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Effect of postoperative non-steroidal anti-inflammatory drugs on anastomotic leakage after pancreaticoduodenectomy

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Background: Although the association between an increase in anastomotic leakage (AL) and non-steroidal anti-inflammatory drugs (NSAIDs) has been reported in gastrointestinal surgeries, this issue has rarely been addressed for pancreaticoduodenectomy (PD). We aimed to investigate the association between postoperative NSAIDs administration and clinically relevant AL (CR-AL) following PD.

Methods: We retrospectively evaluated 2,163 consecutive patients who underwent PD between 2007 and 2019. The patients were divided into two groups; patients who received and did not receive NSAIDs by postoperative day (POD) 5. We conducted a propensity score analysis using inverse probability of treatment weighting (IPTW) to adjust the baseline differences between both groups. We compared the occurrence of CR-AL and other postoperative outcomes before and after IPTW. Further, we used the multivariable binary logistic regression method for a sensitivity analysis for CR-AL.

Results: A total of 2,136 patients were included in the analysis. Of these, 222 (10.4%) received NSAIDs by POD 5. The overall occurrence rate of CR-AL was 14.9%. After IPTW, postoperative NSAIDs were significantly associated with CR-AL (odds ratio [OR]: 1.24, 95% CI [1.05, 1.47], P = 0.012), prolonged postoperative hospitalization (OR: 1.31, 95% CI [1.14, 1.50], P < 0.001), and unplanned readmission within 30 days postoperatively (OR 1.48: 95% CI [1.15, 1.91], P = 0.002). However, this association was not consistent in the sensitivity analysis.

Conclusions: Postoperative NSAIDs use was significantly associated with an increase in CR-AL incidence following PD. However, sensitivity analysis failed to show its association, which precludes a firm conclusion of its detrimental effect.

Keywords: Analgesics; Anastomotic leak; Non-steroidal anti-inflammatory agents; Pancreatic fistula; Pancreaticoduodenectomy; Postoperative complications.

Introduction

Pancreaticoduodenectomy (PD) is the primary surgical treatment for patients with localized benign and malignant periampullary disease. PD patients require three types of anastomoses to retain gastrointestinal continuity: pancreaticojejunal (PJ), gastrojejunal (GJ), and hepaticojejunal (HJ) anastomoses. Such anastomoses are the most problematic sites following PD, and anastomotic leakages (ALs) from these sites are important con-

tributors to postoperative morbidity, prolonged hospitalization, and mortality after PD [1,2]. Thus, several efforts have been made to identify their risk factors [3–5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used non-opioid analgesics in multimodal analgesia, which improve postoperative analgesia while reducing opioid-related side effects due to their opioid-sparing effect [6]. However, several studies have reported the possible harmful association of NSAIDs and ALs in gastrointestinal surgeries [7,8]. In several preclinical studies, NSAIDs have been reported to impair collagen deposition and angiogenesis in healing tissues, which may decrease the strength of the anastomosis and lead to an AL [9,10].

However, the detrimental effect of NSAIDs on AL following a PD has rarely been reported [11–13]. Therefore, investigating the association between NSAID use and the risk of AL, including postoperative pancreatic fistula (POPF), which is the most challenging complication following a PD, is important. In this retrospective study, we conducted a propensity score analysis with inverse probability of treatment weighting (IPTW) to investigate the association between early postoperative NSAID use and the occurrence of clinically relevant AL (CR-AL) in patients with PD.

Materials and Methods

This retrospective observational study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2010-145-1167). The need for informed patient consent was waived due to the anonymization of their medical records before analysis. The manuscript is prepared following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [14].

We retrospectively reviewed the electronic medical records of 2,163 consecutive adult patients who underwent classic PD (Whipple's operation) or pylorus-preserving PD (PPPD) for various periampullary lesions at our institution from January 2007 to December 2019. We did not perform a priori or post-hoc power calculation due to the retrospective design of the study, and all patients who met the abovementioned inclusion criteria were included in the analysis. Patients with missing values for the covariates used in the propensity score calculation (total, n = 10; pancreatic texture, n = 6; and pancreatic duct size, n = 4), patients who died within 30 days after surgery (n = 11), and patients who underwent total pancreatectomy (n = 2) or hepatoduodenectomy (n = 1) due to remnant pancreatic cancer after PD or PPPD during hospitalization were excluded. Patients who received laparoscopic PD were also excluded due to their small number (n = 3). A total of 2,136 patients were included in the final analysis.

The cohort was divided into two groups: patients who received NSAIDs (NSAID group) and those who did not receive NSAIDs (no NSAID group) by postoperative day (POD) 5. In our institution, during the study period, the main postoperative analgesic method was intravenous patient-controlled analgesia (IV-PCA). By March 2019, IV-PCA comprised a mixture of fentanyl and morphine in a bolus of 1 ml (intravenous morphine equivalent dose [IVMED] 1–2.5 mg) with a lockout interval of 15 min and a basal infusion rate of 1 ml/h (IVMED 1–2.5 mg/h). Since April 2019, we have used the IV-PCA comprising only fentanyl, and in July 2019, we introduced the IV-PCA without basal infusion [15]. Ketorolac has been administered as an intravenous rescue analgesic based on the attending surgeon's preference, and ibuprofen has also been administered as an oral rescue analgesic after the resumption of oral intake. Additionally, we investigated all types of NSAIDs available in our institution, including cyclooxygenase (COX)-2 inhibitors. Apart from NSAIDs, morphine, fentanyl, tramadol, and acetaminophen were also administered as intravenous rescue analgesics based on the attending surgeon's preference. In our institution, epidural PCA has been used since 2019 in patients scheduled to receive open PD and agreed to it without contraindications of neuraxial anesthesia. Epidural PCA comprised 0.15% ropivacaine with 2 μg/ml fentanyl at a basal infusion rate of 4 ml/h and a bolus of 2 ml with a lockout interval of 20 min.

