Original article

The efficiency of continuous regional intra-arterial infusion in the treatment of infected pancreatic necrosis

Mengtao Zhou a,*, Bicheng Chen b,c, Hongwei Sun a, Xiaolei Chen a, Zhengping Yu a, Hongqi Shi a, Jianguo Yao a, Zhengkeng Xu a, Qiuyu Zhang a, Roland Andersson d

a Department of Surgery, The First Affiliated Hospital, Wenzhou Medical College, 2 Fuxue Lane, Wenzhou 325000, Zhejiang Province, China
b Zhejiang Provincial Top Key Discipline in Surgery, Wenzhou Key Laboratory of Surgery, The First Affiliated Hospital, Wenzhou Medical College, Wenzhou 325000, Zhejiang Province, China
c Department of Surgery, The First Affiliated Hospital, Wenzhou Medical College, Wenzhou 325000, Zhejiang Province, China
d Department of Surgery, Clinical Sciences Lund, Lund University and Lund University Hospital, SE-221 85 Lund, Sweden

OBJECTIVE: Our aim was to investigate the efficiency of continuous regional intra-arterial infusion (CRAI) with antisecretory agents and antibiotics in the treatment of infected pancreatic necrosis.

MATERIALS AND METHODS: CRAI was used as a new clinical technique to treat acute pancreatitis patients during a 4-year period at the First Affiliated Hospital, Wenzhou Medical College, China. In this retrospective study, thirty-four patients with proven infected pancreatic necrosis were included. Twelve patients were treated with CRAI, and were matched according to age, sex, APACHE II scores, Ranson scores and remote organ dysfunction, with 22 patients with IPN treated surgically. The clinical outcome following surgery and CRAI were compared.

RESULTS: No difference was found between the two groups when comparing age, gender, APACHE II scores, Ranson scores and remote organ dysfunction (p > 0.05). The patients treated with CRAI had a lower incidence of complications (33.3% vs 72.7%), duration of hospitalization (27.1 ± 4.7 days vs 43.0 ± 12.0 days) and cost of hospitalization (4.09 ± 1.64 thousand RMB vs 8.77 ± 3.74 thousand RMB) as compared to patients treated with surgery (p < 0.05). The survival rate was significantly higher in the CRAI group as compared to the surgical group (91.7% vs 63.6%; p < 0.01). However, the two groups had similar rates of concomitant operative treatment and incidence of remote organ dysfunction (p > 0.05).

CONCLUSIONS: CRAI or CRAI in combination with abscess drainage seemingly improve the clinical outcome in patients with infected pancreatic necrosis. Further confirmative prospective randomized multicenter studies are warranted prior to broad introduction of the CRAI concept.

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1. Introduction

The mortality rate in severe acute necrotizing pancreatitis (SAP) still ranges around 15% [1,2] in the best of series, despite advances achieved in critical illness management, including early and controlled fluid resuscitation and overall improved treatment strategies, the latter including e.g. guidelines for the management of acute pancreatitis [3]. Organ failure is a frequent complication of SAP, being a significant prognostic factor and also the main cause of death in SAP during the early phase of SAP [4,5], and during later stages the multiple organ dysfunction syndrome (MODS), combined with infectious complications/sepsis, is a dominating cause of death, not at least in infected pancreatic necrosis (IPN) [6,7]. The incidence rate of IPN may reach up to 40–70% in patients with acute necrotizing pancreatitis (ANP) [8]. During IPN, sepsis is a serious infectious complication, and represents one of the main contributors to the high mortality rate [9]. Traditionally, IPN has been considered an indication for surgical intervention and necrosectomy [10,11], which more recently has come to include various more non-invasive step-up procedures like percutaneous, endoscopic, and laparoscopic interventions/drainage prior to open necrosectomy [3,12]. Overall, a conservative and minimal invasive approach has gradually been implemented and reported to improve outcome [13]. However, the prognosis of patients with IPN remains unsatisfactory. The outcome is partly due to the fact that
surgery may actually aggravate the stress state, and increase the overall inflammatory response [14]. Therefore, future both causal therapies directed at underlying pathophysiological mechanisms, and minimal invasive intervention for IPN is needed.

