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Original article

Efficacy of recombinant human soluble thrombomodulin in preventing walled-off necrosis in severe acute pancreatitis patients

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ABSTRACT

Objective: To investigate the efficacy of recombinant human soluble thrombomodulin (rTM) in preventing the development of walled-off necrosis (WON) in severe acute pancreatitis (SAP) patients.
Methods: We retrospectively analyzed 54 SAP patients divided into two groups: SAP patients treated by rTM (rTM group, 24 patients) and not treated by rTM (control group, 30 patients). rTM was administered to patients with disseminated intravascular coagulation (DIC). Initially, on the admission day, we recorded patient severity and pancreatic necrosis/ischemia positive or negative. Then we investigated development of WON using 4 weeks later CT/MRI. Finally we compared the proportions of patients developing WON in the rTM group and the control group.
Results: On the admission day, the condition of patients treated by rTM was significantly worse than patients in the control group; rTM group vs. control: 71.8 ± 13.9 vs. 59.8 ± 15.3 years for age, 10.7 ± 3.5 vs. 8.0 ± 4.4 for Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and 3.3 ± 1.8 vs. 2.2 ± 1.8 for sequential organ failure assessment (SOFA) score ($p < 0.05$). We found no significant differences on the admission day in rate of pancreatic necrosis/ischemia between patients treated by rTM and controls (58.3% vs. 63.3%, $p = 0.71$). Nevertheless, the proportion of patients developing WON was significantly lower among those administered rTM than in those not administered rTM {29.2% (7/24 patients) vs. 56.7% (17/30 patients), $p < 0.05$}.
Conclusion: Treatment of SAP patients treated by rTM may prevent progression from pancreatic necrosis/ischemia to WON.

Introduction

Severe acute pancreatitis (SAP) is a potentially high mortality disease. Organ failure (OF) is among the major reasons for this high mortality. Pancreatitis-related OFs are either local or systemic. In general, local OF can be divided into three stages: pancreatic ischemia, pancreatic necrosis, and walled-off necrosis (WON) [1]. Pancreatic necrosis is caused by pancreatic ischemia, which leads to WON. Systemic OF, including shock states, respiratory failure, renal failure, and heart failure, is the common origin of patient instability [2–5]. Both local and systemic OFs can be caused by abnormal coagulability, which causes from the endovascular damage caused by pancreatitis.

Some articles report that endovascular damage in acute pancreatitis patients is related to the development of disseminated intravascular coagulation (DIC). Other studies indicate that a high proportion of acute pancreatitis patients with early DIC may develop OFs. Importantly, acute pancreatitis with DIC is associated with high mortality [5–8]. In the light of these reports, controlling DIC in the early stage of acute pancreatitis may help prevent the development of local and systemic OFs, thereby reducing mortality. However, to the best of our knowledge, no effective treatment

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exists with sufficient documented efficacy against both DIC and acute pancreatitis. For example, in recent pancreatitis and DIC practical guidelines deprecate the usefulness of heparin or similar anti-coagulant drugs [9–11]. Evidence for the efficacy of activated recombinant protein C or anti-thrombin III also remains insufficient [12–16].

Recently, recombinant human soluble thrombomodulin (rTM) has been used to treat patients with DIC in Japan, and a phase III clinical trial evaluating the efficacy of rTM in severe sepsis patients with DIC is now ongoing in the USA, South America, Asia, Australia, European Union, and other countries [17–23]. Several studies report that rTM has anti-coagulation effects, resulting in improvements in septic DIC [20–28]. However, the clinical effectiveness of rTM for acute pancreatitis patients with DIC has not been assessed.

This study investigates whether rTM prevents local and/or systemic OFs in acute pancreatitis patients.

Patients and methods

Patients

This study was approved by the institutional review board of Osaka Saiseikai Nakatsu Hospital. From January 2006 to December 2013, we reviewed all pancreatitis patients data in our hospital, retrospectively. Then, >18 years old patients with SAP diagnosed by Japanese criteria were enrolled in this study. Also, patients with cancer related pancreatitis and/or immunosuppressed patients were excluded. Thereby, 54 patients with SAP were enrolled in this study. All patient data was gathered from an electronic database. Age, gender, and etiology were recorded from chart reviews. A diagnosis of acute pancreatitis was made based on 2 of 3 of the following symptoms: abdominal pain, abnormal elevation of amylase and/or lipase, and pancreatic inflammation indicated by computed tomography (CT) imaging [6,29]. SAP was diagnosed using Japanese severity scoring system. The study enrolled patients with SAP whose treatment began within 48 h of onset.

