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ORIGINAL ARTICLE

Lactated Ringer's Solution at a Standard Infusion Rate in Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis Prevention: A Retrospective Comparative Study

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Abstract

Background Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is a common complication, and its prevention remains challenging. Although aggressive infusion of lactated Ringer's solution (hereafter Lactated Ringer's) has shown preventive effects, the efficacy of standard infusion rates remains unclear.

Aim To evaluate whether lactated Ringer's administered at a standard rate reduces the incidence or severity of post-ERCP pancreatitis compared with non-lactated Ringer's solutions.

Methods This single-center retrospective study compared patients who received non-lactated Ringer's solutions before January 2019 with those who received lactated Ringer's after January 2019, at a standard rate. The outcomes were post-ERCP pancreatitis incidence, severity, C-reactive protein (CRP) level, and systemic inflammatory response syndrome (SIRS).

Results Of 1194 patients included (median age, 71 years; 60% male), pancreatitis occurred in 5.6% (30/529) of the non-lactated Ringer's group and 5.3% (35/665) of the lactated Ringer's group (P = 0.76). Severe or moderately severe pancreatitis occurred in six patients each in both groups (approximately 1%). Mean CRP level at 24 h was similar between the groups (1.26 vs. 1.44 mg/dL, P = 0.75), and SIRS rates at 24/48 h did not differ significantly (P = 0.61 and 1.00). Multivariate analysis identified pancreatic injection, naïve papilla, and female sex as independent risk factors; fluid type was not associated with outcome (OR 1.09, P = 0.76).

Conclusions Lactated Ringer's at a standard infusion rate did not reduce the incidence or severity of post-ERCP pancreatitis compared with a non-lactated Ringer's solution. Further research is required to optimize fluid therapy for preventing this complication.

Keywords Post-ERCP pancreatitis · Endoscopic retrograde cholangiopancreatography · Lactated ringer's solution · Fluid therapy

Introduction

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is a significant and potentially life-threatening complication of ERCP [1]. Various strategies have been proposed for the prevention of this complication, including rectal administration of diclofenac [2], placement of pancreatic stents [3], administration of nitroglycerin [4], and aggressive fluid infusion [5–9]. Aggressive fluid infusion is considered beneficial for mitigating dehydration caused by inflammation associated with pancreatitis.

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In an initial randomized controlled trial (RCT) reported in 2014, aggressive fluid administration (3 mL/kg/hour during the procedure, followed by a 20 mL/kg bolus immediately after, and then 3 mL/kg/hour for 8 h) significantly reduced the incidence of post-ERCP pancreatitis compared with standard-dose hydration (1.5 mL/kg/hour during and after the procedure) (0% vs. 17%; P = 0.016) [5]. Subsequent RCTs and systematic reviews have consistently confirmed the protective effect of aggressive hydration without an increase in complications such as fluid overload [6–9]. Based on these findings, clinical guidelines recommend aggressive intravenous hydration as a preventive strategy [10–12].

The American Society for Gastrointestinal Endoscopy (ASGE) guidelines advocate aggressive hydration for the prevention of post-ERCP pancreatitis, and recommend its use even in unselected patients, although the supporting trials mainly enrolled younger individuals less prone to fluid overload. In real-world practice, aggressive hydration is often avoided in elderly or comorbid patients, and both the Japanese and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines advise caution in these populations [10–12]. In addition to the infusion volume, the choice of fluid type is also an important consideration in the prevention of post-ERCP pancreatitis. Lactated Ringer's solution is generally preferred over saline because of its favorable metabolic and anti-inflammatory profile, and is endorsed by both ASGE and ESGE. However, evidence regarding its benefit at standard infusion rates remains inconclusive [13].

In this study, we aimed to assess the preventive effects of lactated Ringer's solution without rapid infusion on post-ERCP pancreatitis by examining the incidence and severity of post-ERCP pancreatitis during the two aforementioned periods (pre- and post-2019).

Methods

Study Design

This single-center retrospective study was conducted using the medical records of 1915 patients who underwent ERCP at Kobe University Hospital between June 2017 and June 2020. All patients treated during the specified period were included, while cases that did not conform to the institutional clinical pathway (n = 554) and post-operative cases (n = 167) were excluded. As a result, 1194 patients were deemed eligible and categorized into two groups based on the type of intravenous fluid administered: non-lactated Ringer's solution group (n = 529) and lactated Ringer's solution group (n = 665). This categorization formed the basis for the primary analysis. A secondary analysis was conducted on patients who developed post-ERCP pancreatitis. A summary of the study flow is presented in Fig. 1. The study protocol received approval from the Kobe University Hospital Ethics Committee (No. B230154) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study. All the authors had full access to the study data, reviewed the findings, and approved the final manuscript.

