pISSN: 2508-5778 • eISSN: 2508-5859
Ann Hepatobiliary Pancreat Surg 2024;28:350-357
https://doi.org/10.14701/ahbps.24-021

AHBPS
Annals of Hepato-Biliary-Pancreatic Surgery

Original Article

Does perioperative hydrocortisone or indomethacin improve pancreatoduodenectomy outcomes? A triple arm, randomized placebo-controlled trial

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Backgrounds/Aims: This trial evaluated whether anti-inflammatory agents hydrocortisone (H) and indomethacin (I) could reduce major complications after pancreatoduodenectomy (PD).
Methods: Between June 2018 and June 2020, 105 patients undergoing PD with > 40% of acini on the intraoperative frozen section were randomized into three groups (35 patients per group): 1) intravenous H 100 mg 8 hourly, 2) rectal I suppository 100 mg 12 hourly, and 3) placebo (P) from postoperative day (POD) 0–2. Participants, investigators, and outcome assessors were blinded. The primary outcome was major complications (Clavien–Dindo grades 3–5). Secondary outcomes were overall complications (Clavien–Dindo grades 1–5), Clinically relevant postoperative pancreatic fistula (CR-POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), surgical site infections (SSI), length of stay, POD-3 serum amylase, readmission rate, and mortality.
Results: Major complications were comparable (8.6%, 5.7%, and 8.6% in groups H, I, and P, respectively). However, overall complications were significantly lower in group H than in group P (45.7% vs. 80.0%, $p = 0.006$). CR-POPF (14.3% vs. 25.7%, $p = 0.371$), PPH (8.6% vs. 14.3%, $p = 0.710$), DGE (8.6% vs. 22.9%, $p = 0.188$), and SSI (14.3% vs. 25.7%, $p = 0.371$) were comparable between groups H and P. Major complications and overall complications in group I were 5.7% and 60.0%, respectively, which were comparable to those in groups P and H. CR-POPF rates in groups H, I, and P were 14.3%, 17.1%, and 25.7%, respectively, which was comparable.
Conclusions: H and I did not decrease major complications in PD.

Key Words: Hydrocortisone; Indomethacin; Pancreatoduodenectomy; Complications; Pancreatic fistula

INTRODUCTION

Pancreatoduodenectomy (PD) is considered a major surgery that has a relatively low mortality of 1%–5% but a very high morbidity of 20% to 60%, even in high-volume centers [1]. The main cause of postoperative morbidity is pancreatojejunostomy (PJ) site leak which can lead to postoperative pancreatic fistula (POPF) [2]. The POPF rate ranges from 12% to 27% in various studies [3,4]. Risk factors for PJ leak include soft pancreatic texture, normal exocrine function, small pancreatic duct, major intraoperative blood loss, ischemia, surgical technique, and so on [5,6]. One possible mediator of POPF is surgical pancreatic damage followed by postoperative pancreatic inflammation at the cut edge of the pancreas which has been shown to predispose patients undergoing PD to POPF [7-9]. Laaninen et al. [10] have shown that a large number of acinar cells covering more than 40% of the cut edge of the pancreas may predispose the pancreas to develop pancreatitis postoperatively. Pharmacological interventions such as perioperative corticosteroids which act by decreasing postoperative inflammatory response secondary to surgical trauma have been shown to decrease postoperative complications related to PD and open distal pancreatectomy (DP) by some authors [11-13]. The role of a single dose of 100 mg per-rectal indomethacin in preventing post-endoscopic retrograde cholangiopancreatography (ERCP)

Received: January 22, 2024, **Revised:** March 14, 2024,
Accepted: April 2, 2024, **Published online:** April 29, 2024

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pancreatitis had been established by a landmark study by Elmunzer et al. [14] in a multicenter randomized controlled trial (RCT). Since indomethacin being an anti-inflammatory agent has a proven role in preventing post-ERCP pancreatitis, we hypothesized that the use of this drug in the perioperative period could reduce the incidence of postoperative pancreatitis and subsequent complications after PD.

This study aimed to evaluate whether post-PD major complications could be reduced in high-risk patients (> 40% acini at the cut edge of the pancreas) with perioperative anti-inflammatory agents–intravenous (IV) hydrocortisone or rectal indomethacin.