In acute pancreatitis, an alternative treatment is continuous regional intra-arterial infusion (CRAI), via one of the arteries supplied the pancreas. This approach allows effective drug delivery to the pancreas and results in that high local concentration can be obtained with relatively minimal side effects [15]. We have demonstrated that CRAI and administration of antibiotics and antisecretory agents is more effective than corresponding intravenous administration in the preventive treatment of pancreatic infection and also results in an improved survival in a canine model of ANP [16]. Clinically, CRAI with antibiotics has been reported to prevent pancreatic infection and with positive overall endpoints, including a decrease in mortality [17]. However, as for established IPN, the clinical efficacy of CRAI has not been studied in detail. In the present report, we present the efficiency of CRAI in an initial study of CRAI used in the treatment of IPN, with results compared to traditional surgical intervention.

2. Patients and methods

2.1. Patients

All patients had to meet the diagnostic criteria for SAP [18]. Besides, the diagnosis of patients with IPN also need to meet the criteria as follows: 1) temperature ≥38°C; 2) White blood cells count ≥20 × 10^9/L; 3) signs of peritoneal irritation in two or more quadrants, 4) signs of infected pancreatic necrosis on the CT scan (bubbles), or verified bacterial growth obtained by fine needle aspiration or intra-operative culture. At the time of admission, the diagnosis and evaluation of the severity of SAP were made according to the criteria for clinical diagnosis and grading severity previously described [19,20]. Twelve patients with SAP and IPN were managed with CRAI with antibiotics and a protease inhibitor during a 4-year period (the CRAI group; Table 1). These patients were matched according to age, sex, APACHE II scores, Ranson scores and organ dysfunction with 22 patients with SAP and IPN treated surgically (the surgical group; Table 1).

2.2. Ethics

The study complies with the Declaration of Helsinki. The clinical research ethics committee at the First Affiliated Hospital of Wenzhou Medical College approved the research protocol and with written informed consent was obtained from all patients or their relatives (in critically ill patients). Patients who agreed to participate had further explanation of the detailed content of the study, including the purpose of the study, medical items, and confidentiality agreement of personal information. These studies were registered in the Chinese Clinical Trial Register Center (No. ChiCTR-ONRC-12002670; URL: http://www.chictr.org/usercenter/project/edit.aspx?proj=3280).

2.3. Therapies

Treatment was started immediately after admission to hospital and management included fasting, adequate fluid resuscitation, pain relief, and use of prophylactic antibiotics (which was advocated during this time period) and antisecretory agents (also valid at that time). Initial treatment for all SAP patients was the same. Continuous respiratory and cardiovascular monitoring was crucial, involving the conscious state, temperature, pulse rate, blood pressure, urinary output, respiratory frequency, and oxygen saturation. Surgical management of necrotizing pancreatitis has changed significantly during recent years. In contrast to the “aggressive” and early surgical interventional of the past, there is now a strong tendency towards a more conservative approach [2]. However, IPN has represented an indication for intervention. In our study, 22 patients were treated surgically (matched controls) within 36 h once diagnosed with IPN. The surgical procedure included debridement of necrosis, peritoneal irrigation and closed continuous drainage.

CRAI therapy was considered as an alternative method to treat IPN. Following angiography of the pancreas, the tip of the catheter was placed at the gastroduodenal artery. Antisecretory agents (Octreotide (Novartis, Basel, Switzerland) 0.1 mg q8h or Stilamin (Serono, Geneva, Switzerland) 6 mg) and antibiotics (Cefoperazone sodium (Pfizer, NY, USA) 1 g and Sulbactam sodium (Pfizer, NY, USA) 1 g in 20 ml saline, q12h) were administered via CRAI for 10–18 days. In the 12 patients with CRAI (within 24 h once diagnosed with IPN), nine were treated with CRAI alone with antisecretory agents in combination with antibiotics, and three had additional abscess drainage of pancreatic/peripancreatic abscess formation. CRAI treatment was terminated when symptoms and signs obviously improved, blood and urine amylase levels dropped towards normal levels, pancreatic imaging seemed to be restored (CT), enteral/oral nutrition was tolerated, and when the CRAI management reached a minimum of 10 days.