Patients and Data Collection

Patient demographic and clinical data, including age, sex, body temperature, heart rate, respiratory rate, white blood cell count, and levels of C-reactive protein (CRP), amylase, pancreatic amylase, lipase, and total bilirubin, were retrospectively collected. Furthermore, details pertaining to the ERCP procedure, such as indications for the procedure, presence of cholangiography, pancreatic injection, periampullary

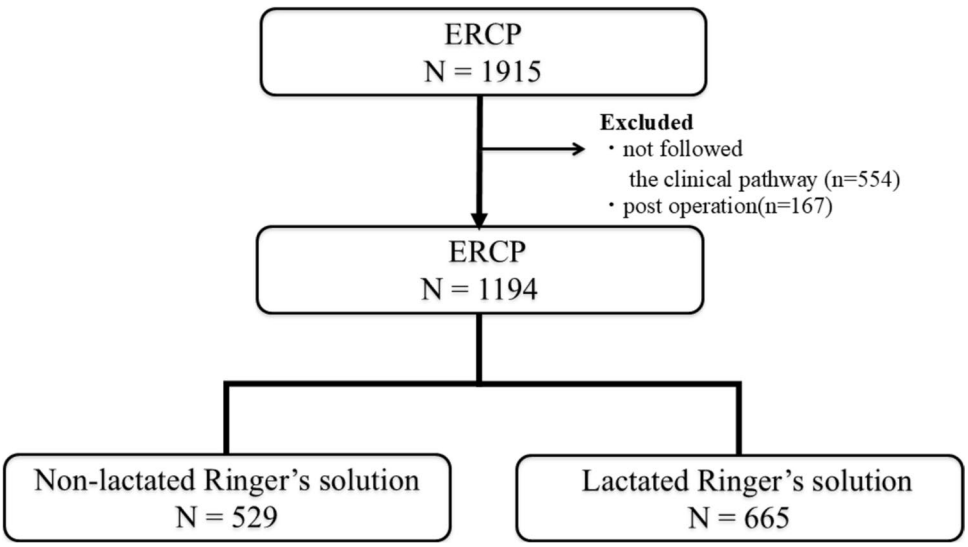

Fig. 1 Inclusion and exclusion criteria. We reviewed 1,915 ERCP cases (June 2017–June 2020). After excluding those not following the clinical pathway (*n* = 554) and post-operative cases (n = 167), 1,194 remained for primary analysis. Of these, 65 developed post-ERCP pancreatitis; 5 lacking 48-h blood data were excluded, leaving 60 for secondary analysis. ERCP endoscopic retrograde cholangiopancreatography

diverticulum, endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), placement of bile duct stents, placement of pancreatic duct stents, administration of diclofenac, occurrence and severity of post-ERCP pancreatitis, and intraoperative and postoperative complications, were retrospectively collected. Additionally, computed tomography (CT) images were reviewed in cases where post-ERCP pancreatitis was clinically suspected.

ERCP Procedure

At our institution, initial biliary cannulation was primarily attempted using a contrast-assisted technique, and guidewire manipulation, when required, was performed by an assistant physician. Endoscopic procedures were performed by operators with varying levels of experience, ranging from trainees to experts. In this study, a trainee was defined as a physician who had performed fewer than 200 ERCP procedures independently. Based on a subset analysis of the study cohort, trainees performed approximately 85% of the ERCP procedures.

Clinical Pathway

At our institution, a clinical pathway—a standardized plan for hospitalization and treatment—is employed for patients undergoing ERCP. This pathway encompasses established protocols that delineate the types and infusion rates of intravenous fluids. Prior to January 2019, the clinical pathway mandated the use of a hypotonic glucose electrolyte solution consisting of 5% dextrose, 0.2% sodium chloride, and 20 mEq/L potassium chloride, administered at a rate of 60 mL/hour. In January 2019, the protocol was revised to specify the administration of 80 mL/hour of lactated Ringer's solution (Fig. 2). Consequently, patients who received the hypotonic glucose-electrolyte solution were classified as the non-lactated Ringer's solution group, whereas those who received lactated Ringer's solution were classified into the lactated Ringer's solution group. According to this pathway, all patients were routinely hospitalized for one day after ERCP for clinical observation. Blood tests, including measurements of amylase, lipase, and CRP, were performed in all patients at 2 and 24 h after ERCP. In the absence of post-ERCP pancreatitis or other complications, the total volume of intravenous fluid administered during the routine post-ERCP hospitalization period was approximately 2000 mL in both groups. Administration of fluid boluses was not included in this protocol and was therefore not performed in the study. Additionally, rectal diclofenac was administered at the discretion of the attending physician and was limited to patients considered to be at high risk for post-ERCP pancreatitis.

Definition of Post-ERCP Pancreatitis

Post-ERCP pancreatitis was diagnosed based on the Cotton classification. While the original definition uses serum amylase, we used serum lipase as a more sensitive biomarker, and defined post-ERCP pancreatitis by the presence of the following three criteria: (1) new or worsened upper abdominal pain consistent with pancreatitis, (2) serum lipase levels ≥ 3 times the upper limit of normal, and (3) prolongation of hospitalization by at least two additional days attributable to pancreatitis [14]. The severity of post-ERCP pancreatitis was classified as mild, moderately severe, or severe, also based on the revised Atlanta classification. Severe pancreatitis was defined as persistent organ failure, moderately severe pancreatitis was defined as organ failure that resolved within 48 h and/or the presence of local or systemic complications without persistent organ failure, and mild pancreatitis was defined as the absence of organ failure and local or systemic complications [15]. Systemic inflammatory response syndrome (SIRS) is diagnosed when at least two of the following four criteria are met: (1) body temperature > 38 ℃