Data on sex, age, body mass index (BMI), smoking, American Society of Anesthesiologists (ASA) physical status classification, pathologic diagnosis, surgical procedure (classic PD vs. PPPD), type of surgical approach (open vs. robot-assisted), neoadjuvant chemotherapy and radiotherapy, preoperative biliary drainage (percutaneous transhepatic biliary drainage or endoscopic retrograde biliary drainage), pathological type, pancreatic duct diameter (mm), pancreatic texture (soft vs. firm), type of pancreatic duct stent (internal, external), estimated blood loss (EBL, ml), intraoperative crystalloid and colloid administration (ml), intraoperative vasopressor use, intraoperative packed red blood cell transfusion, operative time (min), postoperative length of hospital stay (LOS), and reoperation or unplanned readmission within 30 days postoperatively were collected retrospectively using the Seoul National University Hospital Patients Research Environment system. Vasopressors included ephedrine, phenylephrine, norepinephrine, dopamine, or epinephrine. We also extracted information on postoperative complications, including on ALs, from the surgeon's database.

In our institution, PPPD is the standard procedure for periampullary lesions. However, if there is a lesion such as duodenal ulcer, ischemia, and tumor infiltration, PD is also performed at the surgeon's discretion. The robot-assisted approach has been used

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since 2015, and the scope of surgery or the anastomosis method is the same as that for open surgery. PJ anastomosis is performed in a two-layer, end-to-side, duct-to-mucosal manner with an internal or external pancreatic stent [16]. Jackson–Pratt drains are routinely placed adjacent to the PJ site, and an early drain removal strategy (POD 3–5) is favored. To detect any postoperative complications, amylase concentrations in serum and drainage fluid are measured postoperatively (on POD 1, 3, 5, 7, and 10) in all patients, and contrast-enhanced computed tomography scans are performed on POD 5–7. Peripancreatic drains are removed in case of no evidence of leakage.

The primary outcome of the study was the occurrence of CR-ALs. CR-AL was defined as clinically relevant postoperative pancreatic fistula (CR-POPF) or CR-HJ anastomotic leakage (CR-HL). CR-POPF was defined according to the International Study Group on Pancreatic Fistula criteria grades B and C [17]. CR-HL was defined based on the proposed grading system for HJ leakage grade B and C [5]. The secondary outcomes included postoperative acute kidney injury, wound complication, postoperative bleeding, delayed gastric emptying, prolonged postoperative hospitalization, re-operation, and unplanned readmission within 30 days postoperatively. Postoperative bleeding was defined as the need for postoperative transfusion or operation, embolization, or endoscopic hemostasis for bleeding control. Wound complication was defined as the case when aggressive wound dressing, wound repair, or late wound drain removal was required. Delayed gastric emptying was defined as the need to retain nasogastric drainage for 10 days after surgery or the inability to tolerate a semisolid diet 14 days after surgery. Prolonged postoperative hospitalization was defined as a LOS > 75th percentile of that observed for our cohort (> 19 days).

Statistical analysis

R version 3.6.3 (R Foundation for Statistical Computing, Austria) was used for the statistical analysis. Statistical significance was set as a two-sided $P < 0.05$. The normality of data distribution was assessed using a Shapiro–Wilk test. Categorical data were expressed as number (%) and continuous data as median (Q1, Q3). We did not replace missing values for the variables of baseline characteristics.

To evaluate the association between postoperative NSAID use and primary and secondary outcomes, we performed an IPTW analysis using a propensity score [18]. Patients with a probability value of 0 or 1 for receiving postoperative NSAID were excluded from the analyses based on the positivity assumption. In addition, extreme weights greater than the 99th percentile or less than the lowest first percentile were replaced with the value of the 99th percentile or the first percentile, respectively [18]. Balance in variables between the two groups before and after IPTW was evaluated by calculating the standardized mean difference (SMD). The following variables were used as contributors to the propensity score: sex, age, BMI, ASA physical status, neoadjuvant chemotherapy, type of surgical approach, pancreatic texture, pancreatic duct diameter, type of pancreatic duct stent, pathological type (pancreatic adenocarcinoma or pancreatitis vs. all others), EBL (≤ 400 ml, 401–700 ml, 701–1,000 ml, and > 1,000 ml), and intraoperative crystalloid amount per 100 ml. Then, we calculated the odds ratio (OR) and 95% CI of postoperative NSAID use on the primary and secondary outcomes before and after IPTW.