MATERIALS AND METHODS

Study design and patient recruitment

A parallel group, three-arm, triple-blinded, RCT was conducted at our tertiary referral center. Patients undergoing PD who met the eligibility criteria were enrolled from June 2018 to June 2020. This study was approved by the Institute Ethics Committee and prospectively registered with the Clinical Trial Registry of India (CTRI number: CTRI/2018/06/014541, www.ctri.nic.in). This study was HIPAA compliant. It adhered to the tenets of the Declaration of Helsinki. A written informed consent was obtained from each patient before enrolment. This study complied with the Consolidated Standards for Reporting Trials (CONSORT). An overview of this study is depicted in Fig. 1.

Inclusion criteria

Patients who underwent PD at a tertiary referral center with > 40% acini at the cut surface of the pancreas based on frozen section were included.

Exclusion criteria

Patients who were found to be inoperable at exploration, those who were undergoing minimally invasive or hybrid PD, those with a history of steroid use or long-term non-steroidal anti-inflammatory drugs (NSAIDs) treatment, those with coexistent chronic pancreatitis, those with comorbidities including chronic kidney disease, those with a history of acute coronary syndrome, cerebrovascular accident or peptic ulcer disease, those with thrombocytopenia, and those not giving consent for participation were excluded from this study.

Randomization and blinding

Patients meeting eligibility criteria were randomized into three groups (preoperatively receiving IV hydrocortisone, per rectal indomethacin suppository, or placebo) at a 1:1:1 ratio. This was done with a computer-generated randomizer using permuted blocks by the institute's biostatistician. The random sequence generated was transferred to an opaque, sealed envelope to conceal randomization until actual allocation. A study nurse randomized patients to each group after opening the sealed envelope. This was a triple-blind study where study participants, clinical investigators, treating physicians, surgeons, and outcome assessors were unaware of the allocation. Data analysis and primary and secondary outcome calculations were done before the allocation concealment was removed. Participants were enrolled in this study by the principal investigator.

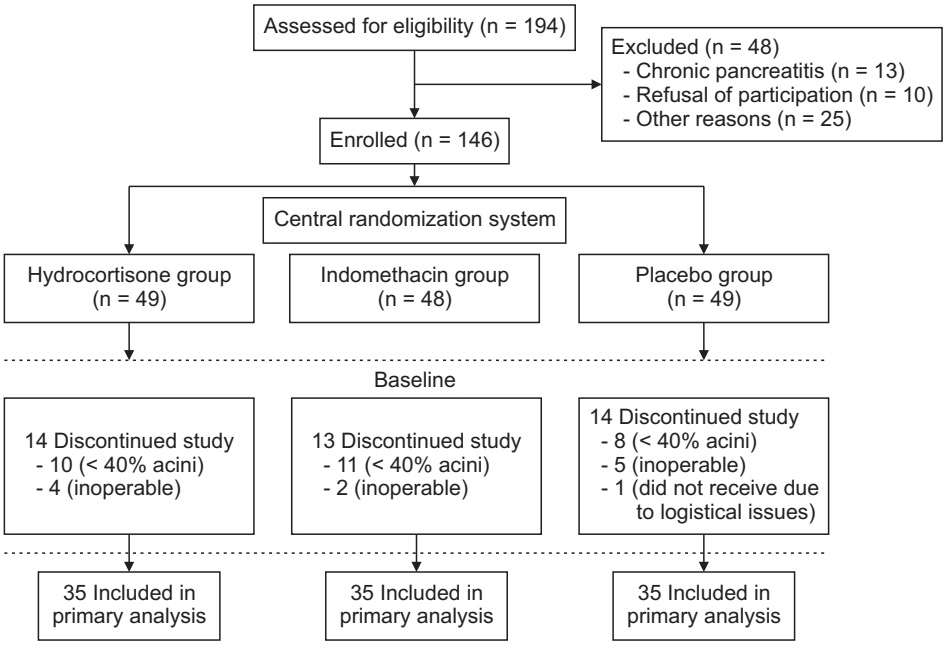

Fig. 1. CONSORT flowchart showing the study profile.

