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Continuous Regional Arterial Infusion of Protease Inhibitors Has No Efficacy in the Treatment of Severe Acute Pancreatitis

A Retrospective Multicenter Cohort Study

Masayasu Horibe, MD,† Mitsuhito Sasaki, MD,‡ Masamitsu Sanui, MD, PhD,§ Daisuke Sugiyama, MD, PhD,|| Eisuke Iwasaki, MD, PhD,* Yoshiyuki Yamagishi, MD, PhD,* Hirotaka Sawano, MD, PhD,¶ Takashi Goto, MD,# Tsukasa Ikeura, MD, PhD,** Tsuyoshi Hamada, MD, PhD,†† Takuya Oda, MD,‡‡ Hideto Yasuda, MD,§§ Wataru Shinomiya, MD,† Dai Miyazaki, MD,|||| Kaoru Hirose, MD,¶¶ Katsuya Kitamura, MD, PhD,## Nobutaka Chiba, MD, PhD,*** Tetsu Ozaki, MD,††† Takahiro Yamashita, MD,‡‡‡ Toshitaka Koinuma, MD,§§§ Taku Oshima, MD, PhD,|||||| Tomonori Yamamoto, MD,¶¶¶ Morihisa Hirota, MD, PhD,### Takashi Moriya, MD, PhD,**** Kunihiro Shirai, MD, PhD,†††† Toshihiko Mayumi, MD, PhD,‡‡‡‡ and Takanori Kanai, MD, PhD**

Objective: The aim of this study is to assess the effectiveness of continuous regional arterial infusion (CRAI) of protease inhibitors in patients with severe acute pancreatitis (SAP) including acute necrotizing pancreatitis.

Methods: This retrospective study was conducted among 44 institutions in Japan from 2009 to 2013. Patients 18 years or older diagnosed with SAP according to the criteria of the Japanese Ministry of Health, Labour and Welfare study group (2008) were consecutively enrolled. We evaluated the association between CRAI of protease inhibitors and mortality, incidence of infection, and the need for surgical intervention using multivariable logistic regression analysis.

Results: Of 1159 patients admitted, 1097 patients with all required data were included for analysis. Three hundred and seventy-four (34.1%) patients underwent CRAI of protease inhibitors and 723 (65.9%) did not. In multivariable analysis, CRAI of protease inhibitors was not associated with a reduction in mortality, infection rate, or need for surgical intervention (odds ratio [OR] 0.79, 95% confidence interval [CI] 0.47–1.32, $P = 0.36$; OR 0.97, 95% CI 0.61–1.54, $P = 0.89$; OR 0.76, 95% CI 0.50–1.15, $P = 0.19$; respectively).

Conclusions: Continuous regional arterial infusion of protease inhibitors was not efficacious in the treatment of patients with SAP.

Key Words: continuous regional arterial infusion, protease inhibitors, severe acute pancreatitis, treatment, acute necrotizing pancreatitis

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Acute pancreatitis is a common disease, but the severe form of the illness is associated with high morbidity and mortality. In the United States, more than 220,000 patients with acute pancreatitis are hospitalized each year.[1] Of these, 15% to 25% are classified with severe acute pancreatitis (SAP) with a mortality rate as high as 30%.[1–3] In Japan, the mortality in patients with SAP, including acute necrotizing pancreatitis (ANP), is approximately 17.1% to 28.1% based on previous studies.[4–6]

As a potential therapeutic option for patients with SAP, protease inhibitors exert broad inhibitory actions on pancreatic enzymes, systemic coagulation, and production of cytokines.[7] In a meta-analysis, however, intravenous administration of protease inhibitors was not associated with favorable clinical outcomes such as reduced mortality rate or the need for surgical intervention, which suggests that an adequate concentration of the drug cannot be achieved, and effects on tissue arterial microcirculation are suboptimal with the intravenous formulation used.[8,9] For this reason, continuous regional arterial infusion (CRAI) of protease inhibitors, with direct delivery of a protease inhibitor into the pancreatic circulation, was proposed to potentially reduce the mortality rate and prevent the development of pancreatic infection in patients

From the *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine; †Department of Gastroenterology and Hepatology, Tokyo Metropolitan Tama Medical Center; ‡Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo; §Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama; ||Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo; ¶Senri Critical Care Medical Center, Osaka Saiseikai Senri Hospital, Osaka; #Department of Anesthesiology and Intensive Care, Hiroshima City Hiroshima Citizens Hospital, Hiroshima; **The Third Department of Internal Medicine, Kansai Medical University, Osaka; ††Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo; ‡‡Department of General Internal Medicine, Iizuka Hospital, Fukuoka; §§Department of Emergency and Critical Care Medicine, Japanese Red Cross Musashino Hospital, Tokyo; ||||Advanced Emergency Medical and Critical Care Center, Japanese Red Cross Maebashi Hospital, Gunma; ¶¶Department of Emergency Medicine, Shonan Kamakura General Hospital, Kanagawa; ##Division of Gastroenterology, Department of Medicine, Showa University School of Medicine; ***Department of Emergency and Critical Care Medicine, Nihon University Hospital, Tokyo; †††Department of Acute Care and General Medicine, Saiseikai Kumamoto Hospital, Kumamoto;‡‡‡Emergency Medical Center, Fukuyama City Hospital, Hiroshima; §§§Division of Intensive Care, Department of Anesthesiology and Intensive Care Medicine, Jichi Medical University School of Medicine, Tochigi; ||||||Department of Traumatology and Critical Care Medicine, Chiba University Graduate School of Medicine, Chiba; ¶¶¶Department of Critical Care Medicine, Osaka City University, Osaka; ###Division of Gastroenterology, Tohoku University Hospital, Miyagi; ****Division of Emergency and Critical Care Medicine, Department of Acute Medicine, Nihon University School of Medicine, Tokyo; ††††Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, Gifu; and ‡‡‡‡Department of Emergency Medicine, School of Medicine University of Occupational and Environmental Health, Fukuoka, Japan.

