include hydrostatic injury by injecting contrast or water, mechanical injury due by endoscopic instruments, thermal injury caused by electrocautery⁵. Female, smoking, use of alcohol, sphincter of Oddi dysfunction (SOD), and normal bilirubin are the factors associated with increased risk of post-ERC pancreatitis⁶.

Multiple drugs have been evaluated as prophylaxis to decrease the risk of post ERC pancreatitis with mixed results⁷. These drugs act by reducing release of intrapancreatic enzymes and by inhibiting activation lysosomal enzymes⁸. Frequency of post ERC pancreatitis

is significantly reduced by using indomethacin as prophylaxis when compared with placebo^{4,8}. Levenik et al. (2016)⁹ reported that there was no significant reduction in PEP using rectal Indomethacin. PEP reduction due to indomethacin is unclear and we have contradictions in results in reported studies.

In previous studies, indomethacin has been used to decrease incidence of post-ERCP pancreatitis but its use for prevention of Post-ERC Sphincterotomy and large balloon Sphincteroplasty related pancreatitis is not reported. In Pakistan, only intravenous preparation of indomethacin are available while oral and suppositories are not available while all previous research reports rectal use of indomethacin.

The current study is designed to see role of post procedure parenteral indomethacin for prevention of Post-ERC Sphincterotomy and large balloon Sphincteroplasty related Pancreatitis.

MATERIALS AND METHODS

The study was conducted in the Department of Gastroenterology, Lahore General Hospital/AMC/PGMI; Lahore during August 2015 to July 2016. It was approved from institutional review board ethical committee and an informed consent was taken from the patients.

Randomized controlled trial design and non-probability consecutive sampling technique was used in this study.

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Subjects with large CBD stone were randomly assigned (using lottery method) in two groups, indomethacin group and control group. All patients aged 40-80 years of either gender with stone size more than 15 mm were considered. Selection of balloon diameter was based on the diameter of distal common bile duct but minimum of 15 mm diameter of balloon considered to be large balloon sphinctroplasty. Out of total 90 subjects, 45 were included in drug arm and were given 100mg indomethacin in 1000ml N/Saline over 4-6 hours and 45 subjects (control group) received 1000ml N/Saline only. Patients with hypersensitivity to indomethacin, an episode of acute pancreatitis two week prior to ERC, Renal dysfunction (creatinine >1.5mg/dL), active or recent gastrointestinal bleeding within four week and patients with confirmed pregnancy were excluded.

All participants were observed for post procedure abdominal pain and rise in serum amylase for 4-6 hours and persistence of abdominal pain longer than 24 hrs. Rise in serum amylase levels more than three times was considered significant and less than that as insignificant⁵. SPSS version 20 was used to analyze data. Quantitative variables like age and different hematological parameters were recorded as mean ± S.D. Qualitative variables like gender, hospital stay and pancreatitis after ERCP were recorded in form of frequency(%). Independent sample test/Mann Whitney U test was used for quantitative data and Chi-square test for categorical data. P-value of ≤ 0.05 was considered significant.

RESULTS

The mean age in experimental group (indomethacin given) was 52.16±14.45 years and in placebo group (indomethacin not given) was 53.76±13.94 years. In experimental group mean, there were 13(28.9%) male and 32(71.1%) females while in placebo group there were 21(46.7%) males and 24(53.3%) female patients (Table 1). In experimental group, post procedure pancreatitis was developed in 7(15.6%) while in placebo it was seen in 10(22.2%) patients, though in placebo the rate of pancreatitis was higher but was statically insignificant (*P* > 0.05) when compared with experimental group (Table 2).

Fig.1: Post-ERCP and ELBS typical and atypical abdominal pain in each group of patients

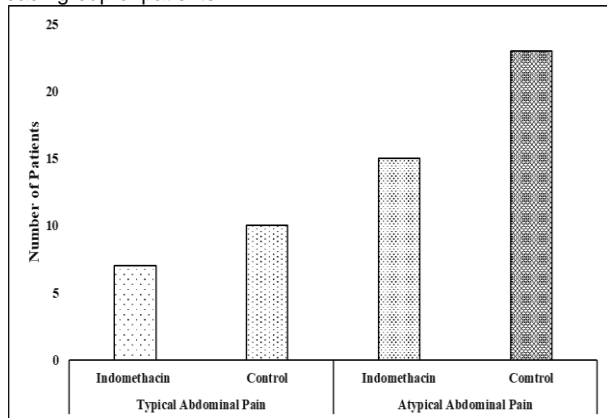


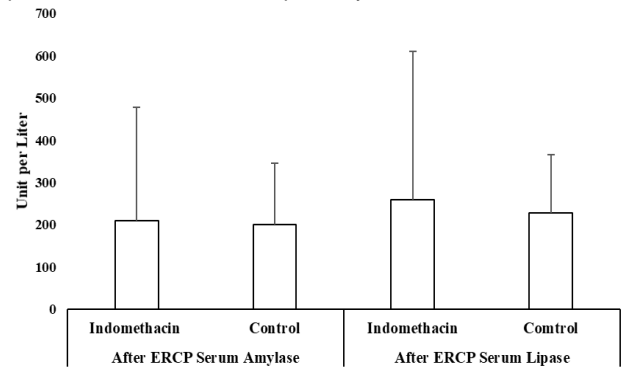
Table 1: Comparisons of age (years) and different hematological parameters in both study groups