For a sensitivity analysis, we performed multivariable binary logistic regression analyses for CR-AL and CR-POPF. Based on previous studies regarding the risk factors of POPF [4,16,19,20], the following variables were included in the analyses: postoperative NSAID use within POD 5, sex, age, BMI, ASA physical status III or IV (vs. I or II), smoking, neoadjuvant radiation therapy, neoadjuvant chemotherapy, pathological type (pancreatic adenocarcinoma or pancreatitis vs. all others), robotic-assisted surgery (vs. open), type of pancreatic duct stent (external vs. none vs. internal), soft pancreatic gland (vs. firm), pancreatic duct diameter (mm), operative time (min), EBL (≤ 400 ml, 401–700 ml, 701–1,000 ml, > 1,000 ml), intraoperative vasopressor use, intraoperative transfusion, and crystalloid and colloid administration per 100 ml. We did not perform preliminary variable selection by univariable logistic regression analysis before multivariable analysis. We investigated 10 interactions between the following five variables using a likelihood ratio test: crystalloid administration per 100 ml, colloid administration per 100 ml, intraoperative vasopressor use, intraoperative transfusion, and EBL. Statistically significant interaction terms were included in our final multivariable analysis. The linearity assumption between each continuous variable and the binary outcome variable was examined using restricted cubic splines.

Finally, we classified patients into four groups according to the 10-point fistula risk score (0: negligible, 1–2: low, 3–6: intermediate, 7–10: high) [21], and conducted the aforementioned analyses in the subgroup with intermediate to high risk of CR-POPF.

Results

Among the 2,136 patients included in the analysis, 222 (10.4%) received NSAIDs within POD 5. Among them, 204 (9.6%) received ketorolac with a median (Q1, Q3) value of 30 (30, 60) mg, and 21 (1.0%) received oral ibuprofen with a median (Q1, Q3)

value of 800 (600, 1650) mg. No other intravenous NSAIDs were administered during that period. During the study period, the overall incidence rates of CR-POPF, CR-HL, and CR-AL were 14.1%, 1.3%, and 14.9%, respectively. There was no GJ anastomosis leakage in the total cohort. Fig. 1 presents the annual occurrence of CR-AL and the major treatment changes in PD in our institution.

Comparisons of demographic and clinical characteristics between the two groups before and after IPTW are shown in Table 1 and Supplementary Table 1. Before IPTW, age, pathology, preoperative albumin, neoadjuvant chemotherapy, type of pancreatic stent, pancreatic duct size, fistula risk score, and intraoperative crystalloid amount were significantly different between the two groups (SMD > 0.1), but there were no significant differences in those variables except pathology and neoadjuvant radiation therapy between the two groups after IPTW (Table 1, Supplementary Table 1). Supplementary Table 2 compares the demographics and clinical characteristics between the two groups before and after IPTW in the subgroup with intermediate to high risk of CR-POPF.

Table 2 compares the primary and secondary outcomes of our study after IPTW. Postoperative NSAID use was significantly associated with CR-AL after IPTW (OR: 1.24, 95% CI [1.05, 1.47], P = 0.012). Furthermore, the incidence of postoperative bleeding (OR: 1.57, 95% CI [1.08, 2.30], P = 0.018), delayed gastric emptying (OR: 1.35, 95% CI [1.04, 1.74], P = 0.024), proportions of prolonged postoperative hospitalization (OR: 1.31, 95% CI [1.14, 1.50], P < 0.001), and unplanned readmission within 30 days postoperatively (OR: 1.48, 95% CI [1.15, 1.91], P = 0.002) were significantly higher in the NSAID group than in the no NSAID group after IPTW. In the subgroup analysis, postoperative NSAID use was also significantly associated with CR-AL after IPTW (OR: 1.30, 95% CI [1.09, 1.54], P = 0.004), delayed gastric emptying (OR: 1.69, 95% CI [1.28, 2.24, P < 0.001), prolonged postoperative hospitalization (OR: 1.41, 95% CI [1.22, 1.64], P < 0.001), and unplanned readmission within 30 days postoperatively (OR: 1.48, 95% CI [1.13.1.93], P = 0.005; Supplementary Table 3).

In multivariable logistic regression analysis, female sex, higher BMI, neoadjuvant chemotherapy, pancreatic adenocarcinoma or pancreatitis, soft pancreatic texture, smaller pancreatic duct size, and internal pancreatic stent were identified as significant predictors of both CR-AL and CR-POPF (Table 3). Additionally, older age was identified as a significant predictor of CR-AL. However, postoperative NSAID use was not significantly associated with CR-AL (OR: 1.19, 95% CI [0.81, 1.76], P = 0.376) and CR-POPF