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Address correspondence to: Masamitsu Sanui, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, 1-847 Amanumachou, Omiya-ku, Saitama, 330-8503, Japan (e-mail: msanui@mac.com).

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with ANP rather than SAP.[10] Subsequently, a randomized controlled trial (RCT) conducted by Piascik et al[11] showed that CRAI of protease inhibitors significantly reduced the mortality rate and surgical intervention rate with SAP. However, in a multicenter retrospective study using a national administrative database with mild and severe acute pancreatitis, CRAI was not independently associated with hospital mortality.[12] A recent systematic review demonstrated that the impact of CRAI of protease inhibitors in patients with SAP or ANP was inconclusive.[6]

To date, there have been no large multicenter trials or observational studies with multivariable analyses for the assessment of outcomes after CRAI of protease inhibitors for the treatment of patients with SAP or ANP. Existing studies either have numerous limitations in the study design or have been conducted as literature reviews, which include studies of various quality. Therefore, the effectiveness of CRAI of protease inhibitors is still unknown. This large multicenter retrospective observational study was conducted to investigate the effectiveness of CRAI of protease inhibitors in the treatment of patients with SAP including ANP.

MATERIALS AND METHODS

This study was approved by the Japanese Society of Intensive Care Medicine (No. 0004) and reviewed and approved by the institutional review board of the Tama Medical Center and was registered with the University Hospital Medical Information Network (No. 000012220). The institutional review board at each participating institution approved the study protocol, with the informed consent process waived based on the study design. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology Statement guidelines.[13]

Study Design and Patients

This retrospective multicenter study was performed at 44 institutions in Japan. Twenty-five institutions were tertiary academic medical centers, and the others were community hospitals with intensive care units. All consecutive patients 18 years or older diagnosed with SAP, including ANP, between June 1, 2009, and December 31, 2013, were enrolled. Severe acute pancreatitis, including ANP, was diagnosed based on the criteria of the Japanese Ministry of Health, Labour and Welfare study group for acute pancreatitis severity (2008) (Table 1) when the total prognostic factor score was 3 points or more, or computed tomography (CT) grade was 2 or more.[14] Computed tomography scans were evaluated by physicians in each institution. Data were collected in each participating institution between November 2013 and November 2014.

Continuous Regional Arterial Infusion of Protease Inhibitors

Briefly, the CRAI techniques used are described as follows. To initiate CRAI of protease inhibitors, a catheter was inserted through the femoral artery, and the tip of the catheter was placed in the celiac artery or a branch of the celiac artery, which perfused the actively inflamed region of the pancreas based on the angiographic findings. When the actively inflamed region was in the head of the pancreas, the tip of the catheter was placed in the celiac artery, common hepatic artery, or gastroduodenal artery at the discretion of the physician-in-charge. When the involved region was in the body or tail of the pancreas, the tip of the catheter was placed in the celiac or splenic arteries. Although this practice was most commonly performed, some institutions had a preference for simultaneous catheterization of the superior mesenteric artery to prevent ischemia of the intestine. A protease inhibitor, including nafamostat mesilate, gabexate mesilate, or ulinastatin, was continuously infused through the catheters. Typically, CRAI was started within 72 hours after the onset of pancreatitis, and the most common duration of infusion was 5 days.[10,11] Carbapenem along with CRAI of protease inhibitors was generally used 2 or 3 times per day as antibiotic prophylaxis.

TABLE 1. The Severity Scoring System for Acute Pancreatitis of the Japanese Ministry of Health, Labour and Welfare (2008)

Prognostic Factors (1 Point for Each Factor)	
1. Base excess ≤ -3 mEq/L or shock (systolic blood pressure < 80 mm Hg)	
2. PaO_2 ≤ 60 mm Hg (room air) or ventilatory failure (ventilator management is needed)	
3. BUN ≥ 40 mg/dL (or Cr ≥ 2.0 mg/dL) or oliguria (daily urine output < 400 mL even after IV fluid resuscitation)	
4. LDH ≥ 2 times upper limit of normal	
5. Platelet count ≤ 100,000/mm^3	
6. Serum Ca ≤ 7.5 mg/dL	
7. CRP ≥ 15 mg/dL	
8. Number of positive measures in SIRS criteria ≥ 3	
9. Age ≥ 70 y	
CT Grade By Contrast-Enhanced CT	
1. Extrapancreatic progression of inflammation	
Anterior pararenal space	0 point
Root of mesocolon	1 point
Beyond lower pole of kidney	2 points
2. Hypoenhanced lesion of the pancreas	
The pancreas is conveniently divided into 3 segments (head, body, and tail).	
Localized in each segment or only surrounding the pancreas	0 point
Covers 2 segments	1 point
Occupies entire 2 segments or more	2 points
1 + 2 = total scores	
Total score = 0 or 1	Grade 1
Total score = 2	Grade 2
Total score = 3 or more	Grade 3

Measures in SIRS diagnostic criteria: (1) temperature, > 38°C or < 36°C; (2) heart rate, > 90 beats/min; (3) ventilatory rate, > 20 breaths/min or $PaCO_2$ < 32 torr; (4) WBC, > 12,000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms.

