New strategy for acute necrotizing pancreatitis: Continuous Regional Arterial Infusion (CRAI) therapy

Mikami Y*, Takeda K, Omura N, Abe H, Fukuyama S, Motoi F, Egawa S, Sunamura M, Matsuno S

Division of Gastroenterological Surgery, Tohoku University, Graduate School of Medicine, Sendai, Japan

Abstract

Acute pancreatitis is an autodigestive disease, of which protease inhibition has been the focus of experimental and clinical research. Different from Europe and the United States, protease inhibitors are often applied in the treatment of acute pancreatitis in Japan. However, in clinical settings, the effect of protease inhibitors on acute pancreatitis is still controversial. Continuous Regional Arterial Infusion (CRAI) of protease inhibitors and antibiotics therapy were developed in Japan and it has been demonstrated that CRAI therapy has beneficial effects on severe acute necrotizing pancreatitis. In the Japanese clinical guidelines for the treatment of acute pancreatitis, published in 2003, CRAI therapy is still classified as a special therapy. However, a Randomized Controlled Trial for CRAI therapy has started and CRAI therapy is expected to become a new standard therapy for severe acute pancreatitis. CRAI therapy is aimed at preventing the progression of pancreatic inflammation and pancreatic infection. CRAI therapy can decrease the mortality rate and the frequency of pancreatic infection in severe acute pancreatitis, but it should be started as soon as possible after the onset of acute pancreatitis.

Key words: acute pancreatitis, Continuous Regional Arterial Infusion (CRAI) therapy, protease inhibitor, nafamostat mesilate, contrast enhanced CT, angiography.

* CORRESPONDING AUTHOR:
Division of Gastroenterological Surgery,
Tohoku University, Graduate School of Medicine
Aobaku, Seiryo-machi 1-1
Sendai 980-8574, Japan
Tel: +81-22-717-7205; Fax: +81-22-717-7209
e-mail: y-mikami@surg1.med.tohoku.ac.jp (Yukio Mikami)

Received 07.07.2005 Accepted 14.07.2005

Abbreviations: CRAI – Continuous Regional Arterial Infusion; RCT – Randomized Controlled Trial; CEA – celiac artery; SMA – supramesenteric artery; ICU – intensive care unit.

Introduction

Acute pancreatitis is an autodigestive disease and protease inhibitors have been expected to be a key factor in the therapeutic approach to its treatment. However, in clinical settings, the effect of protease inhibitors in the treatment of acute pancreatitis is still controversial and a new regimen of anti protease therapy is required to establish the role of protease inhibitors in treating acute pancreatitis.

In 2003, evidence based clinical guidelines for treating acute pancreatitis were published in Japan [1], assessing all proposed therapies and examination techniques for acute pancreatitis, which were then categorized and their efficacies re-evaluated. In these guidelines, fluid resuscitation, intensive care and surgical therapy for pancreatic infection are recommended as the basic therapies for acute pancreatitis. Additionally, Continuous Regional Arterial Infusion (CRAI) of protease inhibitor and antibiotics were proposed as special therapy for severe acute pancreatitis. CRAI of protease inhibitor and antibiotics, which markedly increases the tissue concentration of administered drugs in acute pancreatitis, was pioneered in Japan and has been demonstrated to reduce the mortality rate and the frequency of infected pancreatic necrosis.

In this review, this new strategy for acute pancreatitis – CRAI of protease inhibitor and antibiotics therapy – is summarized and discussed.

Protease inhibitors

Protease inhibitors were developed to inhibit pancreatic proteases, such as trypsin, which have an important role in

Figure 1. **Angiographic appearance of acute pancreatitis. A) normal pancreas; B) acute necrotizing pancreatitis. Diffuse narrowing of the splenic and common hepatic arteries and impaired visualization of the ramifications are shown in acute necrotizing pancreatitis. (9-year-old boy at 56 hours after the onset)**