Procedures

All patients underwent classical PD with duct to mucosa pancreatic PJ, modified Blumgart's technique for biliary anastomosis and retrocolic-infracolic gastrojejunostomy. Anastomoses were done by experienced surgeons who had performed at least 50 open PDs independently. All patients received the first dose of treatment at the induction of anesthesia at 8 AM. The intraoperative, cut surface of the pancreas was sent for preparing a frozen section. The percentage of acini was calculated by two experienced pathologists independently and the average was taken as the actual percentage. Those having < 40% acini were excluded from this study while those who had > 40% acini received further treatment based on randomization.

Patients in all three groups received a combination of IV drugs and rectal suppositories containing either hydrocortisone or indomethacin or placebo. Patients in the hydrocortisone group were given a total of 8 doses of 100 mg IV hydrocortisone sodium succinate (Hydrocort-100; Abbott) dissolved in 2 mL of sterile water. The prepared solution was added to 100 mL of 0.9% sodium chloride and administered as an IV infusion at 8-hour intervals (8 AM, 4 PM, 12 AM) until postoperative day (POD) 2. Six doses of glycerin rectal suppository (Hallen's adult-3gm, Meridian enterprises) were administered at 12-hour interval (8 AM, 8 PM) until POD-2. Patients in the indomethacin group were given a total of 6 doses of 100 mg rectal indomethacin suppository (Indobid 100; Cipla) at 12-hour intervals until POD-2. A total of 8 doses of 2 mL sterile water added to 100 mL 0.9% sodium chloride solution were administered as an IV infusion at 8-hour interval (8 AM, 4 PM, 12 AM) until POD-2. Patients in the placebo group were given a total of 8 doses of 2 mL of sterile water added to 100 mL 0.9% sodium chloride solution administered as an IV infusion at 8-hour intervals (8 AM, 4 PM, 12 AM) and rectal glycerin suppository at 12-hour intervals (8 AM, 8 PM) until POD-2.

Outcome parameters

The primary outcome measure was the rate of major complications defined as Clavien–Dindo (CD) grade ≥ 3 [15]. Secondary outcome measures included clinically relevant postoperative pancreatic fistula (CR-POPF) rate [16], postpancreatectomy hemorrhage (PPH) [17], delayed gastric emptying (DGE) rate [18], surgical site infections (SSI) rate, POD 3 serum amylase, length of hospital stay (LOHS), length of intensive care unit (ICU) stay, overall complications defined as CD grades 1–5, reoperation rate, readmission rate, and mortality. All outcome measures were monitored for up to 30 days after the index surgery.

Statistical analysis

Assuming that perioperative treatment with hydrocortisone could reduce the rate of major complications (CD III, IV, V) to 18% as shown by Laaninen et al. [11] compared to 50% in patients with placebo, 31 patients were required per group to detect difference in major complication rate between the two groups to be statistically significant in Fischer's exact test with 5% alpha error and 80% power. Giving an allowance for losses in the follow-up, 35 patients per group were needed. Since there was no previous data regarding the use of indomethacin in PD, 35 patients were also included in the indomethacin group.

Table 1. Demographic and patient characteristics of study population

Patient parameter	Hydrocortisone (n = 35)	Indomethacin (n = 35)	Placebo (n = 35)
Age (yr)	52 (43–65)	55 (48– 62)	59 (49–61)
Male:Female	20:15	26:9	27:8
Diabetes present	13 (37.1)	13 (37.1)	15 (42.9)
Hypertension present	13 (37.1)	8 (22.9)	10 (28.6)
Serum albumin (g/dL)	3.4 (3.2–7.0)	3.4 (3.2–3.7)	3.6 (3.3–3.8)
Original disease			
Periampullary adenocarcinoma	17	19	20
Carcinoma head of pancreas	2	3	2
Distal cholangiocarcinoma	9	7	8
Neuroendocrine tumor	4	2	0
Benign	3	4	5
Preoperative jaundice	7 (20.0)	9 (25.7)	5 (14.3)
Preoperative biliary drainage	26 (74.3)	19 (54.3)	25 (71.4)
Bile culture positive	23 (65.7)	19 (54.3)	22 (62.9)
Pancreatic duct diameter (mm)	3.33 (2.66–4)	3 (2.33–4)	3.33 (2–4)
Consistency of pancreas (firm:soft:hard)	6:29:0	4:31:0	7:28:0
Duration of surgery (min)	375 (330–430)	405 (315–455)	390 (345–430)

Values are presented as median (interquartile range) or number (%) unless otherwise indicated.

https://doi.org/10.14701/ahbps.24-021

Modified intention to treat analysis was carried out using Statistical Package for Social Sciences (SPSS) version 20 (IBM Co.) and Med Cal C software A (MedCalc Software Ltd). Two-sample t-test, analysis of variance (ANOVA), and Mann–Whitney U test were used to analyze quantitative data. Chi-square test and Fisher's exact test were used to analyze categorical data as appropriate. A two-sided *p*-value of less than 0.05 was considered statistically significant.