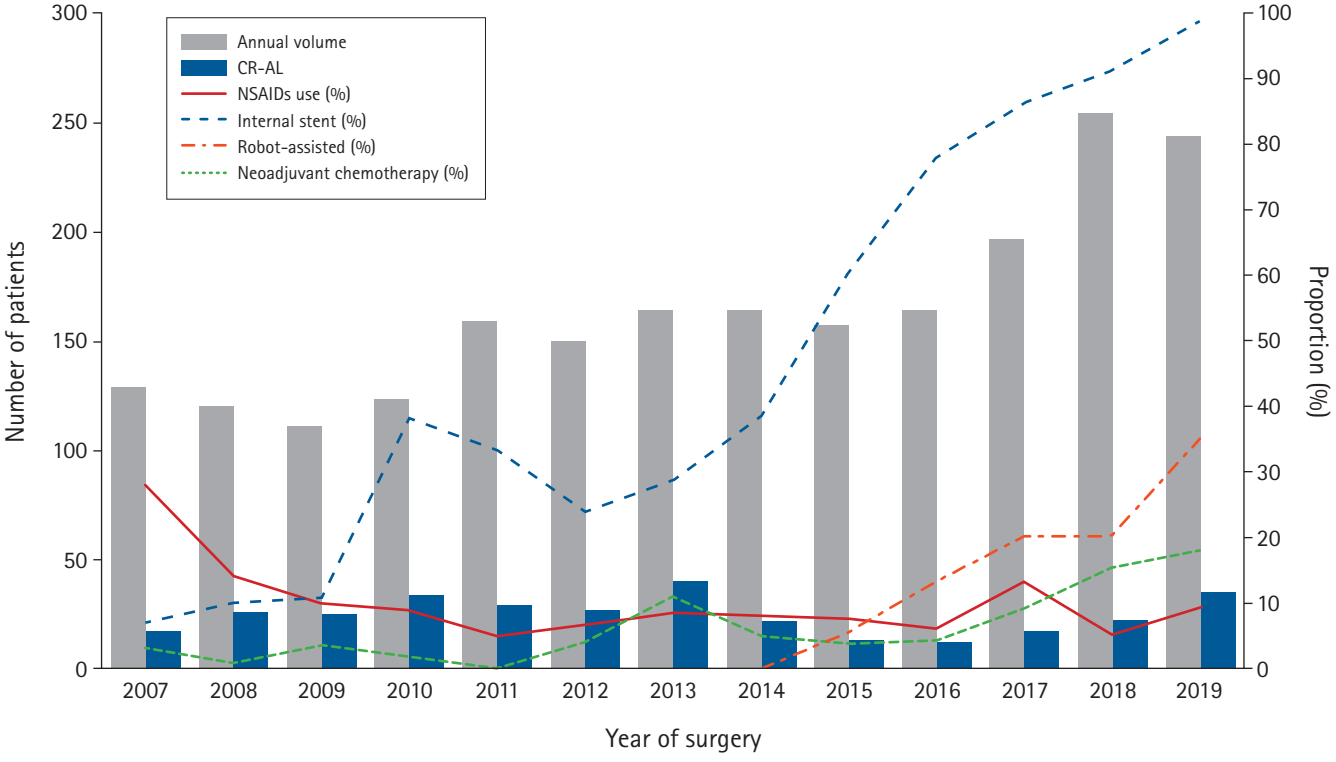

Fig. 1. Annual surgical volume, occurrence of CR-AL, and perioperative parameters according to the year of surgery. Bars indicate number of patients and lines indicate proportion (%). CR-AL: clinically relevant anastomotic leakage, NSAIDs: non-steroidal anti-inflammatory drugs.

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Table 1. Demographic and Clinical Characteristics between Patients with and without Postoperative NSAIDs Use

Characteristics	Before IPTW			After IPTW		
	No NSAID group (n = 1,914)	NSAID group (n = 222)	SMD	No NSAID group (n = 2,136)	NSAID group (n = 1,875)	SMD
Demographic data						
Age (yr)	65 (58, 72)	63 (57, 70)	0.159	65 (58, 71)	64 (57, 70)	0.011
F (vs. M)	751 (39.2)	89 (40.1)	0.017	841 (39.4)	757 (40.4)	0.020
BMI (kg/m^2)	23.1 (21.2, 25.2)	23.6 (21.5, 25.5)	0.084	23.2 (21.2, 25.2)	23.4 (21.3, 25.3)	0.016
Background medical status						
ASA-PS (I/II/III/IV)	371 (19.4)/1,385 (72.4)/157 (8.2)/1 (0.1)	40 (18.0)/164 (73.9)/18 (8.1)/0	0.049	412 (19.3)/1,548 (72.5)/175 (8.2)/1 (0)	337 (18.0)/1,363 (72.7)/175 (9.3)/0	0.057
Preoperative albumin (g/dl)	3.9 (3.6, 4.2)	4.0 (3.7, 4.3)	0.167	3.9 (3.6, 4.2)	4.0 (3.6, 4.2)	0.081
Pancreatic adenocarcinoma or pancreatitis (vs. all others)	582 (30.4)	65 (29.3)	0.025	647 (30.3)	543 (28.9)	0.029
Neoadjuvant chemotherapy	148 (7.7)	9 (4.1)	0.157	157 (7.4)	105 (5.6)	0.071
Operation and anesthesia related						
PPPD (vs. Whipple's operation)	1,449 (75.7)	167 (75.2)	0.011	1,622 (75.9)	1,416 (75.5)	0.009
Robot-assisted (vs. open)	182 (9.5)	27 (12.2)	0.085	209 (9.8)	182 (9.7)	0.002
Pancreatic stent (None/external/internal)	91 (4.8)/782 (40.9)/1,041 (54.4)	14 (6.3)/104 (46.8)/104 (46.8)	0.155	105 (4.9)/886 (41.5)/1,145 (53.6)	98 (5.2)/833 (44.4)/943 (50.3)	0.066
Soft pancreas (vs. firm)	1,280 (66.9)	156 (70.3)	0.073	1,437 (67.2)	1,295 (69.1)	0.040
Pancreatic duct size (mm)	3 (2, 4)	3 (2, 4)	0.156	3 (2, 4)	3 (2, 4)	0.012
EBL (ml)	400 (250, 600)	350 (200, 550)	0.048	400 (250, 600)	374 (200, 550)	0.027
Fistula risk score	5 (3, 6)	5 (3, 6)	0.131	5 (3, 6)	5 (3, 6)	0.012
Operation time (min)	312 (258, 370)	315 (270, 375)	0.073	315 (260, 372)	310 (268, 367)	0.005

Values are presented as median (Q1, Q3) or number (%). NSAID: non-steroidal anti-inflammatory drugs, IPTW: inverse probability of treatment weighting, BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status, PPPD: pylorus-preserving pancreaticoduodenectomy, SMD: standardized difference, EBL: estimated blood loss.