BUN indicates blood urea nitrogen; IV, intravenous; CRP, C-reactive protein; LDH, lactate dehydrogenase; PaO_2, partial pressure of oxygen in blood; SIRS, systemic inflammatory response syndrome; and WBC, white blood cell.

Outcomes

The primary outcome of this study was in-hospital mortality. Secondary outcomes included the incidence of pancreatic infection, the need for surgical intervention, and the incidence of infusion-related complications including catheter obstruction, displacement, thrombosis, damage of catheter, hematoma at the catheter insertion site, and self-decannulation. We defined pancreatic infection as the presence of bacteria based on blood culture or local culture obtained by percutaneous, image-guided, or endoscopic fine-needle aspiration or the presence of extraluminal gas in the pancreatic and/or peripancreatic tissues on contrast-enhanced CT.[15] Surgical interventions included percutaneous, endoscopic, laparoscopic or laparotomy drainage or necrosectomy for infected acute necrotic collection or walled-off necrosis, interventional radiology or endoscopic treatment for bleeding, and the like.

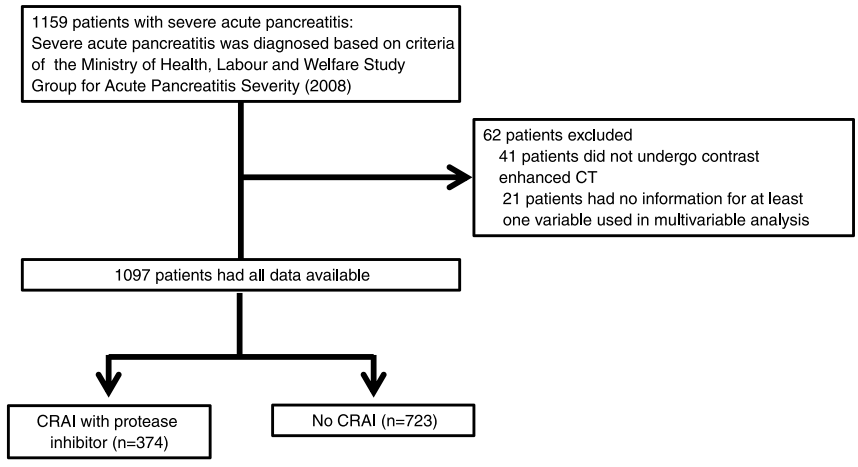

FIGURE 1. Study schema.

Statistical Analysis

We evaluated the association between CRAI of protease inhibitors and mortality, incidence of infection, and the requirement for surgical intervention using multivariable logistic regression analysis adjusted by age, sex, etiology, acute physiology and chronic health evaluation (APACHE) II, prognostic factor score (severity scoring system for acute pancreatitis of the Japanese Ministry of Health, Labour and Welfare, 2008) (Table 1), Charlson index, CT severity index (grading of pancreatitis), CT severity index (pancreatic necrosis), enteral feeding within the first 48 hours, the amount of administered fluid volume within the first 24 hours, hemodiafiltration due to acute renal failure, mechanical ventilation, and prophylactic antibiotics.[16–18] Four categories (alcohol, cholelithiasis, idiopathic, and miscellaneous) were extracted from the literature as the etiologies of pancreatitis.[19–21]

We also performed propensity score–matched sensitivity analyses. Propensity score was calculated for the probability of CRAI with the same variables used in the multivariable analyses. We used a matching technique to create a one-to-one match by the nearest-neighbor approach within a caliper less than 0.25 standard deviation (SD) of the estimated propensity scores.

For preplanned subgroup analysis, we performed a stratified analysis based on the area of pancreatic necrosis: area over 30% and area over 50% of the whole pancreas. A 2-sided *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed with R version 3.0.4 (the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Flow and Patients' Characteristics

Of 1159 patients with SAP, 41 did not undergo contrast-enhanced CT scan, and 21 patients had at least 1 missing data point for variables used in the multivariable analysis. The remaining 1097 patients had data for all variables evaluated and were included for further analysis (Fig. 1). Three hundred seventy-four (34.2%) patients underwent CRAI of protease inhibitors, whereas the remaining 723 (65.8%) patients did not. The incidence of infusion-related complications was 7.7% (29/374) (Table 2). The demographic characteristics and outcomes are shown in Table 3. Based on the univariable analysis, the mortality, incidence of infection, and the need for surgical intervention in the CRAI group were significantly higher than in the non-CRAI group. The odds ratios (ORs) were 2.03 (95% CI [confidence interval], 1.41–2.92) for mortality, 2.37 (95% CI, 1.65–3.41) for the incidence of infection, and 1.83 (95% CI, 1.33–2.51) for the need for surgical intervention by univariable analysis.