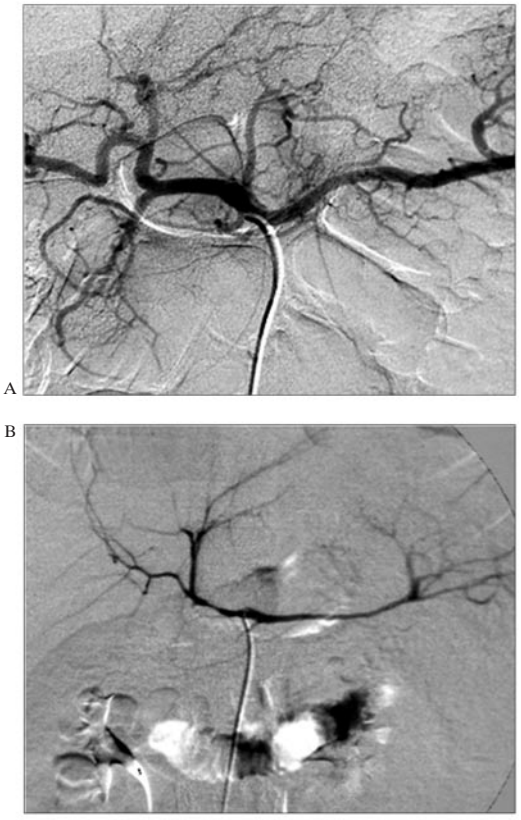
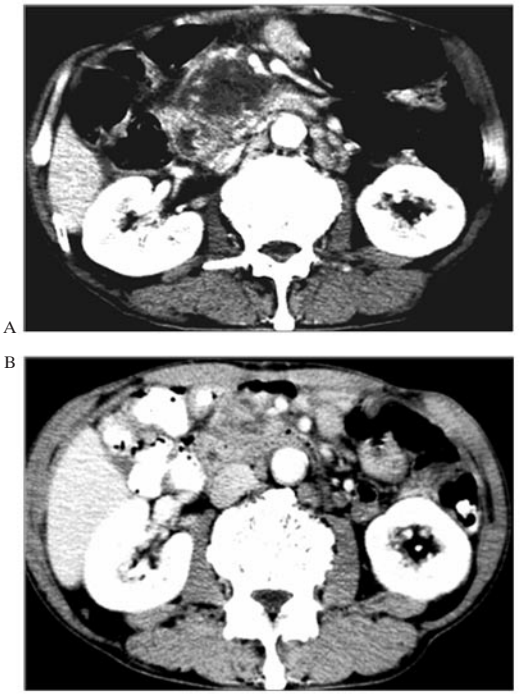


Figure 2. **Contrast enhanced CT finding in a patient with acute necrotizing pancreatitis (68-year-old male). A) before CRAI therapy (at 65 hours after onset); B) after CRAI therapy (at 2 weeks after onset). The inflammation of the pancreatic head (arrow) improved after CRAI therapy**

