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High-dose *versus* low-dose octreotide in the treatment of acute pancreatitis: A randomized controlled trial☆

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ABSTRACT

To evaluate the therapeutic efficacy of high-dose octreotide in patients with predicted severe acute pancreatitis (SAP) or SAP, two hundred and thirty-six patients with predicted SAP and 136 patients with SAP were randomized into control, high-dose octreotide (High-O) and low-dose octreotide (Low-O) groups. In addition to the conventional managements administrated in control group, High-O group received an intravenous infusion of octreotide at 50 μg/h × 3d + 25 μg/h × 4d, and Low-O group received octreotide at 25 μg/h × 7d. The major primary outcomes included the numbers of predicted SAP patients which developed SAP after intervention and the number of patients with SAP amelioration. Secondary outcomes included APACHE II, SIRS scores, plasma levels of somatostatin (SST), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). There were no significant differences between the control and Low-O groups in terms of prevention and treatment for SAP. The incidence of SAP in patients with predicted SAP who received High-O was significantly lower than the Low-O group: 37.5% *vs.* 59.8%, $p = 0.005$. Compared with Low-O group, the number of SAP patients in the SAP arm in the High-O group was reduced by 29.8%. Plasma levels of SST in both predicted SAP and the SAP patients were efficiently recovered (from 132.71 ± 31.40 pg/ml to 180.00 ± 23.50 pg/ml, $p < 0.05$) after high-dose octreotide supplementation, which concomitantly reduced TNF-α and IL-6 levels. High-dose octreotide administration within 48 h after AP onset may efficiently reduce the risk of SAP developing and partly attenuate SAP through raising plasma SST to a normal level and decreasing IL-6 and TNF-α.

1. Introduction

Severe acute pancreatitis (SAP) is a life-threatening illness. A large body of experimental and clinical evidence suggests that excessive inflammatory cascade-like reactions play a key role in the pathogenesis of multiple organ dysfunction (MODS) and extensive pancreatic necrosis in SAP [8]. Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), are recognized as markers of the severity of acute pancreatitis (AP) [28]. Despite the wide use of various supportive modalities for SAP, there are several ongoing investigations of anti-inflammatory agents for the prevention of organ failure in SAP [23,48].

Octreotide, a long-acting synthetic peptide somatostatin (SST) analog, has been indicated for the regulation of immune inflammatory response and for suppression of the release of pro-inflammatory cytokines beside the inhibitory effects on exocrine pancreatic secretions [34]. The anti-inflammatory effects of octreotide suggest that it may be a potential therapeutic option for AP [27,35,55]. Octreotide may ameliorate the deleterious consequences of AP *via* its suppressive effects on the release of IL-6 and TNF-α [2,32,42]. However, the application of octreotide in the treatment of AP remains inconclusive. The variations in the study design of existing clinical trials may contribute to the conflicting results. In these studies, the octreotide doses have varied from 300 μg/d to 1500 μg/d without the consideration of the plasma levels of SST during AP [26]. The dramatic SST decrease in patients with AP and other critical illnesses suggests that a replacement therapy of an exogenous SST supplement or octreotide for AP patients might, therefore, be a rational intervention [51,54].

Theoretically, the optimal dosage and duration of octreotide administration should be tailored on the bases of plasma levels of SST or cytokines because of the variance of the inflammatory reactions in patients. When the plasma SST levels or cytokines cannot be monitored in real time in order to adjust the SST or octreotide

☆ Trial registration chictr.org: ChiCTR-TRC-10000844 at the Chinese Clinical Trial Registry.

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Table 1
Criteria for inclusion of the patients.

Aged between 18–70 years
Symptoms consistent with AP, serum amylase and/or lipase increased at least three times the upper limit of normal range, pancreatitis shown by abdominal ultrasound or CT scan
Admission within 48 h from the onset of symptoms
APACHE II scores ≥8 within 48 h after AP onset
No other severe diseases such as cirrhosis, chronic obstructive pulmonary disease, chronic renal insufficiency, malignant tumors, et al.
No pregnancy, alcohol dependence, drug abuse, or psychosis
Provision of written, informed consent

dosing, an efficient regimen of octreotide for the prevention or treatment of SAP is of great value and should therefore be explored. On the basis of plasma SST and cytokine levels established in the preliminary studies [54], we designed a prospective randomized controlled study in patients with acute pancreatitis to evaluate the efficacy of octreotide at high-dose in preventing and relieving SAP.

2. Materials and methods

2.1. Participants

This randomized controlled trial was conducted from October 2010 to December 2011 in the Department of Gastroenterology, West China Hospital, Sichuan University in the People's Republic of China. The study protocol was registered as ChiCTR-TRC-10000844 at the Chinese Clinical Trial Registry and was approved by the medical ethics committee. Written, informed consents were obtained from all the patients or from their responsible relatives before enrolment.

The criteria for inclusions of the patients were listed in Table 1. Prior to randomization, each patient was evaluated according to multiple scoring systems, including the Acute Physiology and Chronic Health Evaluation scale (APACHE II) [24], the systemic inflammatory response syndrome scale (SIRS) [17,37] and the multiple organ failure scale (MOF) [25]. Patients with alcohol dependence screened by AUDIT and DSM-IV [19] were excluded in this study because chronic alcoholics are predisposed to the development of a systemic inflammatory response syndrome (SIRS) *via* up-regulation of the TLR4–TBK1 pathway [56].

Predicted SAP in this study was defined as an APACHE II score ≥8 but MOF < 2 within 48 h after AP onset [5,21]. SAP was defined as persistent multiple organ failure (APACHE II score ≥8 and MOF score ≥2) and/or CT severity index (CTSI) ≥6, local complications (the size of pancreatic necrosis >50%, pseudocyst, abscess, and hemorrhage) and/or mortality [9,47]. All of the clinical data were evaluated using history-taking, a routine abdominal ultrasound (US) or compute tomography (CT) scan, and biochemical tests.