Results in Patients With SAP Using Multivariable Analysis

As compared with the non-CRAI control group, the OR for mortality in the CRAI group was 0.79 (95% CI, 0.47–1.32; $P = 0.36$) as adjusted by using the multivariable analysis (Table 4). Age, area of pancreatic necrosis, need for dialysis due to renal failure, and use of the ventilator were significantly associated with increased mortality, whereas enteral feeding within the first 48 hours was significantly associated with a reduction in mortality. The ORs for infection and the need for surgical intervention in the CRAI group compared with the non-CRAI control group were 0.97 (95% CI, 0.61–1.54; $P = 0.89$) and 0.76 (95% CI, 0.50–1.15; $P = 0.19$), respectively (Table 4).

After propensity matching, 284 matched pairs were generated from 374 CRAI patients and 723 non-CRAI patients in a one-to-one manner. As compared with the non-CRAI control group, the estimated ORs for mortality rate, infection rate, and the need for surgical intervention in the CRAI group after matching were 0.94 (95% CI, 0.59–1.51; $P = 0.81$), 0.92 (95% CI, 0.58–1.46; $P = 0.72$), and 0.75 (95% CI, 0.50–1.14; $P = 0.18$), respectively.

Subgroup Analysis Based on the Area of Involved Pancreas

Continuous regional arterial infusion was originally developed for patients with ANP but not for those with SAP.[10] Thus,

TABLE 2. Complications Associated With Catheters Used for Arterial Infusion (n = 374)

Complication	N = 29
Catheter obstruction, n (%)	13 (3.48)
Displacement, n (%)	8 (2.14)
Thrombosis, n (%)	3 (0.80)
Damage of catheter, n (%)	3 (0.80)
Hematoma on catheter insertion site, n (%)	1 (0.27)
Self-decannulation, n (%)	1 (0.27)

TABLE 3. Demographic Characteristics of the CRAI Group and the Non–CRAI Group

	All Patients (N = 1097)	CRAI Group (N = 374)	Non–CRAI Group (N = 723)	Univariable *P*
Characteristics				
Age, mean (SD), y	58.7 (17.5)	57.7 (17.2)	59.2 (17.7)	0.18
Sex, male, n (%)	740 (67.7)	265 (70.9)	475 (65.7)	0.08
Etiologic factor, n (%)				0.05
Alcohol	436 (39.7)	166 (44.3)	270 (37.3)	
Cholelithiasis	230 (21.0)	69 (18.4)	161 (22.2)	
Idiopathic	227 (20.7)	82 (21.9)	145 (20.1)	
Post–ERCP	101 (9.21)	30 (8.00)	71 (9.82)	
Hyperlipidemia	24 (2.19)	9 (2.40)	15 (2.08)	
Miscellaneous	79 (7.20)	18 (4.80)	61 (8.44)	
APACHE II, mean (SD)	12.8 (7.60)	14.3 (7.8)	12.0 (7.39)	**<0.001**
Prognostic factor score, mean (SD)	3.04 (2.25)	3.67 (2.26)	2.71 (2.18)	**<0.001**
Charlson index, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	**<0.05**
CTSI (grading of pancreatitis), median (IQR)	4 (4–4)	4 (4–4)	4 (4–4)	**<0.001**
CTSI (pancreatic necrosis), median (IQR)	0 (0–2)	2 (0–4)	0 (0–2)	**<0.001**
CTSI (total), median (IQR)	4 (4–6)	4 (4–8)	4 (4–4)	**<0.001**
Atlanta classification,[15] n (%)				**<0.001**
Mild acute pancreatitis	312 (28.4)	66 (17.6)	246 (34.0)	
Moderately SAP	417 (38.0)	117 (31.3)	300 (41.5)	
SAP	368 (33.5)	191 (51.1)	177 (24.5)	
Treatment				
Enteral feeding within first 48 h, n (%)	299 (27.3)	116 (31.0)	183 (25.3)	**<0.05**
The amount of infused volume within first 24 h, mean (SD)	5618 (3038)	6607 (3162)	5106 (2839)	**<0.001**
Dialysis due to renal failure, n (%)	162 (14.8)	81 (21.7)	81 (11.2)	**<0.001**
Use of ventilator, n (%)	330 (30.1)	182 (48.7)	148 (20.5)	**<0.001**
Preventive antibiotic, n (%)	850 (77.5)	237 (63.4)	613 (84.8)	**<0.001**
Outcomes				
Mortality, n (%)	135 (12.3)	66 (17.6)	69 (9.54)	**<0.001**
Infection, n (%)	136 (12.4)	71 (18.9)	65 (8.99)	**<0.001**
Surgical intervention, n (%)	173 (15.8)	88 (23.5)	104 (14.4)	**<0.001**

The bold values indicate that there was a significant difference.

ERCP indicates endoscopic retrograde cholangiopancreatography; CTSI, computerized tomography severity index; and IQR, interquartile range.

we performed a stratified analysis based on the area involved by pancreatic necrosis. There were 213 patients who had more than 30% of the pancreas involved with necrosis and 101 patients with more than 50% involved. As compared with the non-CRAI control group, the estimated ORs for mortality, infection rate, and the need for surgical intervention in the CRAI group as adjusted by using the multivariable analyses are shown in Figures 2, 3, and 4, respectively. In the group with more than 50% of the area involved with pancreatic necrosis, the requirement for surgical intervention in the CRAI group was significantly lower than in the non-CRAI group.