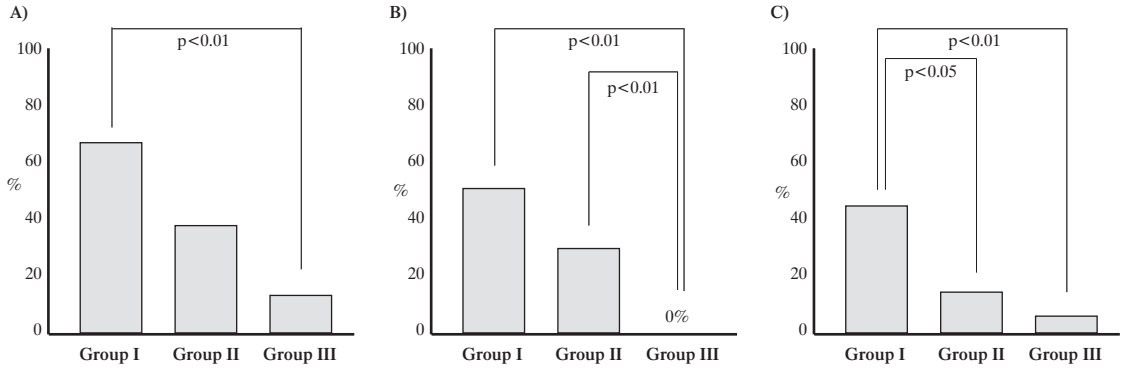


pancreatic inflammation. Aprotinin, which was often used in 1960's-1970's for the treatment of acute pancreatitis, has not shown any beneficial effects on acute pancreatitis in its Randomized Controlled Trials (RCTs) [2-4]. Gabexate mesilate was developed in Japan and some RCTs of gabexate mesilate have been performed [5-7]. However, most of them failed to demonstrate any significant beneficial effects on acute pancreatitis. Especially, in a German RCT of gabexate mesilate [5], more than 200 patients were included and more than 4 g/day of gabexate mesilate was administered for the treatment of acute pancreatitis. However, the RCT did not show any significant beneficial effects on mortality or morbidity of complications in acute pancreatitis. As a result of these RCTs, the European and American guidelines for the treatment of acute pancreatitis do not admit any beneficial effects of protease inhibitors [8-9].

In 2000 Chen et al. reported that the continuous intravenous administration of gabexate mesilate (2400 mg/day for 7 days) significantly decreased the morbidity of complications and mortality rate in severe acute pancreatitis [10]. The meta-analysis [11-13], which does not contain the RCT reported by Chen et al., did not show any clinical beneficial effects of gabexate mesilate on mild and moderate acute pancreatitis. Although the analysis also did not show the beneficial effects of gabexate mesilate on the mortality rate and the frequency of surgical intervention in severe acute pancreatitis, they showed that gabexate mesilate (900-2400 mg/day for 4-12 days) decreased the morbidity of complications in severe acute pancreatitis. In consideration of these results, the effect of protease inhibitors can not be neglected completely, but in Europe and United States, their effects on acute pancreatitis are not accepted. In Japan, there has been no RCT of protease inhibitors which has evaluated the mortality rate for acute pancreatitis and there is no positive evidence for the treatment of acute pancreatitis with protease inhibitors. However, based on the report of Chen et al. and the results of the meta-analysis, the intravenous administration of gabexate mesilate (2400 mg/day) is recommended in Japan. Additionally, the double-blind controlled studies have shown that nafamostat mesilate and urinastatin have nearly the same effect as gabexate mesilate on acute pancreatitis [14-16] and, therefore, nafamostat mesilate and urinastatin are also often used in the treatment of acute pancreatitis in Japan.

As stated above, the clinical effects of protease inhibitors for the treatment of acute pancreatitis are still controversial. In Japan, although the effect of protease inhibitors on acute pancreatitis is recognized, the route, period of treatment and the infusion dose of protease inhibitors are still under investigation.

Figure 3. **Infectious complications and mortality in patients with acute necrotizing pancreatitis. A) frequency of intra-abdominal infection; B) frequency of infected pancreatic necrosis; C) mortality rate. All patients received the protease inhibitor, nafamostat mesilate, and antibiotics. Group I (n=16) received both medications intravenously. Group II (n=22) received nafamostat, via Continuous Regional Arterial Infusion (CRAI), and antibiotics intravenously. Group III (n=15) received both medications via CRAI. (From Reference 24, with permission)**



CRAI of protease inhibitors and antibiotics

It is characteristic that the half-life of the protease inhibitors clinically used is very short because they are promptly broken down by elastase in the blood and metabolized in the liver [17]. Moreover, ischemia and disturbance of the pancreatic microcirculation occur in severe acute pancreatitis and the concentration of protease inhibitor in the pancreas is considered to be decreased [18]. Therefore, CRAI was developed as a new drug delivery system to the pancreas which infuses drugs directly to the pancreatic artery. Kakugawa and Yamauchi et al. [19] investigated the concentration of nafamostat mesilate in the pancreas according to the route of infusion and they reported that the concentration of nafamostat mesilate in the pancreas infused by CRAI was five times higher than that infused intravenously in dog acute pancreatitis. Mikami et al. [20] reported that the concentration of nafamostat mesilate in the pancreas infused by CRAI was ten times higher than that infused intravenously in rat severe acute pancreatitis. In both reports, CRAI of nafamostat mesilate significantly improved the severity of acute pancreatitis compared with the intravenous infusion of nafamostat mesilate. As mentioned above, although more than 4 g/day of gabexate mesilate was infused for the treatment of acute pancreatitis in the German RCT [5], there were no significant differences in the mortality rate and morbidity of complications. This result might imply that the intravenous administration of 4 g/day gabexate mesilate did not increase the concentration of the drug in the pancreas and the amount of the drug was not enough to prevent the spread of inflammation.