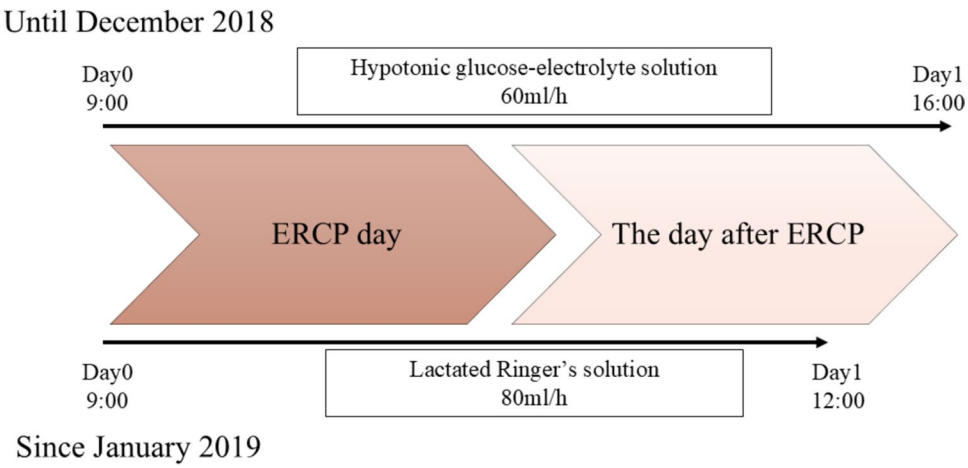

Fig. 2 Clinical pathway. Infusions started at 9:00 a.m. on the day of ERCP. Hypotonic glucose–electrolyte solution ended at 4:00 p.m. on the following day; lactated Ringer's ended at 12:00 p.m. on the following day. ERCP endoscopic retrograde cholangiopancreatography

or < 36 ℃, (2) heart rate > 90 beats per minute, (3) respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg, and (4) white blood cell count > 12,000/mm3 or < 4000/mm3 [16].

Endpoints

The primary endpoint was the incidence of post-ERCP pancreatitis. Secondary endpoints included the severity of post-ERCP pancreatitis, CRP levels, and SIRS at 24 and 48 h post-ERCP.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 29.0.1) and R software (version 4.3.3), with all P values reported as two-sided. Relationships between categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was also applied for binary outcomes. To compare continuous variables such as age, an independent-samples t-test assuming equal variances was conducted. The required sample size was calculated for a two-group comparison of proportions using a two-sided chi-squared test with a significance level of 0.05 and a power of 80% ($\beta = 0.2$). Based on a previous RCT in which the incidence of post-ERCP pancreatitis was 6.7% in the aggressive normal saline group and 3.0% in the aggressive lactated Ringer's solution group [7], we hypothesized that a similar difference might exist between lactated and non-lactated Ringer's solutions when administered at a standard infusion dose. The calculations indicated that approximately 528 patients per group (1054 in total) were required to detect such a difference. The final study cohort included 529 and 665 patients in the non-lactated and lactated Ringer's solution groups, respectively, which exceeded the required sample size. To adjust for potential confounding factors due to differences in baseline characteristics and procedural factors, we applied inverse probability of treatment weighting (IPTW) using propensity scores estimated using logistic regression. The dependent variable was group assignment (non-lactated Ringer's solution vs. lactated Ringer's solution), and independent variables included age, sex, presence of sphincter of Oddi dysfunction (SOD), administration of rectal diclofenac, history of ERCP, post-ERCP pancreatitis, acute pancreatitis, chronic pancreatitis, elevated bilirubin level, presence of a pre-existing bile duct stent, prior endoscopic sphincterotomy (EST), emergency procedure, pancreatic duct injection, use of the double guidewire technique, cannulation time > 15 min, endoscopic papillary balloon dilation (EPBD), use of precut, and performance of cholangioscopy. Unstabilized weights were used, as the distribution of the calculated weights was stable and free of extreme values (median: 1.82; interquartile range: 1.69–2.32; mean: 2.00; maximum: 4.43). Covariate balance before and after weighting was evaluated using absolute standardized mean differences (SMDs), with values < 0.1 considered acceptable. Weighted logistic regression analysis was performed to assess the association between fluid type and the incidence of post-ERCP pancreatitis. Statistical significance was set at $P < 0.05$.

Results

Clinical Background in Primary Analysis.

The clinical background of the patients is summarized in Table 1. While the non-lactated Ringer's solution group demonstrated a higher incidence of a history of post-ERCP pancreatitis and cholecystectomy, no other significant differences were identified in baseline characteristics, including risk factors for post-ERCP pancreatitis as delineated in the ASGE guidelines [1, 17]. The non-lactated Ringer's solution group had a higher frequency of ERCP procedures such as the double-guidewire technique, endoscopic papillary balloon dilation (normal or large) and bile duct stone removal. Conversely, the lactated Ringer's solution group underwent biliary drainage, biliary biopsy/cytology, and cholangioscopy more frequently.

Primary Analysis

No statistically significant difference in the incidence of post-ERCP pancreatitis was observed between the non-lactated and lactated Ringer's solution groups (5.6% vs. 5.3%, $P = 0.76$). Similarly, no significant differences were observed in the incidence of other complications including bleeding, bile duct perforation, post-ERCP cholangitis, and pancreatic fistula (Table 2). No infusion-related complications were observed in either group. Even when the analysis was restricted to cases involving naïve papillae, no significant difference in the incidence of post-ERCP pancreatitis was observed (11.1% [21/188] vs. 10.5% [25/239], $P = 0.81$) (Table 3). Moreover, when the analysis was further limited to patients with a naïve papilla who underwent ERCP for biliary indications—thereby excluding procedures performed for diagnostic or therapeutic purposes involving the pancreatic duct—no significant difference in the incidence of post-ERCP pancreatitis was observed (8.0% [10/124] vs. 6.9% [12/173], $P = 0.81$). Among all patients with a naïve papilla, pancreatic duct injection occurred in 60.4% (258/427) and pancreatic duct stents were placed in 25.3% (108/427). In contrast, in the subset of patients with a naïve papilla who underwent

