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ORIGINAL ARTICLE

Protective Effects of Baicalin and Octreotide on Multiple Organ Injury in Severe Acute Pancreatitis

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Abstract
Purpose To discuss the application value of Baicalin which is a new drug by comparing the protecting effects of Baicalin and Octreotide on multiple organs (pancreas, liver, kidney, and lung) in Severe acute pancreatitis (SAP).
Methods The improved Aho method was adopted to prepare SAP rat models via retrograde injection of 3.5% sodium taurocholate to the pancreatic duct. The 135 SAP rat models after being prepared were randomly divided into the model group, Baicalin treatment group and Octreotide treatment group with 45 rats in each group; another 45 were selected to be the sham operation group, which only received abdomen opening surgery. The groups were then randomly divided into 3 h, 6 h and 12 h groups with 15 rats in each group, 10 min after successful modeling, the Baicalin treatment group was first injected with a 5% Baicalin injection at a dose of 10 mg/100 g via external jugular-vein passage followed by continuous intravenous administration (10 mg/h/100 g) by microinfusion pump; the Octreotide treatment group was first injected by Octreotide at a dose of 0.2 ug/100 g via external jugular-vein passage followed by continuous intravenous transfusion (10 mg/h/100 g) by microinfusion pump at a transfusion speed of 0.2 ug/h/100 g. The sham operation group and model group were injected with saline of equivalent volume at the corresponding time points after operation. The following observations were carried out 3, 6 and 12 h after operation: (1) mortalities of all rat groups followed by batch execution of rats and observation of the gross pathological changes of multiple organs; (2) observation of the pathological changes of multiple organ samples fixed according to the relevant requirements after HE staining; and (3) serum content of amylase, NO, malonaldehyde (MDA), and tumor necrosis factor alpha (TNF-α).
Results (1) The survival rate of the sham operation group and all treatment groups was 100%, whilst the 12 h survival of the model group was 66.67% (10/15), indicating a significant difference ($P < 0.05$). (2) The gross pathological changes and changes under light microscopy of multiple organs aggravated with time after modeling. The pathological changes of all treatment groups were milder

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than those of the model group at different time points by various degrees, most obviously at 6 h and 12 h. The gross pathological changes showed a similarity between the Octreotide and Baicalin treatment groups in terms of the pathological changes of pancreatic tissue. The therapeutic effects of Octreotide on kidney and lung were superior to those in the Baicalin treatment group while the pathological manifestations of the Baicalin treatment group were superior to those of the Octreotide treatment group. (3) There was no marked difference between the Baicalin and Octreotide treatment groups in terms of plasma amylase levels at all time points ($P > 0.05$). Although the plasma amylase levels of the Baicalin treatment group were lower than those of the model group at all time points, the levels in the Baicalin treatment group were significantly lower than those in the model group only at 3 h ($P < 0.05$), and there was no marked difference in the levels between the Baicalin treatment group and model groups at 6 and 12 h ($P > 0.05$); the levels in the Octreotide treatment group were significantly lower than in the model group at 6 h ($P < 0.05$), and there was no marked difference between the levels in the Octreotide treatment group and model group at 3 h and 12 h ($P > 0.05$). (4) The serum NO contents of the Baicalin treatment group were significantly lower than those of the model group ($P < 0.05$), while in the Octreotide treatment group it was obviously lower than in the model group at 3 and 12 h ($P < 0.01$); in this regard there was no marked difference between the Baicalin and Octreotide treatment groups at different time points ($P > 0.05$). (5) The serum MDA contents of the Baicalin treatment group were significantly lower than those of the model group ($P < 0.01$), while in the Octreotide treatment group it was significantly less than the model group at 6 and 12 h ($P < 0.05$), and in the Baicalin treatment group was significantly less than in the Octreotide treatment group at 12 h ($P < 0.05$). (6) There was no marked difference among the model group, Baicalin treatment group and Octreotide treatment group in terms of serum TNF-α content at 3 h and 12 h ($P > 0.05$). At 6 h the value in the Baicalin treatment group was significantly less than in the model group ($P < 0.001$), in the Octreotide treatment group it was significantly less than in the model group ($P < 0.001$), and the Octreotide treatment group it was significantly less than in the Baicalin treatment group ($P < 0.01$).

Conclusions Both Baicalin and Octreotide have obvious protective effects on the multiple organ injury in SAP with mechanisms associated to manifold factors. By comparing the pharmacologic effects of Octreotide and Baicalin, we believe that Baicalin as a new drug has a protective effect on multiple organs of a SAP rat model similar to that of Octreotide and is worth further study and development.