Table 2. Comparison of the Primary and Secondary Outcomes between PD Patients with and without Postoperative NSAIDs Use after IPTW

Clinical outcomes	No NSAID group (n = 2,136)	NSAID group (n = 1,875)	P value	OR (95% CI)
CR-AL	313 (14.7)	332 (17.7)	0.012	1.24 (1.05, 1.47)
CR-POPF	300 (14.0)	291 (15.5)	0.184	1.13 (0.95, 1.34)
CR-HL	20 (0.9)	54 (2.9)	< 0.001	3.11 (1.86, 5.21)
Any POPF	1,237 (57.9)	1,116 (59.5)	0.300	1.07 (0.94, 1.21)
Any HL	23 (1.1)	54 (2.9)	< 0.001	2.67 (1.63, 4.35)
Acute kidney injury	4.6 (0.2)	9.2 (0.5)	0.145	2.30 (0.75, 7.09)
Wound problem	197 (9.2)	183 (9.8)	0.557	1.07 (0.86, 1.32)
Postoperative bleeding	48 (2.3)	66 (3.5)	0.018	1.57 (1.08, 2.30)
Delayed gastric emptying	116 (5.4)	135 (7.2)	0.024	1.35 (1.04, 1.74)
Prolonged postoperative hospitalization	522 (24.4)	557 (29.7)	< 0.001	1.31 (1.14, 1.50)
Reoperation within 30 days after surgery	17 (0.8)	19 (1.0)	0.451	1.29 (0.67, 2.49)
Unplanned readmission within 30 days after surgery	115 (5.4)	146 (7.8)	0.002	1.48 (1.15, 1.91)

Values are presented as number (%). PD: pancreaticoduodenectomy, NSAID: non-steroidal anti-inflammatory drugs, OR: odds ratio, CR-AL: clinically relevant anastomotic leakage, CR-POPF: clinically relevant postoperative pancreatic fistula, CR-HL: clinically relevant hepaticojejunostomy anastomotic leakage.

(OR: 1.07, 95% CI [0.71, 1.60], P = 0.754; Table 3). Supplementary Table 4 shows the results of the multivariable logistic regression analysis for CR-POPF in the subgroup with intermediate to high risk of CR-POPF. In the subgroup analysis, significant associations of all the aforementioned factors except age were maintained.

Table 3. Binary Logistic Regression Analysis for Factors Associated with CR-AL or CR-POPF

Variable	CR-POPF		CR-AL	
	OR (95% CI)	P value	OR (95% CI)	P value
Postoperative NSAIDs use	1.07 (0.71, 1.60)	0.754	1.19 (0.81, 1.76)	0.376
F (vs. M)	0.49 (0.37, 0.66)	< 0.001	0.55 (0.41, 0.73)	< 0.001
Age (yr)	1.01 (1.00, 1.02)	0.127	1.01 (1.00, 1.03)	0.038
BMI (kg/m^2)	1.09 (1.04, 1.13)	< 0.001	1.08 (1.04, 1.13)	< 0.001
Smoking	0.84 (0.58, 1.22)	0.363	0.87 (0.60, 1.25)	0.449
ASA-PS III (vs. I or II)	0.80 (0.47, 1.35)	0.398	0.82 (0.49, 1.37)	0.450
Neoadjuvant chemotherapy	0.20 (0.05, 0.79)	0.022	0.18 (0.05, 0.72)	0.015
Neoadjuvant radiation therapy	0.84 (0.08, 9.23)	0.889	1.58 (0.23, 10.89)	0.645
Pancreatic adenocarcinoma or pancreatitis (vs. all others)	0.37 (0.25, 0.56)	< 0.001	0.45 (0.31, 0.65)	< 0.001
Robotic-assisted surgery (vs. open)	0.79 (0.48, 1.31)	0.367	0.84 (0.53, 1.35)	0.471
Pancreatic stent				
External stent	Reference		Reference	
None	0.66 (0.31, 1.39)	0.270	0.60 (0.29, 1.26)	0.179
Internal stent	0.60 (0.45, 0.81)	< 0.001	0.65 (0.49, 0.87)	0.004
Soft pancreatic texture (vs. firm)	2.14 (1.52, 3.03)	< 0.001	2.14 (1.53, 2.98)	< 0.001
Pancreatic duct diameter (mm)	0.90 (0.83, 0.97)	0.007	0.91 (0.84, 0.98)	0.010
Surgical time (h)	0.99 (0.88, 1.11)	0.847	1.01 (0.90, 1.13)	0.847
Estimated blood loss (ml)				
≤ 400	Reference		Reference	
401–700	0.84 (0.61, 1.16)	0.293	0.87 (0.63, 1.18)	0.367
701–1,000	1.22 (0.74, 2.00)	0.442	1.21 (0.75, 1.96)	0.439
> 1,000	1.02 (0.55, 1.87)	0.963	0.99 (0.55, 1.79)	0.975
Intraoperative vasopressor use	1.12 (0.80, 1.58)	0.501	1.07 (0.77, 1.50)	0.664
Intraoperative transfusion	0.95 (0.61, 1.48)	0.815	0.96 (0.63, 1.49)	0.869
Crystalloid per 100 ml	1.02 (1.00, 1.04)	0.039	1.02 (1.00, 1.04)	0.014
6% hydroxyethyl starch per 100 ml	1.15 (1.05, 1.26)	0.003	1.15 (1.05, 1.26)	0.002
Crystalloid per 100 ml × 6% hydroxyethyl starch per 100 ml	1.00 (0.99, 1.00)	0.026	1.00 (0.99, 1.00)	0.016