Sensitivity Analysis in the CRAI Group in Patients With SAP

To explore better ways of performing arterial infusion, we evaluated the technical aspects of CRAI, including the time of the start of CRAI from the onset of acute pancreatitis, location of catheter placement, choice of the protease inhibitor, use of antibiotics, and the duration of CRAI using multivariable analyses (Table 5). In analysis of the need for surgical intervention, the OR for patients who underwent CRAI within 24 through 48 hours after the onset of acute pancreatitis was significantly lower compared with patients who underwent CRAI after 72 hours. The OR for developing infection in patients who underwent CRAI for more than 5 days was significantly higher compared with that of patients who underwent CRAI for less than 5 days.

DISCUSSION

In this retrospective observational study, we demonstrated no efficacy of CRAI of protease inhibitors in the treatment of patients with SAP. There were no significant differences in mortality, infection rates, or the need for surgical intervention comparing the non-CRAI and CRAI groups with both multivariable and propensity-matching analyses.

To our knowledge, this is the first report to evaluate the efficacy of CRAI using multivariable analysis in a large cohort study. Generally, patients who underwent CRAI have a propensity for higher severity and worse outcomes than those who do not undergo CRAI. Therefore, adjustments for severity and other treatment were necessary. However, it is difficult to have a large

TABLE 4. Odds Ratio of Mortality, Infection Rate, and Surgical Intervention Adjusted by Multivariable Analysis in SAP (N = 1097)

	Mortality		Infection Rate		Surgical Interventions	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CRAI	0.79 (0.47–1.32)	0.36	0.97 (0.61–1.54)	0.89	0.76 (0.50–1.15)	0.19
Characteristics						
Age	1.05 (1.03–1.07)	**<0.001**	1.01 (0.99–1.02)	0.39	1.01 (1.00–1.02)	0.19
Sex, male	1.28 (0.77–2.11)	0.34	1.06 (0.67–1.68)	0.80	1.80 (1.20–2.70)	**<0.001**
Etiologic factor						
Alcohol	1.00	ref	1.00	ref	1.00	ref
Cholelithiasis	0.82 (0.40–1.69)	0.60	2.33 (1.25–4.32)	**<0.05**	3.53 (2.09–5.98)	**<0.001**
Idiopathic	0.88 (0.45–1.72)	0.70	1.40 (0.77–2.54)	0.27	1.86 (1.12–3.11)	**<0.05**
Miscellaneous	1.44 (0.72–2.86)	0.30	1.22 (0.64–2.33)	0.55	1.51 (0.87–2.62)	0.15
APACHE II	1.03 (1.00–1.07)	0.08	0.97 (0.94–1.01)	0.13	1.00 (0.97–1.03)	0.93
Prognostic factor score	0.99 (0.86–1.14)	0.90	1.24 (1.09–1.40)	**<0.001**	1.13 (1.01–1.26)	**<0.05**
Charlson index, mean	1.01 (0.86–1.19)	0.88	1.01 (0.86–1.19)	0.90	0.96 (0.83–1.11)	0.58
CTSI (grading of pancreatitis)	1.00 (0.74–1.35)	0.98	1.17 (0.83–1.65)	0.37	1.48 (1.08–2.03)	**<0.05**
CTSI (pancreatic necrosis)						
None	1.00	ref	1.00	ref	1.00	ref
≤ 30%	1.10 (0.57–2.13)	0.78	4.13 (2.43–7.02)	**<0.001**	1.78 (1.08–2.03)	**<0.05**
> 30%–50%	2.15 (1.05–4.43)	**<0.05**	2.92 (1.53–5.60)	**<0.001**	1.71 (0.97–3.02)	0.06
> 50%	4.05 (2.08–7.87)	**<0.001**	3.69 (1.98–6.86)	**<0.001**	3.09 (1.80–5.33)	**<0.001**
Other treatments						
Enteral feeding within first 48 h	0.49 (0.29–0.83)	**<0.05**	0.70 (0.44–1.10)	0.12	1.03 (0.70–1.51)	0.90
The amount of infused volume within first 24 h	1.00 (1.00–1.00)	0.21	1.00 (1.00–1.00)	0.34	1.00 (1.00–1.00)	0.90
Dialysis due to renal failure	3.68 (2.18–6.21)	**<0.001**	1.49 (0.88–2.50)	0.14	1.17 (0.72–1.89)	0.52
Use of ventilator	9.53 (5.02–18.1)	**<0.001**	4.63 (2.67–8.04)	**<0.001**	3.91 (2.43–6.28)	**<0.001**
Preventive antibiotic	0.95 (0.54–1.68)	0.87	1.22 (0.72–2.05)	0.47	0.76 (0.50–1.18)	0.22

The bold values indicate that there was a significant difference.
ref indicates reference.

database of patients with SAP to allow an adequate multivariable analysis because SAP is not a common disease. A previous systematic review of CRAI of protease inhibitors included 8 observational studies and 2 RCTs.[6] The maximum number of patients in each of the 8 observational studies is 84, and no studies included multivariable analysis. One RCT conducted by Piascik et al[11] was a single-center open-label RCT of 78 patients diagnosed with SAP. Another RCT conducted by Takeda et al[22] was a multicenter open-label RCT of 11 patients diagnosed with ANP. It was worth noting that the current study was performed at 44 institutions and includes 1159 patients to allow for detailed multivariable analyses.