Multiple logistic regression was applied to study effects of age, serum albumin, presence of jaundice at the time of surgery, preoperative biliary drainage, bile culture positivity, preoperative diagnosis (i.e., carcinoma head of the pancreas [CHOP] or non-CHOP), hydrocortisone administration, indomethacin administration, pancreatic duct diameter, intraoperative fluid administration, and intraoperative blood transfusion on developing major complications and overall complications as dependent variables.

RESULTS

A total of 194 patients who underwent PD during the study period were assessed for eligibility. Of them, 48 patients were excluded (chronic pancreatitis, n = 13; refusal to participate, n = 10; chronic kidney disease, n = 4; history of acute coronary syndrome or cerebrovascular accident, n = 14; peptic ulcer disease, n = 2; history of steroid or long-term NSAID intake, n = 5). Intraoperatively, 11 patients were found to be inoperable and 29 patients had < 40% acini. One patient could not receive the drug due to logistical issues. These patients were excluded from this study. Finally, 105 patients were included in the modified intention-to-treat analysis (Fig. 1). Demographic and patient characteristics were comparable among the three groups (Table 1).

Postoperative outcomes are shown in Table 2. Regarding the primary outcome, there was no difference in incidence of major complications (CD grade ≥ 3) among the three groups. In the hydrocortisone group, one patient had severe postoperative hospital-acquired pneumonia which required elective intubation and ventilation with IV antibiotics (CD grade 4b). Another patient had grade B CR-POPF which required ultrasound (USG) guided percutaneous drain (CD grade 3a). A 43-year-old patient had a grade C CR-POPF with intra-abdominal collections and septic shock for which he required re-exploration and abdominal lavage (CD grade 4a). In the indomethacin group, a 75-year-old male patient had grade B CR-POPF with intra-abdominal collections for which he required USG-guided percutaneous drain (grade 3a). Another 70-year-old female patient had grade B CR-POPF which was managed with USG-guided percutaneous drain for intra-abdominal collections (CD grade 3b) along with a late mild intraluminal PPH which was managed conservatively with blood transfusion and hemostatic agents. In the placebo group, a 59-year-old female patient had a grade B CR-POPF for which the patient needed an USG-guided PCD (CD grade 3a). A 61-year-old male patient had a grade C fistula with severe late extraluminal PPH for which he required re-exploration on postoperative day 7. However, the patient did not survive (grade 5). Another 51-year-old male patient had grade C CR-POPF with septic shock for which he required re-exploration and lavage (grade 4a).

Interestingly, overall complications were significantly lower in the hydrocortisone group than in the placebo group (16 [45.7%] vs. 28 [80.0%], $p = 0.006$), although they showed no sig-

Table 2. Primary and secondary outcomes

Outcome	H (n = 35)	I (n = 35)	P (n = 35)	*p*-value		
				H vs. P	I vs. P	H vs. I
Major complications (CD grade ≥ 3)	3 (8.6)	2 (5.7)	3 (8.6)	1.000	1.000	1.000
Overall complications (CD grade 1–5)	16 (45.7)	21 (60.0)	28 (80.0)	0.006	0.117	0.338
CR-POPF	5 (14.3)	6 (17.1)	9 (25.7)	0.371	0.561	1.000
DGE	3 (8.6)	9 (25.7)	8 (22.9)	0.188	1.000	0.110
PPH	3 (8.6)	4 (11.4)	5 (14.3)	0.710	1.000	1.000
SSI	5 (14.3)	10 (28.6)	9 (25.7)	0.371	1.000	0.244
Length of intensive care unit stay (day)	3 (3–4)	3 (2–3)	3 (2–3)	1.000	1.000	1.000
Length of hospital stay (day)	10 (8–11)	10 (9–14)	11 (9–15)	0.052	0.741	0.130
Range	6–59	7–33	7–30			
Reoperation	1 (2.9)	0 (0)	2 (5.7)	1.000	0.493	1.000
Readmission	2 (5.7)	2 (5.7)	2 (5.7)	1.000	1.000	1.000
30-day mortality	0 (0)	0 (0)	1 (2.9)	1.000	1.000	-
POD-3 serum amylase (U/L)	81.97 ± 74.61	105.60 ± 111.62	122.20 ± 123.60	0.104	0.557	0.301