2.2. Randomization, intervention and follow-up

Firstly, all eligible patients were assigned into the predicted SAP and the SAP arms. Then, the patients in each arm were individually randomized into three parallel groups, the control, the high-dose octreotide (High-O) and the low-dose octreotide (Low-O) groups, by using computer-generated randomization numbers. The randomization in six groups of the open study was confirmed by a doctor assigned to oversee enrolment of patients and a nurse assigned to allocate patients into groups. However, the physician responsible for overseeing the randomization process was not directly involved in patient care. The physicians and nurses who managed the patients were blinded so that they did not know the patient has been allocated to and what treatment they had received.

In addition to the conventional managements for AP applied in the control group, the patients in the High-O groups were given an intravenous infusion of octreotide (Sandoz, Basel, Switzerland) at 50 μg/h × 3d + 25 μg/h × 4d, and the patients in the Low-O group received an intravenous infusion of octreotide at 25 μg/h × 7d. The conventional managements included intensive care, supportive treatments, adequate fluid resuscitation (urine >0.5 ml/kg/h), analgesia, oxygen administration, nasogastric suction in the event of gastroparesis or ileus, and the suspension of oral feeding. An intravenous infusion of levofloxacin (Cravit® Daiichi, Beijing, China) at 500 mg/d was prescribed for up to 14d when biliary tract or pancreatic infections were suspected (1 of the following criteria (1) fever, pain in the right upper quadrant, jaundice and shock in the early stage of AP; (2) pancreatic necrosis manifested by septic with leukocytosis, fever, and/or organ failure). Once the infection was deemed unconfirmed or had been well controlled, the antibiotic therapy was discontinued [5,44,53]. Emergent therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with or without biliary drainage was performed for patients with ampullary obstruction [45]. The obvious alleviation of abdominal pain and the recovery of bowel sounds were indicators for the resumption of same oral feeding in every group. Naso-jejunal enteral nutrition was not recommended to the patients because it was often impractical and nasogastric feeding seemed to be equivalent in terms of safety and outcomes while being more practical [1].

On post-treatment day 8, all of the patients were assessed using the APACHE-II, SIRS and MOF scales as well as contrast-enhanced abdominal CT scans. During study day 28 and 30, the second assessment was conducted by using abdominal US or CT scans to detect any localized complications. Patients were discharged when they were afebrile, free of abdominal pain and tolerable of oral diet. The clinical courses of the patients were documented until hospital discharge and at the post-discharge follow-up evaluations.

2.3. Efficacy outcomes

The major primary outcomes included: (1) the percentage of predicted SAP which developed into SAP; (2) the amelioration of SAP. Both were in term of MOF score, organ failure, CTSI ≥6 at day 8 or local complication at 1 month and death rate. Secondary outcomes included APACHE II, SIRS scores, the length of hospitalization, the plasma levels of SST or SST-like immunoreactivity (SST-LIR), cytokines (IL-6, TNF-α), C-reactive protein (CRP), and triglycerides in the peripheral circulation. Other variables such as temperature, pulse, respiratory rate, blood pressure, abdominal pain, vomiting, diarrhea, glucose, SST-LIR, total bilirubin, aspartate aminotransferase, creatinine, and the number of cases which needed antibiotics were monitored for safety reasons during the treatment.

2.4. Radioimmunoassay for plasma SST and inflammatory cytokines

The plasma levels of SST, IL-6, and TNF-α were measured by radioimmunoassay. The plasma samples of normal controls were taken from 64 healthy adult volunteers, aged 18–70 years. All qualified volunteers and patients provided written consents prior to the collection of peripheral vein blood.

The blood samples were collected just before and at the end of 1 week of clinical management. 2 ml of venous blood were mixed with 60 μl of 10% ENDA-Na_2 and aprotinin (Roche, Munich, Germany 25KIU/μl) in pre-cooled tubes and were immediately centrifuged (4 °C, 3000 rpm for 15 min). The 0.5 ml of plasma was moved into another tube filled with 50 μl of acetic acid. The mixture was centrifuged (4 °C, 1500 rpm for 15 min) twice after the addition of 2 ml of 100% acetone pre-cooled at 4 °C. The supernatant was collected, dried with a freeze dryer, and frozen at (−70 °C) until analysed. The levels of SST or SST-LIR, IL-6, and

TNF-α were measured with radioimmunoassay kits (^{125}I-SST, ^{125}I-IL-6, or ^{125}I-TNF-α, Radioimmunity Research Institute, Beijing, China). After the supernatant was completely aspirated, the radioactivity of the pellet was counted in a gamma counter. The plasma levels of SST or SST-LIR, IL-6, or TNF-α were normalized as pg/ml. Because octreotide, a synthetic octapeptide analog of SST, shares up to 11 amino acids with its natural form, and therefore the radioimmunoassay could not distinguish SST and octreotide. In the preliminary SST measurement, octreotide was able to competitively replace the binding of ^{125}I-SST with its antibody. The total SST antibody bindings in the plasma after the octreotide infusion were then defined as SST-LIR. All of the blood samples were evaluated in the Division of Peptides Related to Human Diseases at the Key Laboratory of Biotherapy of Human Diseases, West China Hospital.

CRP, triglyceride, total bilirubin, aspartate aminotransferase, and creatinine were measured in the Clinical Laboratory of West China Hospital.

2.5. Statistical analysis

The sample size was estimated by using two-sided calculations with an α of 0.05 and a power of 90% based on (1) an estimated 23% reduction of the number of patients from predicted SAP to SAP according to our recent data which showed that SAP developed in 22.8% obese patients (high-risk population for SAP) who were treated with conventional management without SST or SST analog [54] and (2) an estimated 30% reduction of the number of patients with MOF score ≥2 at day 8 that needed to evaluate the amelioration of SAP [38]. A priori power calculation indicated that a sample size of 77 in each group within the predicted SAP arm and 45 in each group within SAP arm was sufficient to detect the changes caused by octreotide at high dose. The risk ratio (RR) and relative risk reduction (RRR) were calculated with a confidence interval (CI) of 95%.

Data were collected and entered into a database for analysis (SPSS 11.5 for Windows). Statistical analysis was performed with the Levene's Test for Equality of Variances. Categorical data were analysed using the Pearson Chi-Square test. The APACHE II and MOF scores were compared using the Kruskal–Wallis Test U Test among three groups and Mann–Whitney *U* test between each two groups. One-Way ANOVA and Independent Samples *T* test were applied in the situation of a normal distribution for variables including age, body mass index (BMI), SIRS score, SST, TNF-α, and IL-6 among three and between each two groups, respectively. The threshold of significance was set at $p < 0.05$. No modification of methods was made during the observation period.