Table 1 Patient's characteristics and ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) procedure according to fluid type

	All patients (n = 1194)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 529)	Lactated Ringer's solution (n = 665)	
Age (years), average ± SD[b]	69.6 ± 11.8	69.8 ± 11.0	69.7 ± 11.9	0.89
Sex				0.20
Male	715 (59.9%)	306 (57.8%)	409 (61.5%)	
Female	479 (40.1%)	223 (42.2%)	256 (38.5%)	
Naïve papilla	427 (35.8%)	188 (35.5%)	239 (35.9%)	0.89
History of post-ERCP pancreatitis	53 (4.4%)	32 (6.0%)	21 (3.2%)	0.02
History of acute pancreatitis	148 (12.4%)	68 (12.9%)	80 (12.0%)	0.67
History of chronic pancreatitis	151 (12.6%)	62 (11.7%)	89 (13.4%)	0.39
Suspected sphincter of oddi dysfunction	2 (0.2%)	1 (0.2%)	1 (0.2%)	0.87
Elevation of Bilirubin	259 (21.7%)	111 (21.0%)	148 (22.3%)	0.61
Rectal diclofenac	18 (1.5%)	12 (2.3%)	6 (0.9%)	0.06
Peripapillary diverticulum	183 (15.3%)	72 (13.6%)	101 (15.2%)	0.88
Post-cholecystectomy	242 (20.3%)	130 (24.6%)	112 (16.8%)	0.001
Emergency examination	170 (14.2%)	82 (15.5%)	88 (13.2%)	0.27
Cannulation time 15 min ~	184 (15.4%)	87 (16.4%)	97 (14.6%)	0.38
Endoscopic sphincterotomy	281 (23.5%)	117 (22.1%)	164 (24.7%)	0.30
Endoscopic pancreatic sphincterotomy	69 (5.8%)	28 (5.3%)	41 (6.2%)	0.52
Endoscopic papillary (large) balloon dilation	37 (3.1%)	24 (4.5%)	13 (2.0%)	0.01
Precut	20 (1.7%)	10 (1.9%)	10 (1.5%)	0.61
Double guidewire method	111 (9.3%)	63 (11.9%)	48 (7.2%)	0.001
Pancreatic injection	451 (37.8%)	207 (39.1%)	244 (36.7%)	0.39
Intraductal ultrasonography	180 (15.1%)	85 (16.1%)	95 (14.3%)	0.39
Biliary drainage	688 (59.5%)	285 (53.8%)	403 (60.6%)	0.02
Pancreatic drainage	238 (19.9%)	105 (19.8%)	133 (20.0%)	0.95
Biliary cytology / biopsy	200 (16.8%)	66 (12.5%)	134 (20.2%)	0.001
Pancreatic cytology / biopsy	84 (7.0%)	40 (7.0%)	44 (7.0%)	0.53
Bile duct stone removal	314 (26.3%)	160 (30.2%)	154 (23.2%)	0.006
Cholangioscopy	55 (4.6%)	16 (3.0%)	41 (6.2%)	0.011

(%) indicates the proportion of cases with specific clinical features of each case associated with the fluid type before and after ERCP

[a]*ERCP* Endoscopic retrograde cholangiopancreatography, [b]*SD* Standard deviation

ERCP for biliary indications only, pancreatic duct injection occurred in 45.1% (134/297), and prophylactic pancreatic duct stents were placed in 5.7% (17/297).

Regarding risk factors associated with post-ERCP pancreatitis (Table 4), univariate analysis identified pancreatic injection, naïve papilla, SOD, female sex, and double-guidewire method. Conversely, elevated serum bilirubin levels, the presence of a preplaced bile duct stent, post-EST, and emergency procedures were recognized as protective factors. Multivariate analysis, which incorporated these variables along with the type of infusion, revealed that only pancreatic injection, naïve papilla, and female sex remained as significant risk factors, with no protective factors identified. Infusion type was neither a risk nor protective factor.

Given the significant imbalances in several baseline characteristics between the groups and the inclusion of numerous covariates in the multivariate model, IPTW was employed, using propensity scores to mitigate potential confounding factors and prevent model overfitting. Following IPTW adjustment, weighted logistic regression analysis revealed no significant difference in the incidence of post-ERCP pancreatitis between the non-lactated and lactated Ringer's solution groups (odds ratio [OR]: 1.09, 95% confidence interval [CI]: 0.64–1.83, P = 0.76). Covariate balance before and after weighting is depicted in the Fig. 3. Notably, all covariates demonstrated an acceptable balance even before weighting, with absolute SMDs below 0.1. Nonetheless, IPTW was performed to further reduce residual confounding and enhance

Table 2 Complications of ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography)

	All patients (n = 1194)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 529)	Lactated Ringer's solution (n = 665)	
Post-ERCP pancreatitis incidence	65 (5.4%)	30 (5.6%)	35 (5.3%)	0.76
Severity of post-ERCP pancreatitis				0.72
Mild	53 (4.4%)	24 (4.5%)	29 (4.4%)	
Moderately severe	11 (0.9%)	6 (1.1%)	5 (0.8%)	
Severe	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Local complications				
Bleeding	7 (0.6%)	4 (0.8%)	3 (0.5%)	0.49
Bile duct perforation	4 (0.3%)	1 (0.2%)	3 (0.5%)	0.44
Post-ERCP cholangitis	24 (2.0%)	9 (1.7%)	15 (2.3%)	0.54
Pancreatic fistula	5 (0.4%)	2 (0.4%)	3 (0.5%)	0.85