Of the 2 previously reported RCTs, the study by Piascik et al[11] demonstrated that the mortality rate in patients who underwent CRAI of protease inhibitors was 5.1% (2/39), significantly lower than the 23.1% (9/39) in the non-CRAI group ($P = 0.02$), and the proportion of patients requiring laparotomy was 10.3% (4/39) among patients who underwent CRAI, significantly lower than the 33.3% (13/39) in the non-CRAI group ($P = 0.01$). The other RCT, conducted by Takeda et al,[22] demonstrated that there was no significant difference in either mortality or the need for surgical intervention. However, the power of this study was insufficient because 162 patients are needed based on a preliminary power

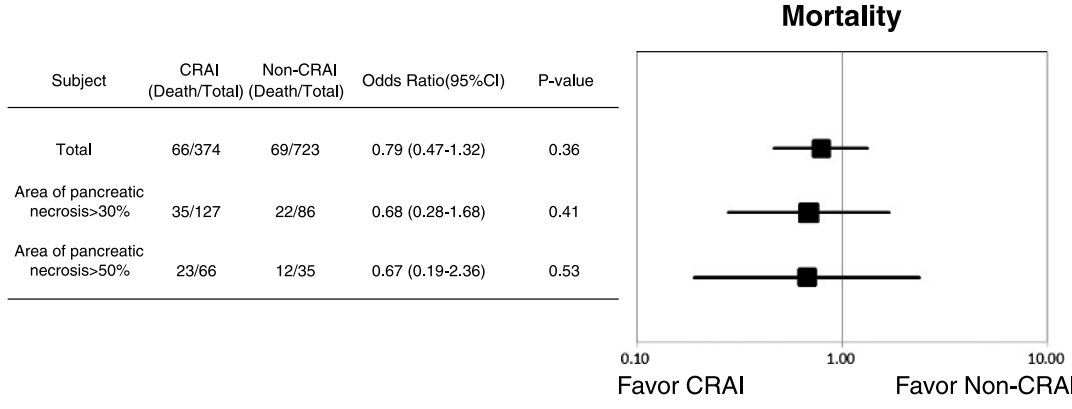

FIGURE 2. Forest plot of hospital mortality in each group.

Subject	CRAI (Infection /Total)	Non-CRAI (Infection /Total)	Odds Ratio(95%CI)	P-value
Total	71/374	65/723	0.97 (0.61-1.54)	0.89
Area of pancreatic necrosis>30%	36/127	17/86	1.00 (0.42-2.40)	0.99
Area of pancreatic necrosis>50%	21/66	10/35	0.64 (0.18-2.25)	0.49

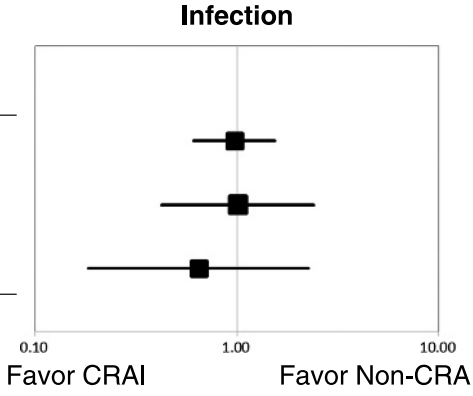

FIGURE 3. Forest plot of infection rate in each group.

analysis. Although a meta-analysis of these 2 RCTs showed no significant risk reduction using CRAI of protease inhibitors on either outcome, the study itself was underpowered to evaluate the efficacy of CRAI of protease inhibitors.[6] It is noteworthy that the current study, with more power than the previous studies, failed to demonstrate the efficacy of CRAI of protease inhibitors in patients with SAP.

Two reasons can be postulated why CRAI of protease inhibitors showed no efficacy in the treatment of SAP in this study. First, patients in this study had an overall lower mortality than that reported in previous studies. Although the APACHE II score and the CT severity index were similar, the mortality in patients with SAP in a systematic review was estimated at 28.1%, whereas it was 12.3% in this study.[6] The treatment impact of CRAI of protease inhibitors may be less prominent for patients with SAP who have decreased mortality if other therapeutic strategies were optimized. One possible explanation of the low mortality in this study is that these patients were included after the publication of the third edition of the Japanese guidelines for the management of acute pancreatitis in May 2009, which may have affected the definition of the disease and patient enrollment.[23] The 44 institutions participating in this study all have intensive care units, where many of the patients in this study received optimal care. These factors may have positively impacted the treatment strategies used other than CRAI for patients in this study, and thus contributed to the lower mortality rates.

The second explanation is that CRAI has no efficacy in patients with SAP, but it may only be effective in patients with ANP. Various derangements of microcirculation in the pancreas occur, including diminution of the capillary network, congestion of the blood stream, and an increase in vascular permeability in patients with ANP.[10] Continuous regional arterial infusion of protease inhibitors may result in 5 times higher concentration of protease inhibitors in the pancreatic tissue compared with intravenous infusions.[24] In fact, CRAI was originally developed for patients with ANP, and not for those with SAP.[10] Thus, we performed a preplanned stratified analysis based on the area of pancreatic necrosis to identify a subgroup which might benefit the most with CRAI of protease inhibitors. In the group with more than 50% pancreatic necrosis (n = 101), there was a significant decrease in the need for surgical intervention in patients who underwent CRAI (Fig. 4). This result may support the effectiveness of CRAI of protease inhibitors in patients with ANP. Whether CRAI of protease inhibitors can reduce the need for surgical intervention in patients with over 50% pancreatic necrosis deserves further study.