2.4. Outcome measures

For obtaining evaluation of the two treatments (CRAI and surgery), factors related to evaluate severity of IPN were recorded prior to the initiation of treatment. Parameters included APACHE II and Ranson scores, and the incidence of remote organ dysfunction. Outcome of IPN was assessed by various parameters, including survival, incidence of complications, need of additional pancreatic surgery, duration of hospital stay (DH) and hospital costs (HC).

2.5. Statistical analysis

Data were analyzed by SPSS software (version 11.0) and expressed as mean ± standard deviation (M ± SD). Statistical significance of differences among two groups was determined by chi-square test and student’s T test. Differences between groups were considered statistically significant when P-values were less than 0.05.

<table>
<thead>
<tr>
<th>Items</th>
<th>Surgical group</th>
<th>CRAI group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range (years)</td>
<td>52 (47–80)</td>
<td>53 (49–72)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>12 vs 10</td>
<td>7 vs 5</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>APACHE II scores</td>
<td>10.5 ± 2.7</td>
<td>11.1 ± 3.4</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Ranson scores</td>
<td>4.5 ± 1.3</td>
<td>4.8 ± 1.7</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Incidence of remote organ dysfunction</td>
<td>27.3% (6/22)</td>
<td>41.7% (5/12)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core rate</td>
<td>63.6% (14/22)</td>
<td>91.7% (11/12)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Incidence of complications</td>
<td>72.7% (16/22)</td>
<td>33.3% (4/12)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Conversion to open</td>
<td>22.7% (5/22)</td>
<td>16.7% (2/12)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>operation/reoperation rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>43.0 ± 12.0</td>
<td>27.1 ± 4.7</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>8.77 ± 3.74</td>
<td>4.09 ± 1.64</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Hospitalization costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(thousand Chinese Yuan)</td>
<td>(n = 13)</td>
<td>(n = 11)</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>
3. Results

3.1. Evaluation of IPN

The details of evaluation of IPN are demonstrated in Table 1. No difference was found between the two groups concerning age, gender, APACHE II and Ranson scores, and the incidence of remote organ dysfunction ($p > 0.05$).

3.2. Survival

Among the 22 patients in the surgical group, 8 died (mortality 36.4%), while mortality in the CRAI group was only 1/12 patients (8.3%), thus a statistically significant difference ($p < 0.01$; Table 1).

3.3. Incidence of complications

Among the 22 patients in the surgical group, sixteen (72.7%; Table 2) had complications, including ARDS, acute renal failure, encephalopathy, MODS, intraabdominal infection/abscess, peri-pancreatic abscess, gastrointestinal hemorrhage, and pancreatic pseudocysts. In the CRAI group, only four patients developed complications (33.3%). The incidence of severe complications between the two groups was significantly different ($p < 0.05$; Table 2).

3.4. Conversion to open operation/reoperation rate

In the surgical group, reoperation was performed in five patients, the reoperation rate thus being 22.7%. In the CRAI group, conversion to open operation was performed in two patients (16.7%) due to pancreatic/peripancreatic abscess formation. In patients with serious illness and excessive peri-pancreatic effusion, CRAI in combination with drainage was performed. After chi-square test, no significant difference was found between the two groups (Table 1).

3.5. Duration of hospitalization (DH)

The mean DH among survivors in the surgical group was 43.0 ± 12.0 days and 27.1 ± 4.7 days in the CRAI group ($p < 0.05$; Table 1).