(%) indicates the proportion of cases with specific clinical features of post-ERCP pancreatitis cases with fluid type

[a]*ERCP* endoscopic retrograde cholangiopancreatography

Table 3 Complications of ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) in Patients with Naïve Papilla

	All patients (n = 427)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 188)	Lactated Ringer's solution (n = 239)	
Post-ERCP pancreatitis incidence	46 (10.8%)	21 (11.1%)	25 (10.5%)	0.81
Severity of post-ERCP pancreatitis				0.94
Mild	38 (8.9%)	17 (9.0%)	21 (8.8%)	
Moderately severe	8 (1.9%)	4 (2.1%)	4 (1.7%)	
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Local complications				
Bleeding	5 (1.2%)	4 (2.1%)	1 (0.4%)	0.17
Bile duct perforation	1 (0.2%)	0 (0.0%)	1 (0.4%)	1.00
Post-ERCP cholangitis	7 (1.6%)	3 (1.6%)	4 (1.7%)	1.00
Pancreatic fistula	3 (0.7%)	2 (1.1%)	1 (0.7%)	0.59

(%) indicates the proportion of cases with specific clinical features of post-ERCP pancreatitis cases with fluid type

[a]*ERCP* endoscopic retrograde cholangiopancreatography

the robustness of causal inference; IPTW distribution was stable without extreme values (Fig. 3).

Secondary Endpoint

Among the 65 cases of post-ERCP pancreatitis, 5 were excluded because of missing CRP and/or SIRS data. We further analyzed 60 patients with post-ERCP pancreatitis, comprising 28 in the non-lactated Ringer's solution group and 32 in the lactated Ringer's solution group. The clinical characteristics of the patients are shown in the Table 5. No significant differences were observed in the background characteristics between the two groups. Regarding the ERCP procedure, the non-lactated Ringer's solution group exhibited a higher frequency of pancreatic injection and cholangiography. The severity of post-ERCP pancreatitis was categorized as follows: in the non-lactated Ringer's solution group, 23 cases were mild and 5 were moderately severe, with no severe cases; in the lactated Ringer's solution group, 25 cases were mild, 6 were moderately severe, and 1 was severe. No statistically significant difference in the severity of post-ERCP pancreatitis was observed between the groups (P = 0.63). The mean serum CRP level at 24 h post-ERCP was higher in the non-lactated Ringer's solution group (1.26 ± 1.78 vs. 1.44 ± 2.45), with no significant difference (P = 0.75). At 48 h post-ERCP, the

Table 4 Risk factor analysis of post-ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) pancreatitis

	Univariate OR (95%CI)	P Value	Multivariate OR (95%CI)	P* Value
Type of infusion	0.92 (0.56–1.53)	0.86	0.97 (0.57–1.63)	0.90
Pancreatic injection	3.71 (2.18–6.34)	< 0.001	1.93 (1.02–3.67)	0.04
Naïve papilla	4.75 (2.75–8.23)	< 0.001	2.54 (1.06–6.09)	0.04
Elevation of Bil	0.35 (0.15–0.82)	0.02	0.41 (0.17–1.00)	0.05
Preplaced bile duct stent	0.20 (0.10–0.40)	< 0.001	0.65 (0.24–1.72)	0.38
Post EST[b]	0.25 (0.13–0.48)	< 0.001	0.77 (0.30–1.96)	0.58
Emergency examination	0.28 (0.09–0.90)	0.03	0.44 (0.13–1.48)	0.19
SOD[c]	17.6 (1.01–285.02)	0.043	5.56 (0.32–96.18)	0.24
Female	1.92 (1.16–3.18)	0.01	1.99 (1.18–3.36)	0.01
Double guidewire method	2.14 (1.01–4.24)	0.03	0.91 (0.43–1.94)	0.81
Age < 40 years old	1.16 (0.15–8.95)	0.88		
Cannulation time > 15 min	1.55 (0.84–2.86)	0.16		
History of post ERCP pancreatitis	1.88 (0.72–4.89)	0.20		
History of acute pancreatitis	1.65 (0.86–3.17)	0.13		
History of chronic pancreatitis	1.12 (0.54–2.31)	0.77		
EPBD[d]	1.56 (0.47–5.22)	0.47		
Precut	1.96 (0.45–8.63)	0.37		
Cholangioscopy	0.51 (0.15–2.60)	0.51		

*The odds ratio was adjusted for type of infusion, and each risk factors for post-ERCP pancreatitis

[a]*ERCP* endoscopic retrograde cholangiopancreatography, [b]*EST* endoscopic sphincterotomy, [c]*SOD* sphincter of Oddi dysfunction, [d]*EPBD* endoscopic papillary balloon dilation