CR-AL: clinically relevant anastomotic leakage, CR-POPF: clinically relevant postoperative pancreatic fistula, OR: odds ratio, NSAIDs: non-steroidal anti-inflammatory drugs, ASA-PS: American Society of Anesthesiologists physical status, BMI: body mass index.

Discussion

In this study, we investigated the association between postoperative NSAID use and CR-AL in patients who underwent PD. Our results with rigorous multivariable adjustments showed a significant association between postoperative NSAID use and CR-AL, especially CR-HL. Additionally, postoperative NSAIDs were significantly associated with prolonged postoperative hospitalization and unplanned readmission within 30 days postoperatively after IPTW.

NSAIDs should be used cautiously due to their possible detrimental effect on anastomotic healing. A recent systematic review and meta-analysis provided evidence of this detrimental effect on gastrointestinal anastomoses, although most of the studies included were conducted in patients with colorectal surgery [22]. Further, in a large cohort study using the nationwide claim database, perioperative ketorolac use was associated with an increase in emergency department visits, re-intervention rate, and readmission rate within 30 days postoperatively not only in colorectal but also in non-colorectal gastrointestinal surgeries [8]. In addition, impairment of angiogenesis and collagen deposition are possible mechanisms of NSAID-induced AL that can contribute to AL following a PD [12,13,23,24]. Therefore, it is important to deliberate on the possible detrimental effects of NSAIDs before prescribing them as an option for multimodal analgesia for patients undergoing PD.

Previous retrospective studies have reported negative results regarding the association between postoperative NSAID use and CR-POPF after PD. The first report related to this issue failed to show an association between postoperative non-selective NSAIDs use and POPF [12]. However, the study had critical shortcomings: not adjusting for important confounders, such as pancreatic tex-

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ture and pancreatic duct size, and a small sample size. Since then, a subsequent study reported that early postoperative ketorolac use was associated with an increase in the incidence of any POPF, including biological leakage [13]. However, there was no significant association between postoperative ketorolac use and CR-POPF. In addition, the study had a small sample size, and there was no information about pancreatic gland texture and duct size in approximately 30% of the patients. The most recent study reported no association between postoperative ketorolac use and CR-POPF [11]. However, it was still difficult to conclude the safety of using ketorolac for PD due to their wide CI, including substantial adverse effects (any ketorolac, OR: 1.99, 95% CI [0.93, 4.26], P = 0.08), but the authors supported the safety of using ketorolac for PD, noting that the incidence of CR-POPF remained stable despite the great increase in the use of ketorolac at their institution. However, the improvement in surgical treatment and accumulated surgeon's experience could have offset the harmful effect of ketorolac on ALs [3].

Compared to previous studies, our study differed in the following respects. First, we performed adjustment analyses with a higher number of confounders reported to be associated with the occurrence of CR-AL. Among them, intraoperative fluid administration was a newly identified predictor of CR-AL in this study. Perioperative fluid administration was reported as a risk factor for AL after colorectal surgery [25]. From the perspective of an anesthesiologist, further research is required on the effect of other intraoperative variables on the development of CR-AL [26]. Second, we included both HL and PJ ALs in the primary outcome. We assumed that NSAID could affect all types of gastrointestinal anastomosis. Third, we increased the statistical power of our findings using the IPTW analysis [18]. Through this method, we tried to overcome the disadvantage of relatively fewer patients in the NSAID group and could perform subgroup analyses for the risk of CR-POPF. Considering that the incidence rate of CR-AL is 15% and an OR of 1.3 is clinically important, at least 1,636 patients are required for each group to achieve 80% power to detect a difference between the two groups with a two-sided α of 0.05. Therefore, to identify the detrimental effect of NSAIDs on AL in PD, a large-scale study is required, as those conducted for colorectal surgery [7,8].

In our study, postoperative NSAID use showed a significant association with an increase in postoperative bleeding, delayed gastric emptying, prolonged postoperative hospitalization, and unplanned readmission, as well as an increase in CR-AL occurrence after IPTW. Since CR-AL might largely contribute to postoperative bleeding or delayed gastric emptying after PD [27,28], postoperative NSAIDs use could increase these complications would have led to the prolonged hospitalization and readmission rate after PD.