3.6. Costs of hospitalization (HC)

HC was estimated among surviving patients and significantly differed between surgical patients ($8.77 ± 3.74$ thousand Chinese Yuan) and the CRAI group ($4.09 ± 1.64$ thousand Chinese Yuan; $p < 0.05$, Table 2).

4. Discussion

In the present study, we investigated the efficiency of CRAI to treat IPN, as compared to open surgery. Based on the severity scoring systems (Ranson score and APACHE II score), the severity of IPN in both groups was the same. When comparing mortality, the incidence of complications, duration of hospital stay and hospital costs, CRAI treatment demonstrated a significant advantage in patients with IPN as compared to traditional surgical treatment (necrosectomy).

Infection, beside organ dysfunction, is the most serious complication in the late phase of SAP, and IPN commonly occur 2–3 weeks or more after admission. In previous reports the incidence of bacterial infection secondary to SAP has ranged from 40 to 70% [21], and has been associated with mortality rates as high as 35% due to IPN and organ failure [22]. In our study, the mortality rate was 36.4% in patients with IPN treated with open surgery. Following CRAI treatment, however, the mortality rate was 8.3%, potentially partly due to the avoidance of an additional surgical trauma that aggravates the stress state and increases the inflammatory response in these critically ill patients.

IPN is thought to be related with pancreatic ischemia [23], and changes in the microcirculation make it difficult to obtain adequate drug concentrations in the pancreas following intravenous administration [12]. Using CRAI, it is possible to administer drugs locally and increase local tissue concentrations of antibiotics in the pancreas in IPN [15, 16, 24, 25]. Thus, CRAI with antibiotic administration seems effective in inhibiting IPN progress. The present study also points at a decrease in inflammatory complications. CRAI could thus represent a useful drug delivery system in IPN.

Even though meta-analysis on antisecretory agents previously have been considered to be of some efficacy, reducing complications in SAP [26], the actual effects have been discussed [27]. The role of antisecretory agents does not seem to have worked as expected, potentially due to the dose-dependently and the effect could be limited by the blood-pancreatic tissue interface [28]. Through CRAI, the level of antisecretory agents in the pancreatic tissues theoretically increased. In the present study, CRAI with an antisecretory agent and antibiotic administration improved outcome in IPN, implying inhibition of the local inflammatory response and tissue injury in IPN. In previous animal experiments, we have also shown that CRAI with antisecretory agents inhibited the local pancreatic inflammation [29]. CRAI was associated with a reduction of the complication rate in IPN (reduced from 72.7% to 33.3%) and CRAI is currently becoming accepted as part of SAP treatment in China [30].

There is general agreement on that surgery in severe pancreatitis should be performed as late as possible [11]. Once IPN is diagnosed, surgical treatment has been recommended, especially if coinciding with systemic organ dysfunction of complications [10]. However, surgery early on in IPN is not beneficial due to the diffuse inflammation, and may even aggravate the systemic inflammatory response syndrome. Antibiotics for prevention or therapy in IPN by CRAI was based on drugs that could reach principally the whole pancreas (via the gastroduodenal artery) and limit infections, as shown in a previous study by intra-arterial digital subtraction angiography (JADSA) [31]. Despite satisfactory outcomes of CRAI, surgery still plays a crucial role [32]. In patients with critical illness and excessive peri-pancreatic effusions, CRAI in combination with drainage can be performed. During CRAI, drainage of the infectious foci, including pancreatic/peri-pancreatic abscesses, may be performed. Operative procedures include appropriate debridement of necrosis, drainage of the peri-pancreatic space, and selective bile duct decompression.

In conclusion, the CRAI concept seemingly improved outcome in IPN. CRAI with local antibiotic infusion was associated with

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Table 2: Complications.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Surgical group (n = 22)</th>
<th>CRAI group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with complications</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>ARDS</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic encephalopathy</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>MODS</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Celiac widespread infection</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pancreas abscess</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic pseudocysts</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

ARDS = Acute respiratory distress syndrome.  
MODS = Multiple organ dysfunction syndrome.
Acknowledgments

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