Regarding antibiotics, a RCT performed in Italy showed that imipenem significantly prevented pancreatic infection in acute pancreatitis [21]. Büchler et al. [22] investigated the concentration of imipenem in pancreatic operations involving acute necrotizing pancreatitis and reported that the concentration of imipenem in the pancreas was very high. However, the specimen they investigated was not the pancreatic necrotic tissue itself, but the edematous tissue around the pancreatic necrotic tissue. Therefore, although they showed that the concentration of imipenem in the pancreas is very high, the concentration of imipenem in the pancreatic necrotic tissue is unclear. In consideration of the complicated pathology of acute necrotizing pancreatitis, CRAI aiming to obtain a high pancreatic concentration of drugs is considered to be an ideal drug delivery system and limiting the extent of pancreatic inflammation and pancreatic infection is expected.

Methodology of CRAI of protease inhibitor and antibiotics

After the admission of a patient with acute pancreatitis, contrast enhanced CT examination and fluid resuscitation are performed as soon as possible. Then, according to the findings of the contrast enhanced CT, clinical findings and laboratory data, the severity of the acute pancreatitis is diagnosed. Patients for whom CRAI therapy is indicated then undergo angiography examination. The femoral artery is punctured by the Seldinger method and a 4Fr or 5Fr catheter is inserted from the femoral artery and angiography of the celiac artery (CEA) and the supramesenteric artery (SMA) is performed. It is important that the artery flowing to the region of inflammation is selected for the route of administration in CRAI therapy. For example, if the main region of inflammation is in the pancreatic head, the tip of the catheter is located in the common hepatic artery or gastroduodenal artery or SMA. If inflammation is located in the pancreatic body-tail, the tip of the catheter is manipulated into the splenic artery, or sometimes the dorsal pancreatic artery. If inflammation extends throughout the whole pancreas, the tip of the catheter is located in the CEA, and in some institutes a separate catheter is located in each of the splenic and gastroduodenal arteries. The catheter for the infusion of drugs is the same as that used for angiography. The catheter is fixed to the femoral skin with silk strings. Before returning to the intensive care unit (ICU) or the ward, the catheter is filled with saline containing

heparin. Nafamostat mesilate (240 mg) dissolved in 500 ml 5% glucose solution is infused through the catheter continuously at 20 ml/h. Imipenem (0.5 g) is dissolved in 100 ml saline and infused intra-arterially every 12 hours. The period of CRAI therapy is 5 days, following which only antibiotics are administrated for 7 days to prevent pancreatic infection.

The efficacy of CRAI therapy

Imaizumi et al. [23] investigated the efficacy of CRAI therapy for severe acute pancreatitis in 51 patients admitted to ICU. They reported that CRAI therapy significantly decreased the rate of surgery and that the survival rate of the patients with CRAI therapy was significantly higher than that of the patients without CRAI therapy.

One aim of CRAI therapy is to prevent the progression of inflammation from pancreatic ischemia to pancreatic necrosis and to prevent early pancreatic infection. Therefore, the indication for CRAI therapy is a patient with severe acute pancreatitis whose pancreas is not enhanced homogenously by contrast enhanced CT on admission. In acute necrotizing pancreatitis, the necrotic, hemorrhagic, ischemic and edematous regions coexist in the early phase of the disease and the necrotic and ischemic regions appear to be heterogeneous low density areas in contrast enhanced CT but not all of these heterogeneous low density areas are actually necrotic. Generally, in acute necrotizing pancreatitis, the necrotic regions are clearly distinguished from the non-necrotic regions in contrast enhanced CT during the first one/two weeks after the onset of pancreatitis and there is no clear demarcation between these two regions within 4-5 days after the onset of pancreatitis [18]. Therefore, the window for the start of CRAI therapy is during this 4-5 days after onset.