3. Results

3.1. Patient characteristics

A total of 377 patients with AP were assessed for eligibility. The final cases available for evaluation were shown in Fig. 1. Sixty-four healthy adult volunteers were enrolled for SST, TNF-α and IL-6 measurement.

Two hundred and thirty-six patients with predicted SAP and 136 patients with SAP were separately randomized into control, High-O and Low-O groups. No patients dropped out of the trial during the observation period. The baseline data for those cases with predicted SAP or with SAP among three groups were comparable, $p > 0.05$ (Tables 2 and 3).

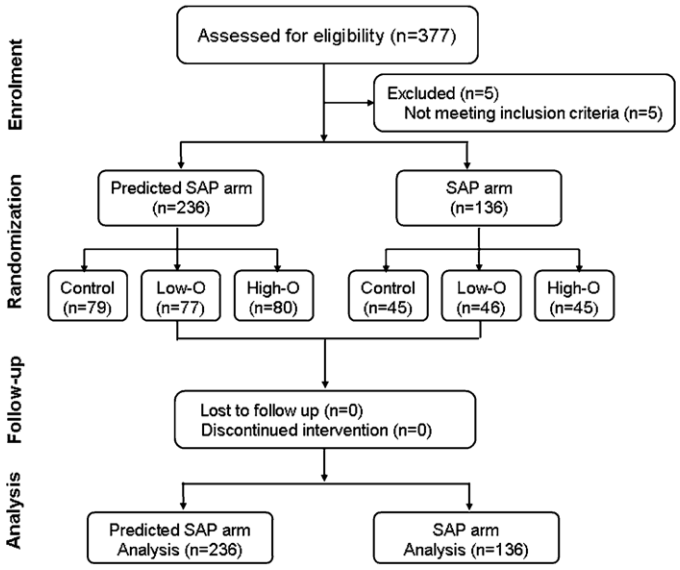

Fig. 1. Flow diagram of the trial. SAP: severe acute pancreatitis; Low-O: low-dose octreotide; High-O: high-dose octreotide.

3.2. Outcomes of the patients with predicted SAP

The total percentage and the variables of SAP in the Low-O group of predicted SAP arm were not significantly different from those in the control group, 59.8% *vs*. 70.9%, $p = 0.143$ (Table 2). They were greatly decreased in High-O group, $p < 0.05$ (Table 2). Compared with other two groups, approximately 33% or 22% reduction of SAP development was separately achieved with higher dosage. The sample size allowed a sufficient power ($1 - \beta = 0.881$) to detect a 22% decrease in SAP progressed from the predicted SAP. RRR for the development of SAP in the High-O group was 0.37 (95% CI, 0.21–0.77) compared with the Low-O group. On the 8th day of octreotide infusion, the mean APACHE II score and CTSI in the High-O group were significantly lower than those in the Low-O group, $p < 0.05$. At one month after AP onset, the percentage of local complications in the High-O group was also significantly lower than that in the Low-O group, $p < 0.05$. The number of cases which required surgical necrosectomy or drainage of pancreatic pseudocysts and the number of death were less than 4 in each group. No statistical significance differences were shown, $p > 0.05$ (Table 2). The days of hospitalization in the patients of the High-O group were significantly fewer than those in the Low-O group, which was close to the control group (Table 2).

3.3. Outcomes of the patients with SAP

The number of patients with amelioration of SAP in the Low-O group was not significantly different from that in the control group (41.3% *vs.* 33.3%, $p = 0.432$), with a power of 88.1%. The incidences of organ failure, local complications, APACHE II, SIRS, and MOF scores were also not significantly different between the two groups, $p > 0.05$ (Table 3).

Compared with the Low-O group, the number of SAP patients at day 8 in the High-O group was reduced by 29.8%, $p = 0.004$ (Table 3), which was very close to the estimation in the sample size calculation. RRR for SAP in the High-O group was 0.51 (95% CI, 0.12–0.68) compared with the Low-O group. Among the variables of amelioration of SAP, APACHE II, SIRS, and MOF scores in the High-O group were significantly lower than those in the Low-O group ($p = 0.000$, 0.000 and 0.019, respectively). There were no significant differences among other primary outcome variables related to SAP

Table 2
Baseline characteristics at enrolment and outcomes of the patients with predicted SAP.

Variables	Control ($n=79$)	Low-O ($n=77$)	High-O ($n=80$)	p
Baseline characteristics				
Gender (m/f) [a]	41/38	40/37	42/38	0.996
Age (years, mean ± SD) [b]	44.09 ± 10.24	45.90 ± 11.60	42.33 ± 8.45	0.089
BMI (kg/m^2, mean ± SD) [b]	26.81 ± 1.54	26.98 ± 1.54	26.65 ± 1.53	0.407
APACHE II score, median (range) [c]	10.0(8–15)	9.0(8–15)	10.0(8–14)	0.122
MOF score, median (range) [c]	1.0(0–1)	1.0(0–1)	1.0(0–1)	0.895
Case with: *n* (%) [a]				0.986
Gallstones	37(46.8%)	36(46.8%)	38(47.5%)	
Alcohol drinking	20(25.3%)	22(28.6%)	22(27.5%)	
Hypertriglyceridemia (>11.3 mmol/L)	22(27.8%)	19(24.7%)	20(25.0%)	
ERCP	18(22.8%)	19(24.7%)	16(20.0%)	0.779
Interval hours, median (range) [c]	25.0(11–48)	24.0(9–48)	24.0(12–48)	0.257
Primary outcomes				
SAP, *n* (%) [a]	56(70.9%)	46(59.8%)	30(37.5%) [△,&]	0.000
MOF score at day 8, median (range) [c]	2.0(0–4)	1.0(0–3)	1.0(0–3) [△,&]	0.000
Organ failure at day 8, *n* (%) [a]	45(57.0%)	35(45.5%)	18(22.5%) [△,&]	0.000
CTSI ≥6 at day 8, *n* (%) [a]	55(69.6%)	45(58.4%)	29(36.3%) [△,&]	0.000
Local complication at 1 m, *n* (%) [a]	55(69.6%)	45(58.4%)	29(36.3%) [△,&]	0.000
Surgical necrosectomy [a]	4(5.1%)	3(3.9%)	2(2.5%)	0.700
Drainage of pancreatic pseudocysts [a]	3(3.8%)	3(3.9%)	3(3.8%)	0.999
Death, *n* (%) [a]	2(2.5%)	3(3.9%)	1(1.3%)	0.574
APACHE II score at day 8, median (range) [c]	6(2–12)	5.0(3–7)	4.0(2–7) [△,&]	0.000
Days of hospitalization (d, mean ± SD) [b]	15.37 ± 3.37	15.52 ± 3.78	13.25 ± 2.46 [△,&]	0.000