There is no existing literature evaluating the impact of the technical aspects of arterial infusion on mortality, infection rates, and the need for surgical intervention in patients treated with CRAI of protease inhibitors. To investigate the optimal approach for arterial infusion, we performed subgroup analyses within the CRAI group, stratified by various approaches for administering CRAI. In an analysis of the time between the onset of acute pancreatitis and the start of CRAI, performing CRAI within 72 hours had a trend toward reducing the mortality, infection rate, and the need for surgical intervention (Table 5), as was shown in a previous RCT.[11] Evaluating the duration of CRAI showed a trend toward increase in the mortality, infection rate, and the need for surgical intervention in patients undergoing CRAI for more than 5 days compared with treatment for less than 5 days (Table 5). The lack of an effect with a longer infusion duration may be because of the fact that pancreatic necrosis is irreversible within a few days after the onset of acute pancreatitis. Moreover, longer

Subject	CRAI (Intervention /Total)	Non-CRAI (Intervention /Total)	Odds Ratio(95%CI)	P-value
Total	88/374	104/723	0.76 (0.50-1.15)	0.19
Area of pancreatic necrosis>30%	44/127	25/86	0.61 (0.28-1.35)	0.22
Area of pancreatic necrosis>50%	26/66	17/35	0.25 (0.07-0.85)	0.03

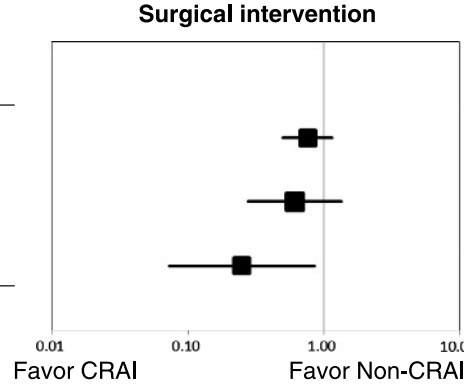

FIGURE 4. Forest plot of the need for surgical intervention in each group.

TABLE 5. The Effect of Treatment Options on Outcomes in the CRAI Group (N = 374)

	Mortality		Infection Rate		Surgical Interventions	
	OR	*P*	OR	*P*	OR	*P*
Time to start CRAI from acute pancreatitis onset						
After 72 h	1.00	ref	1.00	ref	1.00	ref
Within 24 h	0.74	0.62	0.84	0.75	0.69	0.45
From 24 to 48 h	0.58	0.41	0.39	0.11	0.29	**<0.05**
From 48 to 72 h	0.43	0.24	0.78	0.68	0.60	0.72
Location of catheter						
Single route (celiac artery or branch of the celiac artery)	1.00	ref	1.00	ref	1.00	ref
Double route (celiac artery and superior mesenteric artery) or others	0.86	0.69	0.92	0.81	1.58	0.13
Kind of protease inhibitor						
Nafamostat mesilate	1.00	ref	1.00	ref	1.00	ref
Gabexate mesilate or ulinastatin	2.25	0.15	1.67	0.28	1.57	0.30
Antibiotics with artery						
No antibiotics	1.00	ref	1.00	ref	1.00	ref
Use of antibiotics	3.19	0.25	4.46	0.10	4.17	0.07
The length of CRAI						
Within 5 d	1.00	ref	1.00	ref	1.00	ref
Over 5 d	1.50	0.28	2.23	**<0.05**	1.69	0.08
Characteristics						
Age	1.07	**<0.001**	1.02	0.07	1.01	0.32
Sex, male	1.24	0.61	1.47	0.31	1.45	0.29
Etiologic factor						
Alcohol	1.00	ref	1.00	ref	1.00	ref
Cholelithiasis	1.21	0.73	1.83	0.20	2.12	0.08
Idiopathic	0.68	0.49	1.33	0.52	1.17	0.70
Miscellaneous	3.25	**<0.05**	1.42	0.49	2.07	0.11
APACHE II	1.01	0.60	0.97	0.24	0.97	0.22
Prognostic factor score	1.02	0.89	1.19	0.09	1.17	0.09
Charlson index, mean	0.82	0.21	1.64	0.19	0.81	0.12
CTSI (grading of pancreatitis)	3.38	**<0.05**	1.88	0.17	1.60	0.16
CTSI (pancreatic necrosis)						
None	1.00	ref	1.00	ref	1.00	ref
≤ 30%	0.98	0.35	1.76	0.20	0.82	0.63
> 30%–50%	1.33	0.46	2.02	0.13	1.56	0.29
> 50%	3.65	**<0.05**	2.89	**<0.05**	2.30	**<0.05**
Other treatments						
Enteral feeding within first 48 h	0.58	0.19	0.70	0.30	1.02	0.95
The amount of infused volume within first 24 h	1.00	0.56	1.00	0.86	1.00	0.59
Dialysis due to renal failure	3.79	**<0.001**	1.64	0.19	1.60	0.19
Use of respirator	9.11	**<0.001**	2.83	**<0.05**	2.78	**<0.05**
Preventive antibiotic	0.82	0.61	0.77	0.44	0.68	0.20

The bold values indicate that there was a significant difference.
ref indicates reference.

duration of CRAI may worsen the outcomes. Other specific aspects of the treatment including the location of the catheter, selection of the protease inhibitor, and combined administration with antibiotics were considered. However, we could not deduce which factors were important because there is no significant difference. In summary, these results suggest that CRAI of protease inhibitors should be started within 72 hours from the onset of acute pancreatitis and should be stopped within 5 days.