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.
CD, Clavien–Dindo; CR-POPF, clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy hemorrhage; SSI, surgical site infections; POD, postoperative day; H, hydrocortisone; I, indomethacin; P, placebo.

Table 3. Univariate analysis of factors associated with presence of major complications

Serial number	Variable	Category	Odds ratio	*p*-value	95% confidence Interval	
					Lower	Upper
1	Age (yr)	≤ 60	1.00			
		> 60	2.59	0.199	0.61	11.11
2	Serum albumin (g/dL)	≤ 3.0	1.00			
		> 3.0	0.81	0.846	0.09	7.23
3	Presence of jaundice at time of surgery	No	1.00			
		Yes	2.63	0.212	0.58	12.04
4	Preoperative biliary drainage	No				
		Yes	NA	NA	NA	NA
5	Bile culture positivity	No	1.00			
		Yes	0.35	0.172	0.08	1.57
6	Preoperative diagnosis	Non-CHOP	1.00			
		CHOP	0.00	0.999	0.00	-
7	Hydrocortisone given	No	1.00			
		yes	1.22	0.795	0.27	5.42
8	Indomethacin given	No	1.00			
		Yes	0.65	0.605	0.12	3.38
9	Pancreatic duct diameter (mm)	≤ 3	1.00			
		> 3	1.85	0.418	0.42	8.17
10	Intraoperative fluid transfusion (mL)	≤ 3,500	1.00			
		> 3,500	1.28	0.748	0.29	5.69
11	Intraoperative blood transfusion	No	1.00			
		Yes	0.00	0.998	0.00	-

CHOP, carcinoma head of the pancreas; NA, not applicable as all patients with major complications had preoperative biliary drainage.

nificant differences between hydrocortisone and indomethacin or between indomethacin and placebo groups. The rate of CR-POPF in the hydrocortisone group was comparable to that of the indomethacin group (5 [14.3%] vs. 6 [17.1%]) or the placebo group (5 [14.3%] vs. 9 [25.7%]). Overall, CR-POPF, DGE, PPH, POD 3 serum amylase levels, SSI, re-exploration rates, length of ICU stay, LOHS, readmission rates, and mortality rates showed no statistically significant differences among the three groups (Table 2). There was a single mortality in the placebo group due to grade C POPF with PPH.

While no perioperative characteristic was associated with the development of major complications (Table 3), perioperative administration of hydrocortisone was found to have a significant association with decreased overall complications on univariate analysis (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.16–0.83; p = 0.017) (Table 4). Absolute risk reduction was 209 per 1,000 cases. The number of cases needed to treat to prevent one complication was 5. No other factor was found to have a significant association with overall complications.

DISCUSSION

This study aimed to evaluate whether administration of hydrocortisone or indomethacin in the perioperative period could reduce major complications (CD grade 3 to 5) after PD in a high-risk group (patients having > 40% acini at the cut surface of the pancreas). According to the present study, the rate of major postoperative complications was 8.6% in the hydrocortisone group, 5.7% in the indomethacin group, and 8.6% in the placebo group, showing no significant difference among the three groups. There was no significant difference in CR-POPF rate among the three groups either. Our results were in agreement with two recently published trials which did not show any beneficial role of hydrocortisone over somatostatin analogs in reducing CR-POPF [19,20].