Interval hours: the interval between the initiation of octreotide treatment and the onset of AP.
[a] Chi-square test.
[b] One-way ANOVA.
[c] Kruskal–wallis test *U* test.
[△] High-O *vs.* Low-O, $p<0.05$.
[&] High-O *vs.* Control, $p<0.05$.

Table 3
Baseline characteristics at enrolment and outcomes of the patients with SAP.

Variables	Control ($n=45$)	Low-O ($n=46$)	High-O ($n=45$)	p
Baseline characteristics				
Gender (m/f) [a]	25/20	27/19	23/22	0.766
Age (years, mean ± SD) [b]	47.69 ± 11.31	50.04 ± 10.32	46.98 ± 10.78	0.369
BMI (kg/m^2, mean ± SD) [b]	27.18 ± 2.18	26.72 ± 1.56	26.99 ± 2.12	0.537
APACHE II score, median (range) [c]	9(8–18)	9.5(8–18)	10.0(8–18)	0.690
SIRS score, mean ± SD [b]	6.67 ± 2.21	6.87 ± 2.19	6.24 ± 2.26	0.394
MOF score, median (range) [c]	3.0(2–5)	3.0(2–4)	3.0(2–5)	0.958
Case with: *n* (%) [a]				0.925
Gallstones	23(51.1%)	26(56.5%)	21(46.7%)	
Alcohol drinking	9(20.0%)	8(17.4%)	10(22.2%)	
Hypertriglyceridemia (>11.3 mmol/L)	13(28.9%)	12(26.1%)	14(31.1%)	
ERCP	18(40.0%)	20(43.5%)	17(37.8%)	0.855
Interval hours, median (range) [c]	30.0(16–48)	31.0(21–48)	30.0(11–48)	0.363
Primary outcomes – amelioration of SAP				
Patients with amelioration of SAP *n* (%)	15(33.3%)	19(41.3%)	32(71.1%) [△,&]	0.001
MOF score at day 8, median (range) [c]	2.0(0–5)	2.0(0–5)	1.0(0–5) [△,&]	0.016
Organ failure at day 8, *n* (%) [a]	30(66.7%)	27(58.7%)	13(28.9%) [△,&]	0.001
CTSI ≥6 at day 8, *n* (%) [a]	35(77.8%)	29(63.0%)	27(60.0%)	0.159
Local complication at 1 m, *n* (%) [a]	33(73.3%)	26(56.5%)	24(53.3%)	0.112
Surgical necrosectomy [a]	7(15.6%)	5(10.9%)	6(13.3%)	0.804
Drainage of pancreatic pseudocysts [a]	8(17.8%)	8(17.4%)	6(13.3%)	0.817
Death, *n* (%) [a]	4(8.9%)	4(8.7%)	3(6.7%)	0.912
APACHE II score at day 8, median (range) [c]	5(2–12)	5.0(4–12)	4.0(2–12) [△,&]	0.001
SIRS score at day 8, mean ± SD [b]	3.38 ± 1.34	3.70 ± 1.26	2.44 ± 1.34 [△,&]	0.000
Days of hospitalization (d, mean ± SD) [b]	16.00 ± 7.23	15.74 ± 6.52	16.22 ± 7.59	0.949

Interval hours: the interval between the initiation of octreotide treatment and the onset of AP.
[a] Chi-square test.
[b] One-way ANOVA.
[c] Kruskal–wallis test *U* test.
[△] High-O *vs.* Low-O, $p<0.05$.
[&] High-O *vs.* Control, $p<0.05$.

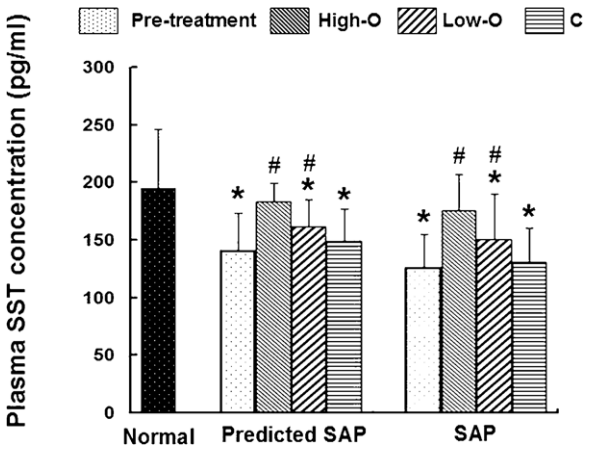

Fig. 2. Plasma levels of SST and SST-LIR in every group. The data of control, High-O or Low-O group was measured on the 7th day after treatment. All values were presented as the mean ± SD from all the patients in every group in which duplicate measurements were made. * *vs.* normal, $p < 0.05$; # *vs.* pre-treatment in every group, $p < 0.05$.

including CTSI, local complications, deaths, and the length of the hospital stay between two groups, $p > 0.05$ (Table 3).

3.4. Plasma levels of SST and SST-LIR in the AP patients

The pre-treatment plasma levels of SST in the patients with either predicted SAP or SAP were significantly lower than in healthy adult volunteers (140.11 ± 33.12 pg/ml or 125.31 ± 29.67 pg/ml *vs.* 195.12 ± 50.77 pg/ml, $p < 0.05$). The SST levels of three arms in the patients with either predicted SAP or SAP were not obviously different at enrolment, $p > 0.05$. The higher dose of octreotide greatly enhanced the SST-LIR level in the peripheral circulation, approximating the level in healthy persons (Fig. 2). In contrast, the plasma levels of SST-LIR in the patients in the arms treated with low doses of octreotide were still significantly lower than those of healthy controls, $p < 0.05$.