As an expert in postoperative pain management, anesthesiologists should try to explore other effective analgesic methods, including regional analgesia, in patients undergoing PD and avoid the use of NSAIDs. With the advent of the opioid crisis, the use of opioids in major abdominal surgeries is being discouraged. Epidural analgesia, previously known as the gold standard for postoperative pain control after major abdominal surgeries, is also being replaced by another multimodal analgesia due to disadvantages such as hypotension, urinary retention, rare but serious complications, and low cost-effectiveness [29,30]. Therefore, anesthesiologists should find the optimal analgesic method to effectively control postoperative pain while reducing postoperative complications in patients undergoing PD, based on the latest evidence.

However, our results should be interpreted cautiously for the following reasons. First, an inherent limitation of the retrospective nature of this study is that unmeasured and unknown confounders may have affected our results, although we performed IPTW to reduce the bias. Our results could not demonstrate a causal relationship but only reveal associations. Second, this study analyzed a cohort of a single tertiary hospital in Korea. Therefore, center-specific factors and the ethnic uniformity of the cohort limit the generalizability of our findings. Third, we could not consider the effect of surgeons' experience, such as surgical skills, on the occurrence of POPF [3,31]. However, our results were obtained from the leading institution in South Korea in this field, with a large hospital volume [32]. During the study period, the incidence rate of CR-AL in our institution was lower than in other institutions [3]. Therefore, the effect of surgeons' experience on the primary outcome in this study would have been small. Fourth, the median value of the ketorolac dose in this study was 30 mg, which was relatively small compared to that in previous studies [11–13]. Therefore, we could not identify the dose-dependent effect of ketorolac on the development of POPF. Fifth, although our primary outcome included both PJ and HJ ALs, adjustment for confounders was mainly focused on the risk of PJ AL. HJ AL is relatively rare, and its risk factors are not well-known. Last, if there was a large imbalance in the treatment allocation as in our study, IPTW could affect the results by giving excessive weights to some marginal subjects. However, IPTW can operate without a significant increase in the type I error rate in the context of low prevalence of treatment [33]. We also performed weight truncation to reduce excessive weights.

In conclusion, we found a significant association between the use of postoperative NSAIDs and the occurrence of CR-AL in pa-

tients with PD. This detrimental effect of postoperative NSAID use could lead to an increase in prolonged postoperative hospitalization and unplanned readmission within 30 days after surgery. However, the significant association only presented in CR-HL, and the rarity of CR-HL precludes a firm conclusion regarding the clinically meaningful detrimental effect of its use in these patients. Further sensitivity analysis failed to show its detrimental effect. Our study supports the demand for more research with sufficient power on the effects of NSAIDs on AL following a PD.

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Conflicts of Interest

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

Author Contributions

Susie Yoon (Formal analysis; Writing – original draft)
Hyerin Kim (Data curation)
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Supplementary Materials

Supplementary Table 1. Baseline and perioperative variables between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use before and after inverse probability of treatment weighting (IPTW) in the total cohort
Supplementary Table 2. Baseline and perioperative variables between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use before and after inverse probability of treatment weighting (IPTW) in the subgroup with intermediate to high risk of CR-POPF
Supplementary Table 3. Comparison of the primary and secondary outcomes between patients with and without postoperative non-steroidal anti-inflammatory drugs (NSAIDs) use after pancreaticoduodenectomy before and after inverse probability of treatment weighting (IPTW) in the subgroup with intermediate to high risk of clinically relevant postoperative pancreatic fistula (CR-POPF)
Supplementary Table 4. Binary logistic regression analysis for factors associated with clinically relevant anastomotic leakage (CR-AL) or clinically relevant postoperative pancreatic fistula (CR-POPF) in the subgroup with intermediate to high risk of CR-POPF

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References

1. Vollmer CM Jr, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD, et al. A root-cause analysis of mortality following major pancreatectomy. J Gastrointest Surg 2012; 16: 89-102.
2. Jester AL, Chung CW, Becerra DC, Molly Kilbane E, House MG, Zyromski NJ, et al. The impact of hepaticojejunostomy leaks after pancreatoduodenectomy: a devastating source of morbidity and mortality. J Gastrointest Surg 2017; 21: 1017-24.
3. Trudeau MT, Casciani F, Ecker BL, Maggino L, Seykora TF, Puri P, et al. The fistula risk score catalog: toward precision medicine for pancreatic fistula after pancreatoduodenectomy. Ann Surg 2022; 275: e463-72.
4. Roberts KJ, Hodson J, Mehrzad H, Marudanayagam R, Sutcliffe RP, Muiesan P, et al. A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy. HPB (Oxford) 2014; 16: 620-8.
5. Burkhart RA, Relles D, Pineda DM, Gabale S, Sauter PK, Rosato EL, et al. Defining treatment and outcomes of hepaticojejunostomy failure following pancreaticoduodenectomy. J Gastrointest Surg 2013; 17: 451-60.
6. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth 2017; 118: 22-31.
7. Hakkarainen TW, Steele SR, Bastaworous A, Dellinger EP, Farrokhi E, Farjah F, et al. Nonsteroidal anti-inflammatory drugs and the risk for anastomotic failure: a report from Washington State's Surgical Care and Outcomes Assessment Program