This study has acknowledged limitations. This is a multiinstitution retrospective study, which means that treatment strategies might vary among participating institutions. Although we identified and adjusted as many treatment variables as possible, unidentified factors could affect the results. The second limitation is due to the diagnostic accuracy of acute necrotic pancreatitis. The data of the percentage area of necrosis on contrast-enhanced CT scans were obtained from institutional investigators including intensive care specialists, gastroenterologists, and surgeons or emergency physicians and not from a designated radiologist in a double-blinded fashion. Another limitation is the fact that the results of the subgroup analysis might have high alpha error to

demonstrate the efficacy of CRAI of protease inhibitors. This is because we performed statistical analyses of 3 outcomes including mortality, infection rate, and the need for surgical intervention and the subgroup analysis examining 2 groups including patients with over 30% pancreatic necrosis and those with over 50%.

CONCLUSIONS

Continuous regional arterial infusion of protease inhibitors was not efficacious in the treatment of patients with SAP. In patients with more than 50% area of pancreatic necrosis, significantly fewer patients required surgical intervention when they underwent CRAI. A well-powered RCT to evaluate CRAI for the treatment of patients with severe ANP is justified based on these results.

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REFERENCES

1. Whitcomb DC. Clinical practice. Acute pancreatitis. *N Engl J Med*. 2006; 354:2142–2150.
2. Forsmark CE, Baillie J, AGA Institute Clinical Practice and Economics Committee, et al. AGA Institute technical review on acute pancreatitis. *Gastroenterology*. 2007;132:2022–2044.
3. Fagenholz PJ, Castillo CF, Harris NS, et al. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. *Ann Epidemiol*. 2007;17:491–497.
4. Yokoe M, Mayumi T, Hayashi K. Clinical evaluations of the revised staging system for acute pancreatitis in Japan. *Suizo*. 2009;24:140–146.
5. Otsuki M, Takeda K, Matsuno S, et al. Revised proposal of clinical diagnostic criteria and staging system for acute pancreatitis in Japan. *Journal of Biliary Tract & Pancreas*. 2008;29:301–305.
6. Horibe M, Egi M, Sasaki M, et al. Continuous regional arterial infusion of protease inhibitors for treatment of severe acute pancreatitis: systematic review and meta-analysis. *Pancreas*. 2015;44:1017–1023.
7. Gabryelewicz A, Prokopowicz J, Bodzenta A, et al. Effect of FUT-175 (nafamstat mesilate) on platelets in canine acute experimental pancreatitis. *Digestion*. 1988;40:19–24.
8. Heinrich S, Schafer M, Rousson V, et al. Evidence-based treatment of acute pancreatitis: a look at established paradigms. *Ann Surg*. 2006;243: 154–168.
9. Satoh H, Harada M, Tashiro S, et al. The effect of continuous arterial infusion of gabexate mesilate (FOY-007) on experimental acute pancreatitis. *J Med Invest*. 2004;51:186–193.
10. Takeda K, Matsuno S, Sunamura M, et al. Continuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. *Am J Surg*. 1996;171:394–398.
11. Piaścik M, Rydzewska G, Milewski J, et al. The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: a randomized controlled study. *Pancreas*. 2010;39: 863–867.
12. Hamada T, Yasunaga H, Nakai Y, et al. Continuous regional arterial infusion for acute pancreatitis: a propensity score analysis using a nationwide administrative database. *Crit Care*. 2013;17:R214.
13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.
14. Takeda K, Yokoe M, Takada T, et al. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. *J Hepatobiliary Pancreat Sci*. 2010;17:37–44.
15. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
16. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818–829.
17. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47:1245–1251.
18. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 1990;174:331–336.
19. Spanier BW, Dijkgraaf MG, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. *Best Pract Res Clin Gastroenterol*. 2008;22:45–63.
20. Gullo L, Migliori M, Oláh A, et al. Acute pancreatitis in five European countries: etiology and mortality. *Pancreas*. 2002;24:223–227.
21. Bai Y, Liu Y, Jia L, et al. Severe acute pancreatitis in China: etiology and mortality in 1976 patients. *Pancreas*. 2007;35:232–237.
22. Takeda K, Matuno M, Ura H, et al. Multicenter, randomized controlled trial of continuous regional arterial infusion of protease inhibitor for acute necrotizing pancreatitis. *Journal of Biliary Tract & Pancreas*. 2007;28:967–972.
23. Takada T, Hirata K, Mayumi T, et al. Cutting-edge information for the management of acute pancreatitis. *J Hepatobiliary Pancreat Sci*. 2010;17:3–12.
24. Kakugawa Y, Takeda K, Sunamura M, et al. [Effect of continuous arterial infusion of protease inhibitor on experimental acute pancreatitis induced by closed duodenal loop obstruction] (In Japanese). *Nihon Shokakibyo Gakkai Zasshi*. 1990;87:1444–1450.