3.5. Plasma levels of cytokines and biochemical markers in the AP patients

Peripheral blood levels of IL-6 and TNF-α in healthy adult volunteers were 114.33 ± 19.43 pg/ml and 1270 ± 240 pg/ml, respectively. The plasma levels of both cytokines were greatly increased at the onset of AP ($p < 0.05$) when compared with healthy volunteers. They dramatically declined in all patients treated with octreotide when compared with pre-treatment, $p < 0.05$. The High-O group in both the predicted SAP and SAP arms showed lower cytokine levels than did the Low-O group, $p < 0.05$ (Fig. 3).

CRP and triglyceride levels were comparable at enrolment among three groups, $p > 0.05$. The great decreases of the serum level of CRP (243.27 ± 91.80 mg/L to 191.30 ± 72.14 mg/L, $p = 0.000$) and triglyceride (9.86 ± 9.47 mmol/L to 5.19 ± 4.98 mmol/L, $p = 0.000$) after one week of treatment were only observed in the High-O group in both the predicted SAP and SAP arms. There were no significant differences of cases which needed antibiotics among three groups either in the predicted SAP (Control, Low-O *vs.* High-O: 55.7%, 49.4% *vs.* 50.0%, $p = 0.681$) or SAP (Control, Low-O *vs.* High-O: 55.6%, 63.0% *vs.* 57.8%, $p = 0.757$) arms after one week treatment. No adverse events related to the octreotide infusion were observed.

4. Discussion

AP is characterized by a broad pathologic spectrum, ranging from minimal edema to fulminant pancreatic necrosis, which can lead to severe cases of SIRS, MODS, and even death [4,11]. Similar to other reports [14,30,49], predicted SAP developed into SAP in about 70.9% of the patients in this study. However, octreotide at high dose (intravenous infusion at 50 μg/h × 3d + 25 μg/h × 4d) efficiently prevented the occurrence of SAP with RRR = 0.37 (95% CI, 0.21–0.77). It is of clinical implication that in patients with predicted SAP that organ failure at day 8 and local complications were decreased by 34.5% and 33.3% separately after high-dose octreotide treatment. As a result, the hospital stay was also obviously reduced. The total surgical procedures (<8%) and the death rates (<3%) in predicted SAP patients were much lower than the detect power (22%) designed in this study. Whether the high-dose regime can reduce the incidence of surgical necrosectomy, drainage or death rate requires further clinical studies with large-size samples. Unlike the patients with predicted SAP, High-O regime only significantly attenuated organ failure in the SAP patients. Even so, this outcome might also be beneficial for patients in terms of less need for organ supports and less medical expenses. The failure to reduce local complications might indicate that octreotide may not be effective for the already necrotic pancreas.

The clinical outcomes of octreotide on the treatment of AP have been evaluated since 1990s [3]. The octreotide doses varied from 300 μg/d to 1500 μg/d in those studies (Table 4) without considering the plasma levels of SST during AP. The significant differences of efficacies on AP between the Low-O and High-O regimens in this study may partly interpret the controversies of previous conclusions. Even at higher doses, the divergent prognoses of mixture with mild AP, predicted SAP and SAP may influence the various responses to a curative strategy (Table 4). The curative outcomes of octreotide in the patients with predicted SAP were superior to those in the patients with SAP in the present study, indicating the necessity of separately assessing the variables of AP patients at different stages of illness.

SAP is a dynamic process that diverges from the course of mild disease mainly by an overwhelming inflammatory reaction [16]. Through the anti-inflammatory effect, inhibition of pancreatic secretion, regulation of sphincter tone of Oddi [6,13] preventing mucosal damage [18] and preservation of the microvascular barrier [50], suppression of the rapidly deteriorating AP at its mild stage with octreotide may transform this disease into a self-limiting condition. This result has been demonstrated in multiple animal experiments when SST or octreotide treatment was started along with or before the onset of AP [12,27]. However, the octreotide dose that was previously found to have positive effects on mortality in more than 80% of animal studies of AP had only shown similar effects in less than 10% of human trials [39]. There were no significant improvements among moderate or severe acute pancreatitis patients with respect to mortality and level of complications [29,43]. These negative results may have resulted from the delay in administration of SST or octreotide in AP patients [20]. The interval between the initiation of octreotide treatment and the onset of AP has not been addressed in clinical studies (Table 4). Only one study included patients within 12 h of the onset of symptoms, and this study had shown favorable effects for octreotide with respect to Il-6 levels [32]. By contrast, a multicentre randomized controlled trial which initiated octreotide treatment of AP within 96 h after the onset of symptoms, reported no benefit for octreotide [43]. The data from this study suggested that within 48 h after AP onset may be recommendable for octreotide treatment till the optimum interval is determined. Moreover, octreotide, a peptide with a much longer half-life than native SST, is also suitable for subcutaneous administration. To achieve the earlier intervention, an intravenous infusion of octreotide is also necessary because subcutaneous administration may be slower in terms of the absorption of the agent.

SST released from the sensory nerve endings and neuroendocrine cells in the gastrointestinal tract not only exerts the local