https://doi.org/10.4097/kja.21096

(SCOAP). JAMA Surg 2015; 150: 223-8.
8. Kotagal M, Hakkarainen TW, Simianu VV, Beck SJ, Alfonso-Cristancho R, Flum DR. Ketorolac use and postoperative complications in gastrointestinal surgery. Ann Surg 2016; 263: 71-5.
9. Jones MK, Wang H, Peskar BM, Levin E, Itani RM, Sarfeh IJ, et al. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. Nat Med 1999; 5: 1418-23.
10. Muscará MN, McKnight W, Asfaha S, Wallace JL. Wound collagen deposition in rats: effects of an NO-NSAID and a selective COX-2 inhibitor. Br J Pharmacol 2000; 129: 681-6.
11. Kunstman JW, Brandt WS, Azar SA, Jean RA, Salem RR. Comprehensive analysis of the effect of ketorolac administration after pancreaticoduodenectomy. J Am Coll Surg 2020; 230: 935-42.
12. Behman R, Karanicolas PJ, Lemke M, Hanna SS, Coburn NG, Law CH, et al. The effect of early postoperative non-steroidal anti-inflammatory drugs on pancreatic fistula following pancreaticoduodenectomy. J Gastrointest Surg 2015; 19: 1632-9.
13. Kowalsky SJ, Zenati MS, Steve J, Lee KK, Hogg ME, Zeh HJ 3rd, et al. Ketorolac use may increase risk of postoperative pancreatic fistula after pancreaticoduodenectomy. J Surg Res 2018; 221: 43-8.
14. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573-7.
15. Jung H, Lee KH, Jeong Y, Lee KH, Yoon S, Kim WH, et al. Effect of fentanyl-based intravenous patient-controlled analgesia with and without basal infusion on postoperative opioid consumption and opioid-related side effects: a retrospective cohort study. J Pain Res 2020; 13: 3095-106.
16. Jang JY, Chang YR, Kim SW, Choi SH, Park SJ, Lee SE, et al. Randomized multicentre trial comparing external and internal pancreatic stenting during pancreaticoduodenectomy. Br J Surg 2016; 103: 668-75.
17. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017; 161: 584-91.
18. Schulte PJ, Mascha EJ. Propensity score methods: theory and practice for anesthesia research. Anesth Analg 2018; 127: 1074-84.
19. Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: analysis of 539 successive cases of pancreaticoduodenectomy. World J Gastroenterol 2016; 22: 7797-805.
20. Kawai M, Yamaue H, Jang JY, Uesaka K, Unno M, Nakamura M, et al. Propensity score-matched analysis of internal stent vs external stent for pancreatojejunostomy during pancreaticoduodenectomy: Japanese-Korean cooperative project. Pancreatology 2020; 20: 984-91.
21. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013; 216: 1-14.
22. Jamjittrong S, Matsuda A, Matsumoto S, Kamonvarapitak T, Sakurazawa N, Kawano Y, et al. Postoperative non-steroidal anti-inflammatory drugs and anastomotic leakage after gastrointestinal anastomoses: systematic review and meta-analysis. Ann Gastroenterol Surg 2019; 4: 64-75.
23. Khajanchee YS, Johnston WC, Cassera MA, Hansen PD, Hammill CW. Characterization of pancreaticojejunal anastomotic healing in a porcine survival model. Surg Innov 2017; 24: 15-22.
24. Katsuno A, Aimoto T, Uchida E, Tabata Y, Miyamoto M, Tajiri T. The controlled release of basic fibroblast growth factor promotes a rapid healing of pancreaticojejunal anastomosis with potent angiogenesis and accelerates apoptosis in granulation tissue. J Surg Res 2011; 167: 166-72.
25. Boesen AK, Maeda Y, Rørbaek Madsen M. Perioperative fluid infusion and its influence on anastomotic leakage after rectal cancer surgery: implications for prevention strategies. Colorectal Dis 2013; 15: e522-7.
26. van Rooijen SJ, Huisman D, Stuijvenberg M, Stens J, Roumen RM, Daams F, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. Int J Surg 2016; 36: 183-200.
27. Lee HG, Heo JS, Choi SH, Choi DW. Management of bleeding from pseudoaneurysms following pancreaticoduodenectomy. World J Gastroenterol 2010; 16: 1239-44.
28. Parmar AD, Sheffield KM, Vargas GM, Pitt HA, Kilbane EM, Hall BL, et al. Factors associated with delayed gastric emptying after pancreaticoduodenectomy. HPB (Oxford) 2013; 15: 763-72.
29. Babazade R, Saasouh W, Naylor AJ, Makarova N, Udeh CI, Turan A, et al. The cost-effectiveness of epidural, patient-controlled intravenous opioid analgesia, or transversus abdominis plane infiltration with liposomal bupivacaine for postoperative pain management. J Clin Anesth 2019; 53: 56-63.
30. Bos EM, Posner KL, Domino KB, de Quelerij M, Kalkman CJ, Hollmann MW, et al. Haematoma, abscess or meningitis after

neuraxial anaesthesia in the USA and the Netherlands: a closed claims analysis. Eur J Anaesthesiol 2020; 37: 743-51.
31. Hogg ME, Zenati M, Novak S, Chen Y, Jun Y, Steve J, et al. Grading of surgeon technical performance predicts postoperative pancreatic fistula for pancreaticoduodenectomy independent of patient-related variables. Ann Surg 2016; 264: 482-91.
32. Kim CG, Jo S, Kim JS. Impact of surgical volume on nationwide hospital mortality after pancreaticoduodenectomy. World J Gastroenterol 2012; 18: 4175-81.
33. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity score methods for estimating marginal odds ratios in case of small sample size. BMC Med Res Methodol 2012; 12: 70.

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