Assessment of severity

To evaluate the severity of acute pancreatitis, C-reactive protein (CRP) [2], number of patients with Blood Urea Nitrogen (BUN) ≥20 mg/dl [30], Acute Physiology and Chronic Health Evaluation II (APACHE II) score [31,32], Systemic Inflammatory Response Syndrome (SIRS) score [33], Sequential Organ Failure Assessment (SOFA) score [34], and Japanese severity score [35] were calculated before treatment (admission day = day 0) and after the start of treatment (day 3 and 7), based on retrospective reviews of medical charts. A diagnosis of pancreatic necrosis (or ischemia) based on conventional contrast-enhanced CT (CECT) was recorded. Also, patients with acute necrotizing collection (ANC) ≥6 cm (maximum transverse diameter) (n = 20) was measured based on CT or magnetic resonance imaging (MRI) image.

We defined organ failure as the followings: renal failure: serum creatinine >1.9 mg/dL; respiratory failure: PaO_2/FiO_2 ratio <300 mmHg; central nervous system failure: Glasgow coma score <13; coagulopathy: platelet count ≤8.0×10^{10}/L; and cardiovascular failure: systolic blood pressure ≤90 mmHg despite fluid replacement [36]. We defined persistent organ failure (POF) as organ failure persisting for at least 48 h.

Clinical outcomes

Length of hospital stay, need for Intensive Care Unit (ICU) care, length of ICU stay, development of WON and/or POF, and mortality were recorded. WON was diagnosed according to revised Atlanta criteria [37] and previous study [38], using CT or MRI obtained at 4 weeks or later after admission. Single board certificated radiologist, who had 20 years over experience as abdominal image, reviewed blindly all of images.

Treatment strategy for early stage acute pancreatitis

Enrolled patients were treated based on the strategy recommended in the Japanese guidelines for early stage acute pancreatitis [39–42]: in brief, fasting, aggressive fluid therapy, and administration of a protease inhibitor (nafamostat mesilate: 0.06–0.20 mg/kg/hours infused continuously; gabexate mesilate: 20–39 mg/kg/day). Continuous regional arterial infusion of the protease inhibitor (nafamostat mesilate) and prophylactic antibiotics (CRAI) [43–45] was undertaken for patients with ischemic or necrotizing pancreatitis [46,47]. Intravenous antibiotics were admitted for patients suspected to have sepsis (high fever with shock-like states).

Recombinant human soluble thrombomodulin

All patients with DIC were treated using recombinant human soluble thrombomodulin (rTM) (Recomodulin® Injection, Asahi Kasei Pharma Corporation, Tokyo, Japan) (380 U/kg/day or 130 U/kg/day for patients on hemodialysis) [18]. DIC was diagnosed based on a JAAM criteria score of 4 points or higher [18,48]. JAAM criteria assign 1 point for cases involving SIRS, mild thrombopenia (platelet count ≥8.0 and <12.0×10^{10}/L, or >30% decrease within 24 h from admission), and prolongation of prothrombin time-international normalized ratio (≥1.2) and mild elevation of fibrin/fibrinogen degradation products (FDP) values (≥10 and <25 μg/mL). JAAM criteria also assign 3 points for severe thrombopenia (<8.0×10^{10}/L or >50% decrease within 24 h), severe elevation of FDP values (≥25 μg/mL). The rTM treatment was maintained until DIC scores improved to a JAAM score of ≤3.

Changes involving severity, coagulation abnormality and inflammatory response

We investigated patient severity (CRP, SOFA score, APACHE II score, JPN score) on day 0, day 3, and day 7. At the same timing of the severity evaluations, we also measured platelet count, FDP, plasma thrombin–antithrombin III complex (TAT), D-dimer, Interleukin-6 (IL-6), and high morbidity group box 1 (HMGB-1).

Clinical outcomes patients with and without development of WON

We finally investigated length of hospital stay, need for ICU care, length of ICU stay, number and cost of follow-up CT/MRI within 1 year from onset, POF, and mortality, according to patients with and without development of WON.

Statistical analysis

Of the 54 patients, 24 (44.4%) developed DIC and were treated by rTM. The patients were divided into two groups, based on whether rTM was administered or not administered: rTM(+) (rTM group, n = 24) and rTM(−) (control group, n = 30). Then, outcomes, and involving severity coagulation abnormality and inflammatory response were compared between rTM group and control group.

Descriptive statistics are presented as mean ± standard deviation (SD) or a number (percent). Between the two groups, values were compared using the chi-square test or Mann–Whitney U test with Bonferroni corrections. A p-value of <0.05 was deemed to