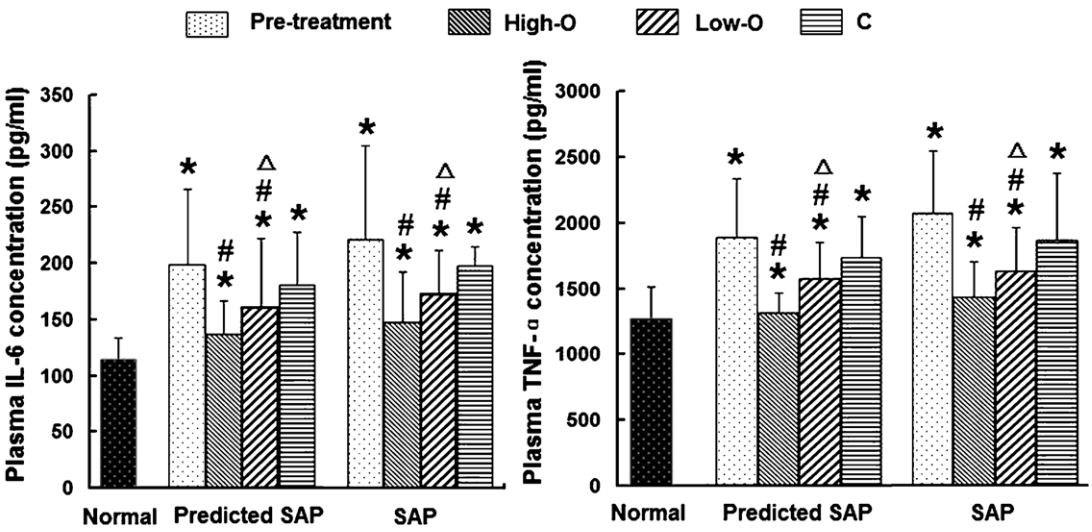

Fig. 3. Plasma levels of IL-6 and TNF- α in every group. The data of control, High-O or Low-O group was measured on the 7th day after treatment. All values were presented as the mean ± SD from all the patients in every group in which duplicate measurements were made. * *vs.* normal, $p < 0.05$; # *vs.* pre-treatment in every group, $p < 0.05$; △ High-O *vs.* Low-O, $p < 0.05$.

interactions with inflammatory mediators, but also reaches distant parts of the body *via* the systemic circulation, acting as a systemic anti-inflammatory agent [40]. Experiments in rats and macaques performed by our group have revealed that SST targets multiple cytokines *via* the intestinal mucosal mast cells and the Toll-like receptor 4 (TLR4)–nuclear factor-κB (NF-κB) cytokine pathway simultaneously [41,52]. The present data showed a 32% decrease of plasma SST in patients with predicted SAP and SAP at the early stage of the disease compared with healthy controls. At the same time, the plasma levels of IL-6 and TNF-α increased by 84% and 56% in those patients. The reduction of endogenous SST might be attributed to intestinal ischemia-reperfusion, which led to the injury of the intestinal mucosa as SAP progressed [51,52]. An immediate intravenous infusion of high-dose octreotide greatly enhanced the SST levels in the peripheral circulation, nearing the levels measured in healthy adult. The SST replacement was associated with the dramatic decline of IL-6, TNF-α, CRP, and triglyceride in the circulation. In comparison with low-dose octreotide treatment, the potent anti-inflammatory effects of high-dose octreotide were impressive and were not associated with other side effects like corticosteroid therapy [10] during treatment.

In previously published trials of SAP, the duration of the octreotide treatment has ranged from 5 to 14 days to the full length of the hospitalization (Table 4). It is not yet clear whether exogenous supplementation of octreotide inhibits the endogenous secretion of SST. Various desensitizing effects after long-term administration of high-dose octreotide have been observed, thought to be related to fatigue and the internalization of SST

Table 4
Clinical outcomes of acute pancreatitis treated with octreotide in literatures and the present study.

Reference	Study design	Type	No.	Interval	Dosage & duration	Major variables	Outcomes	Design weaknesses
Beechey [7] 1993	Prospective case-control study	MAP	19	N	250 μg i.h, then 0.5 μg/kg/h, i.v, × 10d *vs.* placebo	Organ dysfunction Mortality	Negative	Not RCT Small sample size Unclear interval
Nikou [32] 2004	Prospective RCT	MAP	36	<12 h	200 *vs.* 500 μg, i.h, 3 times/d × 5d	IL-6, CRP	Positive in high dosage	Small sample size Indirect clinical meaning
Yang [54] 2012	Multi-center RCT	MAP	161	<48 h	50 μg/h, i.v, × 3d *vs.* placebo	P-SAP SAP-v	Positive	Small sample size for mortality
Fiedler [15] 1996	Prospective case-control study	SAP	39	N	100 μg 3 times/d, i.v, × 10d *vs.* placebo	SAP-v	Positive	Small sample size Unclear interval
Paran [33] 2000	Case-controlled study	SAP	50	N	100 μg 3 times/d, i.h, × 14d *vs.* placebo	Organ dysfunction Local complications Hospital stay	Positive	Not RCT Small sample size Unclear interval
Mckay [29] 1997	Multi-center RCT	Mix	58	N	40 μg/h, i.v, × 5d *vs.* placebo	Complications Mortality	Negative	Unclear type & interval
Uhl [43] 1999	Multi-center RCT	Mix	302	<96 h	100 *vs.* 200 μg 3 times/d, i.h, × 7d *vs.* placebo	The duration of pain APACHE II scores SAP-v	Negative	Unclear type
Nikou [31] 2001	Prospective RCT	Mix	120	N	100 *vs.* 200 *vs.* 300 μg, 3 times/d, i.h, × 7d	The duration of pain Organ dysfunction Local complications	Little benefit only at two high dosage	Unclear type & interval
Present study	Prospective RCT	P-SAPSAP	15791	<48 h	50 μg/h, i.v, × 3d + 25 μg/h, i.v, × 4d *vs.* 25 μg/h, i.v, × 7d	SAP-v	Positive in high dosage	Not multi-center Small sample size for mortality

MAP: mild acute pancreas; SAP: severe acute pancreas; Mix: mixture of MAP and SAP; P-SAP: predicted SAP; No.: Number of patients; Interval: the time interval between onset of AP and initiation of octreotide treatment; N: Not mentioned; i.h.: subcutaneously; i.v: intravenous infusion; SAP-v: including variables as organ dysfunction, local complications and mortality.

receptors [22,36,46]. Therefore, the intravenous infusion of octreotide at 50 μg/h in this study was only administered for 3d and then decreased to 25 μg/h for 4d. The positive curative results of the octreotide treatment and the normal plasma SST levels obtained post-treatment in patients receiving twice the conventional dose of octreotide in this study implied that the 7-d treatment duration was an efficient and safe regimen.

5. Conclusions

In summary, intravenous infusion of octreotide at high dose within 48 h after AP onset may efficiently prevent and partly attenuate SAP by raising plasma SST to a normal level and inhibiting the inflammatory cytokine pathway.