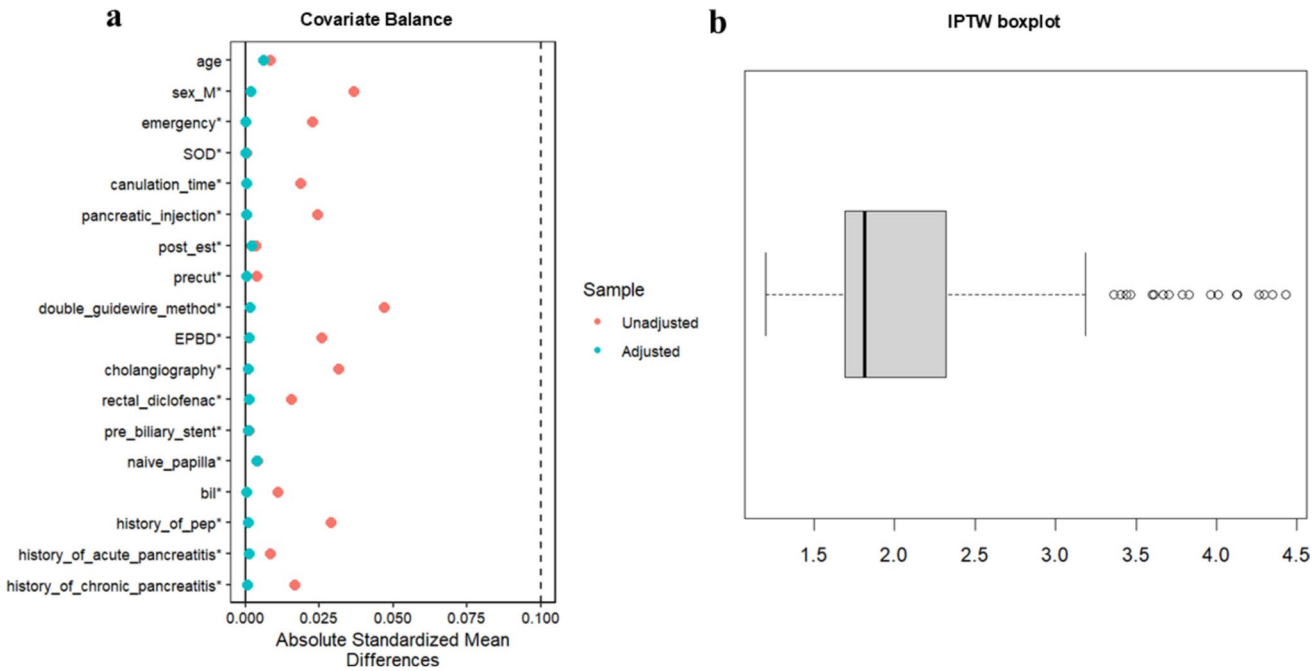

Fig. 3 Covariate balance and IPTW distribution. **a** Standardized mean difference (SMDs) of covariates before and after inverse probability of treatment weighting (IPTW) based on propensity scores. All covariates achieved an acceptable balance after weighting, with the SMDs reduced to below 0.1. **b** Box plot of IPTW distribution. The median weight was 1.83 (interquartile range: 1.69–2.32), the mean was 2.00, and the maximum was 4.43. No extreme weights were observed and the distribution was within an acceptable range, indicating the stability of the weighting procedure

Table 5 Characteristics and ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) procedures among patients with post-ERCP pancreatitis, according to fluid type

Characteristics and ERCP procedure	All patients (n = 60)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 28)	Lactated Ringer's solution (n = 32)	
Age (years), Average (SD[b])	68.8 ± 10.1	69.1 ± 9.5	68.3 ± 11.1	0.77
Sex				0.33
Male	26 (43.3%)	14 (50.0%)	12 (37.5%)	
Female	34 (56.7%)	14 (50.0%)	20 (62.5%)	
Naïve papilla	42 (70.0%)	19 (67.9%)	23 (71.9%)	0.74
History of post-ERCP pancreatitis	5 (8.3%)	2 (7.1%)	3 (8.6%)	1.00
History of acute pancreatitis	11 (17.7%)	8 (28.6%)	3 (8.6%)	0.06
History of chronic pancreatitis	8 (18.3%)	6 (21.4%)	2 (6.3%)	0.08
Suspected sphincter of Oddi dysfunction	1 (1.7%)	0 (0.0%)	1 (3.1%)	1.00
Elevation of Bilirubin	6 (10.0%)	3 (10.7%)	3 (8.6%)	1.00
Rectal diclofenac administration	5 (8.3%)	4 (14.3%)	1 (3.1%)	0.11
Peripapillary diverticulum	12 (20.0%)	6 (21.4%)	6 (18.8%)	0.80
Post-cholecystectomy	11 (17.7%)	5 (17.9%)	6 (18.8)	1.00
Emergency examination	3 (5.0%)	1 (3.6%)	2 (6.3%)	1.00
Cannulation time 15 min ~	12 (20.0%)	5 (17.9%)	7 (21.9%)	0.76
Endoscopic sphincterotomy	12 (20.0%)	5 (17.9%)	7 (21.9%)	0.76
Endoscopic pancreatic sphincterotomy	11 (17.7%)	5 (17.9%)	6 (18.8%)	1.00
Endoscopic papillary (large) balloon dilation	2 (3.3%)	1 (3.6%)	1 (3.1%)	1.00
Precut	2 (3.3%)	1 (3.6%)	1 (3.1%)	1.00
Double guidewire method	9 (15.0%)	5 (17.9%)	4 (12.5%)	0.49
Pancreatic injection	41 (68.3%)	23 (82.1%)	18 (56.3%)	0.03
Cholangiography	34 (56.7%)	12 (42.9%)	22 (68.8%)	0.04
Intraductal ultrasonography	16 (26.7%)	7 (25.0%)	9 (28.1%)	0.79
Biliary drainage	20 (33.3%)	7 (25.0%)	13 (40.6%)	0.20
Pancreatic drainage	23 (38.3%)	13 (46.4%)	8 (25.0%)	0.08
Biliary biopsy/ cytology	15 (25.0%)	4 (14.3%)	11 (34.4%)	0.08
Pancreatic biopsy/ cytology	10 (16.7%)	6 (21.4%)	4 (12.5%)	0.49
Bile duct stone removal	12 (20.0%)	6 (21.4%)	6 (18.8%)	0.80
Cholangioscopy	2 (3.3%)	1 (3.6%)	1 (3.1%)	1.00