Evidence supporting the use of perioperative corticosteroids in pancreatic resections is limited and inconclusive. To the best of our knowledge, there are only four RCTs on this topic. A systematic literature review and meta-analysis of prophylactic treatment with corticosteroids (8 RCTs, n = 546) or n-acetyl cysteine (4 RCTs, n = 178) of induced pancreatitis in rodent models showed that prophylactic administration of corticosteroid agents and n-acetyl cysteine could reduce the severity of pancreatitis as indicated by histopathologic markers, serum amylase, and IL-6 levels [21]. One RCT on PD and one RCT on DP have shown the benefit of perioperative hydrocortisone in reducing major complications [11,12]. Laaninen et al. [11] had randomized patients undergoing PD with > 40% acini at the

Table 4. Univariate analysis for risk factors associated with overall complications

Serial number	Variable	Category	Odds ratio	*p*-value	95% confidence interval	
					Lower	Upper
1	Age (yr)	≤ 60	1.00			
		> 60	0.96	0.933	0.41	2.28
2	Serum albumin (g/dL)	≤ 3.0	1.73	0.439	0.43	6.95
		> 3.0	1.00			
3	Presence of jaundice at time of surgery	No	1.00			
		Yes	0.78	0.616	0.29	2.06
4	Preoperative biliary drainage	No	1.04	0.934	0.44	2.44
		Yes	1.00			
5	Bile culture positivity	No	1.11	0.799	0.49	2.49
		Yes	1.00			
6	Preoperative diagnosis	Non-CHOP	2.29	0.294	0.49	10.84
		CHOP	1.00			
7	Hydrocortisone given	No	1.00			
		Yes	0.36	0.017	0.16	0.83
8	Indomethacin given	No	1.00			
		Yes	0.89	0.776	0.39	2.04
9	Pancreatic duct diameter (mm)	≤ 3	1.00			
		> 3	0.78	0.528	0.35	1.71
10	Intraoperative fluid transfusion (mL)	≤ 3,500	1.00			
		> 3,500	1.44	0.403	0.61	3.41
11	Intraoperative blood transfusion	No	1.00			
		Yes	1.54	0.394	0.57	4.15

CHOP, carcinoma head of the pancreas.

cut edge of the pancreas into hydrocortisone (28 patients) and placebo (34 patients) groups. Patients in the hydrocortisone group had significantly fewer major complications (CD III-IV) (18% vs. 41%, p-value < 0.05). Antila et al. [12] have randomized 40 consecutive patients undergoing open DP to receive IV hydrocortisone 100 mg or placebo every 8 hours for 2 days postoperatively. Patients receiving hydrocortisone had significantly less major (C-D III-V) complications (5.9% vs. 21.4%, p = 0.034) and CR-POPF (5.9% vs. 42.9%, p = 0.028).

Conversely, two RCTs have shown no benefit of hydrocortisone compared to somatostatin analogs in preventing CR-POPF in high-risk pancreas [19,20]. Kriger et al. [20] have stratified 78 patients into high-risk (> 40% functioning acini) for POPF and low-risk (< 40% functioning acini) groups based on intraoperative frozen section. A total of 38 high-risk group patients were randomized to receive a combination of somatostatin analogs and glucocorticoids (n = 25) or somatostatin analogs only in the control group (n = 13). Forty low-risk patients were randomized to receive somatostatin analogs (n = 18) or nothing in the placebo group (n = 22). They concluded that a combination of somatostatin analog and glucocorticoid did not show efficiency in preventing CR-POPF in high-risk patients.

Similarly, Tarvainen et al. [19] have conducted an RCT to assess the noninferiority of hydrocortisone compared with pasireotide in reducing complications after partial pancreatectomy. Treatment included pasireotide 900 μg subcutaneously twice a day for 7 days or hydrocortisone 100 mg intravenously 3 times a day for 3 days. Postoperative pancreatic fistula was detected in 34 (54%) patients in the pasireotide group and 39 (62%) patients in the hydrocortisone group (OR, 1.39; 95% CI, 0.68–2.82; p = 0.37). The authors concluded that hydrocortisone was not noninferior to pasireotide in patients undergoing partial pancreatectomy.

Perioperative indomethacin did not significantly reduce major complications or CR-POPF after PD. This indicates different mechanisms of pancreatitis secondary to surgical trauma and ERCP. Following ERCP, intraductal pressure is increased, which can affect the whole pancreas. Following pancreatic transection, local inflammation and pancreatitis at the transection line can occur. The role of indomethacin in preventing post-ERCP pancreatitis had been questioned by an RCT by Levenick et al. [22] in 2016 which showed that rectal indomethacin did not prevent post-ERCP pancreatitis.