Conflict of interest

The authors declare no conflicts of interest in this study. All authors have declared no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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References

[1] Al Samaraee A, McCallum IJ, Coyne PE, Seymour K. Nutritional strategies in severe acute pancreatitis: a systematic review of the evidence. Surgeon 2010;8:105–10 [PMID: 20303893].
[2] Andoh A, Hata K, Shimada M, Fujino S, Tasaki K, Bamba S, et al. Inhibitory effects of somatostatin on tumor necrosis factor-α-induced interleukin-6 secretion in human pancreatic periacinar myofibroblasts. Int J Mol Med 2002;10:89–93 [PMID: 12060857].
[3] Andriulli A, Leandro G, Clemente R, Festa V, Caruso N, Annese V, et al. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. Aliment Pharmacol Ther 1998;12:237–45 [PMID: 9570258].
[4] Bai Y, Liu Y, Jia L, Jiang H, Ji M, Lv N, et al. Severe acute pancreatitis in China: etiology and mortality in 1976 patients. Pancreas 2007;35:232–7 [PMID: 17895843].
[5] Banks PA, Freeman ML. The Practice Parameters Committee of the American College of Gastroenterology, Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–400 [PMID: 17032204].
[6] Barreto SG, Carati CJ, Schloithe AC, Toouli J, Saccone GT. Octreotide negates the benefit of galantide when used in the treatment of caerulein-induced acute pancreatitis in mice. HPB (Oxford) 2010;12:403–11 [PMID: 20662791].
[7] Beechey-Newman N. Controlled trial of high-dose octreotide in treatment of acute pancreatitis. Evidence of improvement in disease severity. Dig Dis Sci 1993;38:644–7 [PMID: 8462363].
[8] Bhatia M, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, et al. Pathophysiology of acute pancreatitis. Pancreatology 2005;5:132–44 [PMID: 15849484].
[9] Bollen TL, van Santvoort HC, Besselink MG, van Leeuwen MS, Horvath KD, Freeny PC, et al. The Atlanta classification of acute pancreatitis revisited. Br J Surg 2008;95:6–21 [PMID: 17985333].
[10] Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol 2001;33:289–94 [PMID: 11588541].
[11] Carnovale A, Rabitti PG, Manes G, Esposito P, Pacelli L, Uomo G. Mortality in acute pancreatitis: is it an early or a late event? JOP 2005;6:438–44 [PMID: 16186665].
[12] Chen CC, Wang SS, Tsay SH, Lee FY, Wu SL, Lu RH, et al. Effects of high dose octreotide on retrograde bile salt-induced pancreatitis in rats. Peptides 1998;19:543–7 [PMID: 9533643].
[13] Chen P, Hu B, Tan Q, Liu L, Li D, Jiang C, et al. Role of neurocrine somatostatin on sphincter of Oddi contractility and intestinal ischemia reperfusion-induced acute pancreatitis in macaques. Neurogastroenterol Motil 2010;22:935–44 [PMID: 20497509].
[14] Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Prediction of the severity of acute pancreatitis. Am J Surg 1993;166:262–8 [PMID: 8368436].
[15] Fiedler F, Jauernig G, Keim V, Richter A, Bender HJ. Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. Intensive Care Med 1996;22:909–15 [PMID: 8905425].
[16] Greer SE, Burchard KW. Acute pancreatitis and critical illness: a pancreatic tale of hypoperfusion and inflammation. Chest 2009;136:1413–9 [PMID: 19892682].
[17] Gregoric P, Sijacki A, Stankovic S, Radenkovic D, Ivancevic N, Karamarkovic A, et al. SIRS score on admission and initial concentration of IL-6 as severe acute pancreatitis outcome predictors. Hepatogastroenterology 2010;57:349–53 [PMID: 20583441].
[18] Güler O, Akturan S, Kisli E, Dolapçi I, Caydere M, Akova A. Acute pancreatitis, bacterial translocation, and different octreotide regimens: an experimental study. Surg Today 2009;39:876–83 [PMID: 19784727].
[19] "Helping Patients Who Drink Too Much: A Clinician's Guide and Related Professional Support Resources", [online] Available: www.niaaa.nih.gov/guide
[20] Kaplan O, Kaplan D, Casif E, Siegal A, Paran H, Graf E, et al. Effects of delayed administration of octreotide in acute experimental pancreatitis. J Surg Res 1996;62:109–17 [PMID: 8606496].
[21] Khan AA, Parekh D, Cho Y, Ruiz R, Selby RR, Jabbour N, et al. Improved prediction of outcome in patients with severe acute pancreatitis by the APACHE II score at 48 h after hospital admission compared with the APACHE II score at admission. Acute Physiology and Chronic Health Evaluation. Arch Surg 2002;137:1136–40 [PMID: 12361419].
[22] Lamberts SW, van der Lely AJ, Hofland LJ. New somatostatin analogs: will they fulfil old promises? Eur J Endocrinol 2002;146:701–5 [PMID: 11980627].
[23] Lankisch PG, Lerch MM. Pharmacological prevention and treatment of acute pancreatitis: where are we now? Dig Dis 2006;24:148–59 [PMID: 16699273].
[24] Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet 1989;2:201–5 [PMID: 2568529].
[25] Lefering R, Goris RJ, van Nieuwenhoven EJ, Neugebauer E. Revision of the multiple organ failure score. Langenbecks Arch Surg 2002;387:14–20 [PMID: 11981679].
[26] Li J, Wang R, Tang C. Somatostatin and octreotide on the treatment of acute pancreatitis – basic and clinical studies for three decades. Curr Pharm Des 2011;17:1594–601 [PMID: 21548873].
[27] Marton J, Szasz Z, Nagy Z, Jarmay K, Takacs T, Lonovics J, et al. Beneficial effect of octreotide treatment in acute pancreatitis in rats. Int J Pancreatol 1998;24:203–10 [PMID: 9873955].
[28] Matull WR, Pereira SP, O'Donohue JW. Biochemical markers of acute pancreatitis. J Clin Pathol 2006;59:340–4 [PMID: 16567468].
[29] McKay C, Baxter J, Imrie C. A randomized, controlled trial of octreotide in the management of patients with acute pancreatitis. Int J Pancreatol 1997;21:13–9 [PMID: 9127169].
[30] Neoptolemos JP, Kemppainen EA, Mayer JM, Fitzpatrick JM, Raraty MG, Slavin J, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. Lancet 2000;355:1955–60 [PMID: 10859041].
[31] Nikou GC, Arnaoutis TP, Giamarellos-Bourboulis EJ, Samolada O, Vafiadis-Zouboulis I, Katsilambros N, et al. The significance of the dosage adjustment of octreotide in the treatment of acute pancreatitis of moderate severity. Hepatogastroenterology 2001;48:1754–7 [PMID: 11813617].
[32] Nikou GC, Giamarellos-Bourboulis EJ, Grecka P, Toumpanakis Ch, Giannikopoulos G, Katsilambros N. Effect of octreotide administration on serum interleukin-6 (IL-6) levels of patients with acute edematous pancreatitis. Hepatogastroenterology 2004;51:599–602 [PMID: 15086213].
[33] Paran H, Mayo A, Paran D, Neufeld D, Shwartz I, Zissin R, et al. Octreotide treatment in patients with severe acute pancreatitis. Dig Dis Sci 2000;45:2247–51 [PMID: 11215748].
[34] Pintér E, Helyes Z, Szolcsányi J. Inhibitory effect of somatostatin on inflammation and nociception. Pharmacol Ther 2006;112:440–56 [PMID: 16764934].
[35] Rau B, Baumgart K, Krüger CM, Schilling M, Beger HG. CC-chemokine activation in acute pancreatitis: enhanced release of monocyte chemoattractant protein-1 in patients with local and systemic complications. Intensive Care Med 2003;29:622–9 [PMID: 12589535].
[36] Reubi JC, Waser B, Cescato R, Gloor B, Stettler C, Christ E. Internalized somatostatin receptor subtype 2 in neuroendocrine tumors of octreotide-treated patients. J Clin Endocrinol Metab 2010;95:2343–50 [PMID: 20228164].
[37] Roumen RM, Schers TJ, de Boer HH, Goris RJ. Scoring systems for predicting outcome in acute hemorrhagic necrotizing pancreatitis. Eur J Surg 1992;158:167–71 [PMID: 1356457].
[38] Siriwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, et al. Randomized, double blind, placebo controlled trial of intravenous antioxidant (n-acetylcysteine, selenium, vitamin C) therapy in severe acute pancreatitis. Gut 2007;56:1439–44 [PMID: 17356040].
[39] Steinberg WM, Schlesselman SE. Treatment of acute pancreatitis. Comparison of animal and human studies. Gastroenterology 1987;93:1420–7 [PMID: 2445620].