Keywords Severe acute pancreatitis · Baicalin · Octreotide · Pancreas · Liver · Kidney · Lung · Multiple organ protection

Introduction

Severe acute pancreatitis (SAP), which is a common surgical abdomen with rapid onset and progression, and high mortality, is a hot topic of clinical studies and an important, tough medical problem. Multiple organ dysfunction syndrome (MODS) is a common, severe complication of SAP as well as one of its main causes of death [1, 2]. Enhancing protection against multiple organ injury at an early stage during treatment of SAP is a significant factor for increasing the total survival rate of SAP. As one of the commonly used clinical medications for treating SAP [3–7], Octreotide can effectively decrease SAP complications and improve the survival rate [8, 9]. However, because of its high price it is hard to popularize its clinical application especially in remote regions with poor economic status, which makes it necessary to find other cheap and effective medications. Baicalin can resist bacteria, inflammation, inhibit platelet aggregation, remove oxygen free radicals, and reduce the generation of endotoxin. Baicalein, its metabolite in the body, also has a relatively effective pancreatin-inhibiting effect. Some studies have shown its protective effects on organs outside the pancreas in SAP [10–13]. Its many pharmacological effects can block many phases during SAP onset, similar to the effects of Somatostatin and its analogues, and it is therefore a hopeful SAP treatment [14–22]. Also Baicalin is both cheap and, having more-extensive effective approaches, has sound prospects for application. Therefore, we raise the idea of treating SAP MODS by intravenous injection of Baicalin. We compared this approach with Octreotide and studied the protective effects and mechanisms of Baicalin and Octreotide on multiple organs in SAP.

Material and examination methods

Experimental animals

Clean grade healthy male Sprague-Dawley (SD) rats with a body weight of 250–300 g were purchased from the Experimental Animal Center of the Medical School of Zhejiang University.

Experimental medicine and reagents

Sodium taurocholate and sodium pentobarbital was purchase from the USA Sigma Co.); Octreotide was purchased from the Swiss pharmaceutical company Novartis; the 5%

Baicalin injection (China national invention patent number ZL200310122673.6) was prepared by the first author at a 305 mmol/l osmotic pressure; a serum NO and MDA kit was purchased from Nanjing Jiancheng Bioengineering Institute of China with μmol/l and nmol/ml content units; a tumor necrosis factor alpha (TNF-α) enzyme-linked immunosorbent assay (ELISA) kit was purchased from China Jingmei Biotech Co., Ltd.

Determination of plasma amylase content

The fully automatic biochemistry analyzer was used to determine the plasma amylase level (U/L).

Determination of serum NO content

The serum NO content was determined by the clorimetric method.

Determination of serum MDA content

The serum NO content was determined by the clorimetric method.

Determination of serum TNF-α content

The serum TNF-α content was determined by the ELISA method in unit of pg/ml (ng/l).

Experimental methods

The improved Aho method was adopted to prepare SAP rat models via retrograde injection of 3.5% sodium taurocholate to the pancreatic duct through an epidural catheter and duodenal papilla. The 135 SAP rat models, after being prepared, were randomly divided into a model group, Baicalin treatment group and Octreotide treatment group, with 45 rats in each group; another 45 rats were selected to be the sham operation group, which only received abdomen opening surgery. These groups were then randomly divided into 3, 6 and 12 h groups, with 15 rats in each group. The following observations were made at 3, 6 and, 12 h after operation: (1) the mortalities of all rat groups, followed by batch execution of rats. The general pathological changes of multiple organs (pancreas, liver, kidney, lung) were observed; (2) collected multiple organ tissue samples were fixed according to the relevant requirements, and pathological changes and multiple organs pathological score changes under HE staining were recorded; (3) the plasma content of amylase, serum NO, MDA, and TNF-α were examined by collecting blood samples via heart puncture (operating according to the reagent instructions).

Preparation methods of animal models

Fasting with restricted water was imposed on all rat groups 12 h prior to operation. The rats were anesthetized by intraperitoneal injection of 2% sodium pentobarbital (0.25 ml/100 g) after were lain and dixed, before performing routine shaving, disinfection, and draping. After establishing the right external jugular-vein transfusion passage a microinfusion pump was used for continuous transfusion (1 ml/h/100 g), followed by 3.5% sodium taurocholate to prepare SAP model.