(%) indicates the proportion of cases with specific clinical features of each case associated with the fluid type before and after ERCP

[a]*ERCP* Endoscopic retrograde cholangiopancreatography, [b]*SD* Standard deviation

mean serum CRP level was 4.67 ± 5.15 mg/dL in the non-lactated Ringer's solution group and 4.26 ± 4.69 mg/dL in the lactated Ringer's solution group, also showing no significant difference (P = 0.75). At 24 h post-ERCP, one case of SIRS was observed in the non-lactated Ringer's solution group, whereas three cases were identified in the lactated Ringer's solution group; however, this difference was not statistically significant (P = 0.61). At 48 h post-ERCP, SIRS was present in one case both in the non-lactated Ringer's solution group and the lactated Ringer's solution group, with no significant difference between the groups (P = 1.00) (Table 6). Even when limited to cases with naïve papillae, the severity of post-ERCP pancreatitis did not significantly differ between the groups (P = 0.71), with moderately severe cases observed in four patients (22.2%) in the non-lactated Ringer's solution group and four patients (17.4%) in the lactated Ringer's solution group, and no severe cases in either group. SIRS positivity was also comparable between the groups at 24 h (0.0% vs. 8.7%, P = 0.50) and 48 h (5.6% vs. 4.3%, P = 1.00) post-ERCP. The mean CRP level at 24 h was 0.75 ± 0.99 mg/dL in the non-lactated Ringer's group and 1.34 ± 2.74 mg/dL in the lactated Ringer's group (P = 0.39), while at 48 h it was 3.52 ± 3.09 mg/dL and 4.41 ± 4.56 mg/dL, respectively (P = 0.48) (Table 7).

Table 6 Severity of post-ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) pancreatitis, SIRS and mean C-reactive protein at 24 or 48 h after ERCP

	All patients (n = 60)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 28)	Lactated Ringer's solution (n = 32)	
Severity of post-ERCP pancreatitis				0.63
Mild	48 (80.0%)	23 (82.1%)	25 (78.1%)	
Moderate	11 (18.3%)	5 (17.9%)	6 (18.8%)	
Severe	1 (1.7%)	0 (0.0%)	1 (3.1%)	
SIRS[b] positive				
At 24 h after ERCP	4 (6.7%)	1 (3.6%)	3 (9.4%)	0.61
At 48 h after ERCP	3 (5.0%)	1 (3.6%)	1 (3.1%)	1.00
Mean C-reactive protein				
At 24 h after ERCP		1.26 ± 1.78	1.44 ± 2.45	0.75
At 48 h after ERCP		4.67 ± 5.15	4.26 ± 4.69	0.75

(%) indicates the proportion of cases with specific clinical features of post-ERCP pancreatitis cases with fluid type

[a]*ERCP* Endoscopic retrograde cholangiopancreatography, [b]*SIRS* Systemic inflammatory response syndrome

Table 7 Severity of Post-ERCP(*ERCP* Endoscopic retrograde cholangiopancreatography) Pancreatitis, SIRS(*SIRS* Systemic inflammatory response syndrome) and Mean C-Reactive Protein Levels at 24 and 48 h After ERCP in Patients with Naïve Papilla

	All patients (n = 41)	Fluid type		*P* value
		Non-lactated Ringer's solution (n = 18)	Lactated Ringer's solution (n = 23)	
Severity of post-ERCP pancreatitis				0.71
Mild	33 (80.5%)	14 (77.8%)	19 (82.6%)	
Moderate	8 (19.5%)	4 (22.2%)	4 (17.4%)	
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	
SIRS positive				
At 24 h after ERCP	2 (4.9%)	0 (0.0%)	2 (8.7%)	0.50
At 48 h after ERCP	2 (4.9%)	1 (5.6%)	1 (4.3%)	1.00
Mean C-reactive protein				
At 24 h after ERCP		0.75 ± 0.99	1.34 ± 2.74	0.39
At 48 h after ERCP		3.52 ± 3.09	4.41 ± 4.56	0.48

(%) indicates the proportion of cases with specific clinical features of post-ERCP pancreatitis cases with fluid type

[a]*ERCP* Endoscopic retrograde cholangiopancreatography, [b]*SIRS* Systemic inflammatory response syndrome

Discussion

In this study, we examined the effect of fluids administered at a standard infusion rate on the prevention of post-ERCP pancreatitis. To our knowledge, no previous study has been conducted to specifically evaluate the efficacy of a standard dose of lactated Ringer's solution in this context. Our analysis did not show a statistically significant difference in the incidence of post-ERCP pancreatitis between the different fluid types. This finding indicates that under standard infusion conditions, the type of fluid used may not significantly influence the risk of post-ERCP pancreatitis.