[40] Szolcsányi J, Helyes Z, Oroszi G, Németh J, Pintér E. Release of somatostatin and its role in the mediation of the anti-inflammatory effect induced by antidromic stimulation of sensory fibres of rat sciatic nerve. Br J Pharmacol 1998;123:936–42 [PMID: 9535023].
[41] Tang C, Lan C, Wang C, Liu R. Amelioration of the development of multiple organ dysfunction syndrome by somatostatin via suppression of intestinal mucosal mast cells. Shock 2005;23:470–5 [PMID: 15834315].
[42] Tian H, Zhang X, Wu C, Chen L, Ying R, Ye J, et al. Effects of Baicalin and Octreotide on the serum TNF-α level and apoptosis in multiple organs of rats with severe acute pancreatitis. Inflammation 2009;32:191–201 [PMID: 19387806].
[43] Uhl W, Büchler MW, Malfertheiner P, Beger HG, Adler G, Gaus W. A randomized, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. Gut 1999;45:97–104 [PMID: 10369711].
[44] UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute, pancreatitis. Gut 2005;54:iii1–9 [PMID: 15831893].
[45] van Santvoort HC, Besselink MG, de Vries AC, Boermeester MA, Fischer K, Bollen TL, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 2009;250:68–75 [PMID: 19561460].
[46] Waser B, Tamma ML, Cescato R, Maecke HR, Reubi JC. Highly efficient in vivo agonist-induced internalization of sst2 receptors in somatostatin target tissues. J Nucl Med 2009;50:936–41 [PMID: 19443580].
[47] Werner J, Hartwig W, Uhl W, Müller C, Büchler MW. Useful markers for predicting severity and monitoring progression of acute pancreatitis. Pancreatology 2003;3:115–27 [PMID: 12748420].
[48] Wilmer A. ICU management of severe acute pancreatitis. Eur J Intern Med 2004;15:274–80 [PMID: 15450983].
[49] Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. Br J Surg 1990;77:1260–4 [PMID: 2253005].
[50] Woeste G, Wullstein C, Meyer S, Usadel KH, Hopt UT, Bechstein WO, et al. Octreotide attenuates impaired microcirculation in postischemic pancreatitis when administered before induction of ischemia. Transplantation 2008;86:961–7 [PMID: 18852663].
[51] Wu H, Deng YY, Kang Y, Huang MH, Hu L, Tang CW. Clinical implication of blood somatostatin determination in critically ill patients. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2009;21:307–10 (Article in Chinese). [PMID: 19439122].
[52] Wu H, Liu L, Tan Q, Wang C, Guo M, Xie Y, et al. Somatostatin limits intestinal ischemia-reperfusion injury in macaques via suppression of TLR4–NF-kappaB cytokine pathway. J Gastrointest Surg 2009;13:983–93 [PMID: 19184243].
[53] Wu XN. Guidelines for treatment of severe acute pancreatitis. Hepatobiliary Pancreat Dis Int 2002;1:446–51 [PMID: 14607725].
[54] Yang F, Wu H, Li YQ, Li ZS, Wang CH, Yang JL, et al. Prevention of severe acute pancreatitis with octreotide in obese patients: a prospective multi-center randomized controlled trial. Pancreas 2012;41:1206–12.
[55] Zhang XP, Zhang L, Yang P, Zhang RP, Cheng QH. Protective effects of baicalin and octreotide on multiple organ injury in severe acute pancreatitis. Dig Dis Sci 2008;53:581–91 [PMID: 17549629].
[56] Zhou C, Li J, Wang HY, Tang C. Decreased somatostatin is related to the hypersensitivity of intestinal epithelia to LPS via up-regulated TLR4–TBK1 pathway in rats chronically exposed to ethanol. Alcohol 2009;43:293–303 [PMID: 19375882].