Model group

After entering the abdomen via a median epigastrium incision, confirming the bile-pancreatic and hepatic hilus common hepatic ducts, disclosing the pancreas, and identifying the duodenal papilla inside the duodenum duct wall, a no. 5 needle was used to drill a hole in the mesenterium avascular area. After inserting a segmental eqidural catheter into the duodenum cavity via the hole, reaching the bile-pancreatic duct in the direction of papilla in a retrograde way, a microvascular clamp was used to nip the duct head temporarily with another microvascular clamp to temporarily occlude the common hepatic duct at the confluence of hepatic duct. After connecting the anesthetic tube end with the transfusion converter, 3.5% sodium taurocholate (0.1 ml/100 g) was transfused in a retrograde fashion using the microinjection pump (made by Zhejiang University) at a speed of 0.2 ml/min. After waiting for 4–5 min after injection the microvascular clamp and epidural catheter were removed. After checking for bile leakage, the hole in the duodenum lateral wall was sutured. A disinfected cotton ball was used to absorb the anesthetic in the abdominal cavity and the abdomen was closed. The sham operation group, after receiving abdomen opening, only had the pancreas and duodenum turned over before final closing of the abdomen [14].

Dosage and methods

Baicalin treatment group

The animal experiments for 5% Baicalin injection were completed, includingan acute toxicity test and SAP rat treatment with small, medium, and large doses. The large dose can achieve the best therapeutic effect (dose is 10 mg/h/100 g) and the dosage referred to the result of the previous preliminary experiment. 10 min after successful modeling, Baicalin treatment group was first injected 5% Baicalin injection 10 mg/100 g via external jugular vein passage followed by continuous intravenous administration (10 mg/h/100 g) by microinfusion pump; Octreotide

treatment group was first injected Octreotide 0.2 ug/100 g via external jugular vein passage followed by continuous intravenous transfusion (10 mg/h/100 g) by microinfusion pump at a transfusion speed of 0.2 ug/h/100 g. All above dosages have been proved as effective dosages in the previous preliminary experiment.

Sham operation group and model group

Both of them were injected saline of equivalent volume at the corresponding time points after operation.

Statistic methods

The SPSS11.5 software was used for statistical analysis after arranging the experimental results. The Kruskal–Wallis test or variance analysis was used for comparison among four groups; the Bonfferoni test was used for comparison between two groups; the likelihood ratio chi-squared test was used for survival comparison. There is statistic significance when $P \leq 0.05$.

Results

Survival

The mortality rates of the model group were 0% (0/15), 13.33% (2/15), and 33.33% (5/15), at 3 h, 6 h and 12 h, respectively. All the mortality rates in the Baicalin and Octreotide treatment groups were 0% at each time point. The whole sham operation group survived at each time point. The survival rate of the model group was 66.67% (10/15) at 12 h, while the survival rate of both the Baicalin and Octreotide treatment groups was 100% at 12 h, indicating a significant difference ($P < 0.05$).

Comparison of plasma amylase content among all groups

The plasma amylase content of the model group and the two treatment groups significantly exceeded that of the sham operation group at each time point ($P < 0.001$); there was no significant difference between the Baicalin and Octreotide treatment groups at each time point ($P > 0.05$). Although the plasma amylase content of the Baicalin treatment group was lower than that of the model group at different time points, the level in the Baicalin treatment group was significantly lower than that in the model group at 3 h ($P < 0.05$). There was no significant difference between the Baicalin treatment group and the model group at 6 and 12 h ($P > 0.05$); the value in the Octreotide treatment group was significantly less than in the model group at 6 h ($P < 0.05$). There was no significant difference between the Octreotide treatment group and the model group at 3 and 12 h ($P > 0.05$). See Table 1.

Comparison of serum NO content among all groups

The model, Baicalin treatment and Octreotide treatment groups all significantly exceeded the sham operation group at different time points ($P < 0.001$). At the 3 and 12 h time points the value for the Baicalin treatment group was significantly less than that in the model group ($P < 0.05$), and in the Octreotide treatment group it was obviously less than in the model group ($P < 0.01$). There was no significant difference between the Baicalin and Octreotide treatment groups at different time points ($P > 0.05$). See Table 2.

Table 1 Plasma amylase level of each group [M (Q_R)]

Groups	3 h*	6 h**	12 h***
SO	1582.0000 (284.0000)	1769.0000 (362.0000)	1618.0000 (302.0000)
Model	5303.0000 (1373.0000)	6276.0000 (1029.0000)	7537.5000 (2933.5000)
Baicalin	4342.0000 (1496.0000)	5130.0000 (1591.0000)	5571.0000 (2307.0000)
Octreotide	5419.0000 (1670.0000)	5058.0000 (1314.0000)	6531.0000 (2280.0000)

* $\chi^2 = 36.289$, $P = 0.000$; ** $\chi^2 = 35.502$, $P = 0.000$; *** $\chi^2 = 34.040$, $P = 0.000$

Table 2 Serum NO level of each group [M (Q_R)]