	Indomethacin Group (n = 45)		Control Group (n= 45)	
	Mean	Sd	Men	An
Age	53.76	13.94	52.16	14.45
Hb	11.05	2.13	11.26	1.92
TLC	9409.33	3224.52	9127.33	5770.01
Platelets	321777.78	152613.57	275377.78	86591.85
T. Bilirubin	4.38	4.64	4.07	4.03
ALT	79	68.81	90.31	115.41
AST	75.82	61.48	72.73	55.37
Alk Phosphatase	349.76	277.61	523.89	531.84

Table 2: Comparisons of gender, hospital stay and post procedure pancreatitis and different hematological parameters in both study groups

	Indomethacin Group	Control Group
Gender		
Male	13 (28.9%)	21 (46.7%)
Female	32 (71.1%)	24 (53.3%)
Hospital stay		
Up to 6 hours	15 (33.3%)	11 (24.4%)
6-12 hours	14 (31.1%)	21 (46.7%)
12-18 hours	2 (4.4%)	4 (8.9%)
18-24 hours	13 (28.9%)	9 (20%)
≥ 24 hours	1 (2.2%)	0 (0%)
Post procedure pancreatitis		
Yes	7 (15.6%)	10 (22.2%)
No	38 (84.4%)	35 (77.8%)

Fig. 2: Serum amylase and lipase levels (U/L) after ERCP and endoscopic large balloon sphinctroplasty (ELBS) in patients with large CBD stone. There were 45 patients in each group i.e., indomethacin and control. The p values for serum amylase and lipase were 0.88 and 0.59, respectively.



DISCUSSION

Although ERCP plays a vital role in management of pancreaticobiliary diseases however it carries a significant risk of certain complication because of its invasive nature. One of these risks is post-ERC pancreatitis. ERCP is minimally invasive procedure as compare to surgery, still it can result in serious complication that can occur in 10% of patients including, bleeding, perforation and pancreatitis. These complication can lead to prolong hospital stay and even death¹⁰.

Over the past few decades multiple pharmacological therapies have been used to prevent post ERC pancreatitis but only few of them were affective. Among all of these, indomethacin is used successfully to prevent post ERC pancreatitis. In previous studies indomethacin is

administered per rectally, however in our study, we used intravenous indomethacin. Also, we used indomethacin in prevention of pancreatitis in patients with endoscopic large balloon sphincteroplasty (ELBS) for extraction of large stone/stones in CBD.

In our study pancreatitis occurred in 17(18.8%) out of total 90 patients. In a previous study, acute pancreatitis was developed in 127 (5.4%) patients out of total 2347 patient who underwent EST. Out of these 127 patients, 53(2.3%) patients had mild attack, 65(2.8%) had moderate while 9(0.4%) patients had severe pancreatitis¹¹. We have found that there was no significant effect of intravenous indomethacin in preventing post ERC pancreatitis in patients with large stone/stones in requiring EST and ELBS for stone extraction.

A study reported that post-ERC pancreatitis developed in 9.2% patients in indomethacin group while in 16.9% patients of placebo group ($p=0.005$). It showed 7.7% reduction in absolute risk of one episode of post ERC pancreatitis with a 46% reduction in relative risk¹². While another study reported that among 490 patients, of which half received indomethacin, there was no significant ($P=0.06$) difference in indomethacin and placebo group¹³. A meta-analysis reported the pooled proportion estimate of the frequency of pancreatitis was 5.1% in indomethacin group while 10.3% in placebo group. The frequency of pancreatitis was decreased to 3.9% and 7.9% respectively once high risk patients were excluded¹⁴. All above studies were done to assess the efficacy of indomethacin given per rectum while we included patients with large CBD stone who underwent endoscopic biliary sphincterotomy as well as endoscopic large balloon sphincteroplasty (ELBS). We found that in experimental group post procedure pancreatitis was developed in 7(15.6%) while in placebo it was seen in 10(22.2%) patients, though in placebo the rate of pancreatitis was higher in placebo but was statically insignificant when compared with experimental group, p -value > 0.05. Hence Post ERC and ELBS pancreatitis can be reduced if patients are selected carefully¹⁵.

CONCLUSION

Post ERC sphincterotomy (EST) and large balloon Sphincteroplasty procedure infusion of Indomethacin doesn't reduce the incidence of Pancreatitis but it reduces the incidence of Post-ERCP Asymptomatic Hyperamylasemia. Though the number of the cases is small, it has been observed that Indomethacin infusion did not have any advantage on the standard post procedure care patients. Further larger multicenter studies are request to confirm Role of Intravenous Indomethacin in prevention of Post Endoscopic Retrograde Cholangio (ERC) Sphincterotomy and Sphincteroplasty Pancreatitis.

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