Incidence of CR-POPF and levels of POD-3 serum amylase were lower in the hydrocortisone group than in indomethacin and placebo groups, although differences were not statistically significant. Our incidence of CR-POPF (14.3% in hydrocorti-

sone and 25.7% in placebo) was comparable to that in a previous study by Laaninen et al. [11] in 2016, in which the CR-POPF rate was 11% in the hydrocortisone group and 27% in the placebo group.

In this study, the incidence of DGE was 8.6% in the hydrocortisone group, 25.7% in the indomethacin group, and 22.9% in the placebo group. The incidence of DGE in a study by Laaninen et al. [11] in 2016 was 29% in the hydrocortisone group and 44% in the placebo group. Differences in DGE in this study and our study were not statistically significant. In the present study, the incidence of PPH was 8.6% in the hydrocortisone group, 11.4% in the indomethacin group, and 14.3% in the placebo group. The incidence of bleeding was the least in the hydrocortisone group. Although indomethacin is an NSAID, the incidence of bleeding was not increased. It was lower than that in the placebo group. The incidence of PPH in a study by Laaninen et al. [11] in 2016 was 14% in the hydrocortisone group and 24% in the placebo group.

The hydrocortisone group had fewer SSIs than placebo and indomethacin groups (5 [14.3%] vs. 9 [25.7%] vs. 10 [28.6%]). However, such differences were not significant ($p > 0.05$). A retrospective study of 679 PDs that analyzed patients who had received intraoperative dexamethasone showed that overall morbidity and 30-day major morbidity were similar among all resected patients [23]. However, the dexamethasone group had fewer infectious complications (18.8% vs. 28.5%, $p = 0.032$) [23]. It has been shown that perioperative steroid usage in liver resections can decrease overall complications, organ space SSIs, length of stay, postoperative serum bilirubin, and prothrombin time-international normalized ratio [24]. Significantly less SSI in the hydrocortisone group could be explained by decreased steroid-mediated inflammatory response that could ultimately lead to less septic complications.

In this study, the median LOHS was 10 days in the hydrocortisone group, 10 days in the indomethacin group, and 11 days in the placebo group. Hospital stays were shorter in both intervention groups than in the placebo group, although the difference was not statistically significant. In a study by Fernández-del Castillo et al. [25] in 2012, the mean duration of hospital stay was 9.5 days which was comparable to that of this study. In a study by Cameron and He [3] in 2015), the mean LOHS was 10 days after 2000. There was no mortality in the hydrocortisone or indomethacin group. However, there was one (2.9%) mortality in the placebo group due to POPF leading to PPH. In a study by Laaninen et al. [11] in 2016, the was no mortality in the hydrocortisone or placebo group.

The main strength of this study is that this study provides randomized evidence regarding the usefulness of hydrocortisone in PD. This is the first RCT to examine the role of indomethacin in PD. Perioperative administration of hydrocortisone is safe. It is associated with decreased overall complications. This can be explained by a decreased perioperative inflammatory response. However, in this study, levels of inflammatory markers were not studied to give solid evidence for this association, although previous studies have shown this association [26]. Rates of major complications in all three groups were comparable, which might explain the similar length of stay, major morbidity, and mortality of the three groups. We did find that overall complications were lower in the hydrocortisone group than in the placebo group (45.7% vs. 80.0%, $p = 0.006$). This could be explained by downregulated postoperative inflammatory response in the steroid group resulting in less overall complications due to lesser minor complications (CD grades 1 and 2).

Additional limitations of this study include limited sample size and lack of long-term follow-up. The difference in major complications (CD grade > 2) that was used to calculate the sample size was not found in this study. Therefore, the trial was underpowered. Thus, an adequately powered trial is needed in the future to explore this research question. Perioperative hydrocortisone or indomethacin administration did not decrease major complications or CR-POPF rate after PD. Indomethacin has no benefit in PD, although hydrocortisone can decrease overall complications.

ACKNOWLEDGEMENTS

We would like to thank Mr. HVV Murthy for his help in statistical analysis.

FUNDING

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: KK, PR, RD. Data curation: KK, ZA, RD, PR. Methodology: KK, ZA, MK, PA. Writing - original draft: KK, ZA, MK, GVR. Writing - review & editing: KK, ZA, MK, GVR.

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