Takeda et al. [24] reported that the mortality rates of patients with acute necrotizing pancreatitis who were started on CRAI therapy within 48 hours, during 48-72 hours and after 72 hours after onset were 3.2%, 9.1% and 26.3%, respectively. The mortality rate of patients on CRAI therapy within 48 hours after onset was significantly lower than that after 72 hours after onset. Similarly, the cooperative survey of CRAI therapy in Japan has shown that the mortality rate of patients who beginning CRAI within 48 hours and after 48 hours after onset was 11.9% and 23.6%, respectively, and there was a significant difference between them [25]. In our department, CRAI therapy was performed only for the patients with acute necrotizing pancreatitis within seven days after onset, and we have recognized that it is important to begin CRAI therapy as soon as possible after onset.

The characteristic effect of CRAI therapy on acute pancreatitis is improvement in abdominal pain. Takeda et al. reported that abdominal pain was improved in all patients on whom abdominal pain could be evaluated during CRAI therapy [26]. Similarly, the cooperative survey of CRAI therapy in Japan has reported that abdominal pain disappeared in 76% of the patients at 48 hours after initiation of CRAI therapy and the pain had disappeared in 87% of patients at 72 hours after initiation of the therapy [25]. This may be an effect of the protease inhibitor, which inhibits the inflammatory process in the pancreatic parenchyma caused by activation of pancreatic enzymes.

In Japan, both protease inhibitor and antibiotics are infused during CRAI therapy. Takeda et al. compared retrospectively the effect of CRAI therapy among (1) patients with both intravenous infusion of protease inhibitor and antibiotics, (2) patients with intra-arterial infusion of protease inhibitor and intravenous infusion of antibiotics and (3) patients with intra-arterial infusion of both protease inhibitor and antibiotics. They reported that the mortality rate of patients with both intra-arterial infusions was significantly lower than that of the patients with both intravenous infusions. They also reported that there was no significant difference between patients with intra-arterial infusion of protease inhibitor and intravenous infusion of antibiotics and patients with both intra-arterial infusions in the mortality rate, but the frequency of the infected pancreatic necrosis in patients with both intra-arterial infusions was significantly lower than for patients with intra-arterial infusion of protease inhibitor and intravenous infusion of antibiotics [26]. Therefore, CRAI of both protease inhibitor and antibiotics is effective both for the improvement of mortality rate and the prevention of infected pancreatic necrosis and especially, CRAI of protease inhibitor may have an effect on the prevention of infected pancreatic necrosis.

Recently, Hirota et al. [27] reported enteric necrosis combined with severe acute pancreatitis due to non-occlusive mesenteric ischemia and they proposed a modified CRAI therapy via infusion through the SMA in addition to the pancreatic artery to prevent enteric necrosis. The indication of this therapy is patients with vascular spasm of the SMA. Takagi and Isaji et al. reported that the intra-arterial infusion of protease inhibitors to the SMA has an effect on the prevention of pancreatic infection in dog acute necrotizing pancreatitis [28]. They also reported that the infusion of antibiotics through the SMA is effective for the prevention of gut bacterial translocation. However, there is still little clinical evidence for the effectiveness of their method and further clinical study is required. The protease inhibitors used in CRAI therapy are also applied in the treatment of disseminated intravascular coagulation. In acute necrotizing pancreatitis, patients with vascular spasm are often observed in the early phase of the disease and the blood circulation is likely to be disturbed. Although there is still no method to dramatically improve vascular spasm in acute pancreatitis, the effect of protease inhibitor, which also has an anticoagulant effect, is being re-evaluated with a view to the prevention of embolization when the blood circulation is disturbed [18].

Conclucions

This review discussed the role, method and the results of new therapy for acute necrotic pancreatitis – CRAI of protease inhibitor and antibiotics therapy. Although CRAI therapy is still one of the special therapies for acute pancreatitis in Japan, the efficacy of this therapy on the early phase of acute severe pancreatitis is widely recognized. Currently, RCTs of CRAI therapy for acute pancreatitis are in progress and it is expected that the efficacy of this therapy will eventually be recognized internationally.

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