Lactated Ringer's solution is widely considered advantageous in the treatment of acute pancreatitis, primarily because of its composition as an extracellular fluid, which contributes to maintaining effective microcirculatory perfusion, an essential factor in preventing pancreatic ischemia and mitigating disease severity. In addition, it is less likely to induce metabolic acidosis and has anti-inflammatory properties. Experimental studies have shown that lactate activates G-protein-coupled receptor 81 (GPR81), which subsequently inhibits the activation of the NLRP3 inflammasome, reduces

interleukin-1β production, and alleviates pancreatic inflammation [13]. Because of these anti-inflammatory mechanisms, lactated Ringer's solution is the preferred fluid for studies evaluating the efficacy of aggressive hydration protocols. Consequently, several clinical guidelines advocate the use of lactated Ringer's solution to prevent post-ERCP pancreatitis. However, in the present study, no significant benefit was observed in the prevention of post-ERCP pancreatitis. This prompts the question of why lactated Ringer's solution, which has shown both mechanistic and limited clinical benefits, did not provide an advantage in our study. One potential explanation is that the anti-inflammatory effects of lactated Ringer's solution may not be fully realized at a standard infusion rate, likely necessitating a higher total volume or more rapid administration to achieve a clinically meaningful benefit.

The preventive efficacy of aggressive hydration using lactated Ringer's solution has been substantiated in several RCTs [5–9], consistently demonstrating its superiority over standard-dose infusion. Nonetheless, the patient cohorts included in these RCTs were frequently younger and healthier than those typically encountered in clinical practice. Indeed, many RCTs may have excluded elderly patients and those at an elevated risk of complications from large-volume hydration, such as individuals with compromised cardiac or renal function, resulting in study populations that do not fully represent routine clinical settings. This exclusion likely reflects concerns about fluid overload and other adverse effects associated with aggressive hydration. Supporting this concern, de Madaria et al. reported that aggressive hydration protocols may lead to complications such as fluid overload in the management of acute pancreatitis [18]. Although prevention and treatment contexts differ, these findings highlight the inherent risks associated with aggressive hydration strategies. Therefore, although aggressive hydration may be effective in reducing the risk of post-ERCP pancreatitis, its routine application may be limited in elderly patients and those with significant comorbidities owing to safety concerns. In Japan, patients undergoing ERCP in daily practice are frequently elderly and have multiple comorbidities. Accordingly, the Japanese clinical practice guidelines for the management of post-ERCP pancreatitis do not endorse aggressive hydration [11]. At our institution, we therefore adopted a standardized clinical pathway using standard-rate hydration in order to prioritize patient safety in this real-world population. Consequently, further research is warranted to develop improved hydration protocols that are both effective and feasible in these patient populations.

In our cohort, the overall incidence of post-ERCP pancreatitis was 5.4%, but it increased to 10.8% among patients with a naïve papilla, which is slightly higher than previously reported rates. One possible reason for this is that a substantial number of procedures involved diagnostic or therapeutic interventions related to the pancreatic duct. In fact, among patients with a naïve papilla who underwent ERCP for biliary indications only, the incidence was 7.4%. According to previous reports, the incidence of post-ERCP pancreatitis has been reported to be approximately 8% in average-risk patients, approximately 15% in high-risk patients [10], and around 10–11% in patients managed with standard hydration [7.8]. Taken together, these data indicate that the incidence observed in the present study falls within the expected range.

In our study, we identified pancreatic injection, naïve papilla, and female sex as risk factors for post-ERCP pancreatitis, consistent with previous reports. Furthermore, unmeasured confounding variables, such as operator experience or procedural complexity, may have influenced the outcomes. Therefore, these factors should be addressed in future prospective studies.

Our study has several limitations. First, the non-lactated and lactated Ringer's solution groups were derived from different time periods, raising the possibility of unmeasured differences in operator techniques or procedural factors that could not be fully adjusted. Second, following the suspicion of post-ERCP pancreatitis, the determination of the type and volume of intravenous fluid was left to the discretion of individual physicians. This approach is based on the clinical pathway at our institution, which focuses on the prevention of post-ERCP pancreatitis; however, once pancreatitis is suspected, aggressive fluid administration is typically initiated as part of the standard treatment protocol. Third, although the total infusion volume was comparable between the groups, the infusion rates differed: 60 mL/hour in the non-lactated Ringer's solution group and 80 mL/hour in the lactated Ringer's solution group. Nevertheless, given that no preventive effect was observed even with a relatively faster infusion rate in the lactated Ringer's group, the impact of this difference is considered limited. Furthermore, when calculated for a 60 kg body weight, the infusion rate in our study was approximately 1.0–1.3 mL/kg/hour, which is slower than the standard rate of 1.5 mL/kg/hour reported in the literature. This discrepancy likely reflects the retrospective design of the study and the fact that infusion rates were determined according to routine clinical practice and therefore may not fully align with those in previous reports.

In conclusion, the findings of our study suggest that administering lactated Ringer's solution at a standard infusion rate does not offer a significant benefit in preventing post-ERCP pancreatitis. Further research is required to optimize the fluid therapy to prevent post-ERCP pancreatitis.

Author Contributions Tetsuhisa Ko collected and analyzed data and wrote the manuscript. Arata Sakai designed the study concept, analyzed data, and wrote the manuscript. Ryota Nakano, Masahiro Tsujimae, Masanori Gonda, Noriko Inomata, Hisahiro Uemura, Shinya Kohashi, Kae Nagao, Yoshiyuki Harada, Mika Miki, Yosuke Irie,

Noriko Juri, Yuki Oka, Yusuke Yokotani, Akira Shirohata, Kenta Yamamoto, Kaoruko Kanamaru, and Takafumi Tokunaga collected, analyzed, and interpreted data. Takashi Kobayashi, Atsuhiro Masuda, Hideyuki Shiomi, Norimitsu Uza and Yuzo Kodama were involved in study supervision and revised the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interest The authors declare no competing interests.

Ethical approval The study protocol received approval from the Kobe University Hospital Ethics Committee (No. B230154).

Consent to participate The requirement for informed consent was waived due to the retrospective nature of the study.

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