Groups	3 h*	6 h**	12 h***
SO	7.5000 (5.0000)	7.5000 (5.0000)	10.0000 (5.0000)
Model	65.0000 (7.5000)	62.5000 (38.7500)	74.1000 (26.1500)
Baicalin	57.5000 (22.5000)	47.5000 (37.5000)	57.5000 (27.5000)
Octreotide	52.5000 (15.0000)	57.5000 (15.0000)	45.0000 (12.5000)

* $\chi^2 = 39.025$, $P = 0.000$; ** $\chi^2 = 34.711$, $P = 0.000$; *** $\chi^2 = 40.453$, $P = 0.000$

Comparison of serum malonaldehyde (MDA) content among all groups

The MDA content in the model group, the Baicalin treatment group and the Octreotide treatment group all significantly exceeded that in the sham operation group at different time points ($P < 0.05$); the value in the Baicalin treatment group was obviously less than that in the model group ($P < 0.01$); the value in the Octreotide treatment group was significantly less than that in the model group at 6 and 12 h ($P < 0.05$); the value in the Baicalin treatment group was significantly lower than that in the Octreotide treatment group at 12 h ($P < 0.05$). See Table 3.

Comparison of serum TNF-α content among all groups

The serum TNF-α content in the model and treatment groups significantly exceeded that in the sham operation group at different time points ($P < 0.001$). There was no marked difference in its value among the model, Baicalin treatment and Octreotide treatment groups at 3 and 12 h ($P > 0.05$). At 6 h both the Baicalin and Octreotide treatment groups obviously had lower values than the model group ($P < 0.001$); the Octreotide treatment group had a significantly lower value than the Baicalin treatment group ($P < 0.01$). See Table 4.

Pancreas gross and pathological changes under light microscope

Sham operation group

Gross changes

There was a small amount of amber ascitic fluid within the abdominal cavity. There was no pathological change visible to the naked eye in other organs. The overall structure of the pancreas remained intact. There was no change in hemorrhage in the pancreas, which was yellowish without volume reduction; there was no obvious abnormity of rat pancreas, peripancreatic and epiploon at any time point.

Observation under light microscopy

Most samples remained normal with intact gland structure, although mild interstitial edema occurred in a very few cases; neutrophil infiltration was occasional, but no acinar cells, fat necrosis, or hemorrhage was observed.

Model group

Gross changes

The gross and pathological changes under light microscopy of pancreas tail were a little more obvious than those of pancreas head; 5 min after model induction, pancreas manifested edema, hemorrhage, and necrosis. The overall severity of the pathological changes at 3 h, 6 h and 12 h increased with time after modeling. In the 3 h group a small amount of ascitic fluid, most of it slightly bloody, was visible to the naked eye, along with obvious hyperemia and edema of pancreas, and a part with gel-like hemorrhage and necrosis. Most ascitic fluid after 6 and 12 h was bloody, with a larger amount, on average, than at 3 h. The amount and characteristics of the ascitic fluid increased and deepened with time after modeling, and the degree and range of pancreas edema; hemorrhage and necrosis were more obvious than at 3 h. Many saponified spots on peripancreatic great epiploon and peritoneum were observed, plus a gel-like change, contour vanishing, quite obvious hemorrhage, and changes in the necrosis of pancreatic tissue.

Table 3 The serum MDA level of each group [M (Q_R)]

Groups	3 h*	6 h**	12 h***
SO	9.9000 (9.9000)	16.5000 (13.2000)	16.5000 (13.2000)
Untreated	36.3000 (13.4000)	39.7000 (9.9000)	54.3500 (19.0000)
Baicalin	21.9000 (13.4500)	23.8000 (14.6000)	36.0000 (11.6000)
Octreotide	29.6000 (18.6000)	33.0000 (9.9000)	40.3000 (16.8000)

* χ^2= 27.883, P = 0.000; ** χ^2 = 32.621, P = 0.000; *** χ^2 = 32.920, P = 0.000

Table 4 Serum TNF-α level of each group [$M(Q_R)$]

Groups	3 h*	6 h**	12 h***
SO	3.9000 (3.2000)	4.0000 (1.7000)	5.3000 (3.0000)
Untreated	41.4380 (37.7210)	92.1510 (23.1185)	65.0160 (26.8058)
Baicalin	44.9280 (45.8420)	65.1040 (27.5050)	47.6450 (25.5180)
Octreotide	39.3000 (30.6000)	47.6000 (16.5000)	54.5000 (41.4000)

* χ^2 = 33.787, P = 0.000; ** χ^2 = 47.198, P = 0.000; *** χ^2 = 33.188, P = 0.000

Changes under light microscope

In the 3 h group obvious pancreas interstitial hyperemia and edema, a small amount of inflammatory cell infiltration, sporadic focal necrosis, and interstitial hemorrhage occurred, with some hemorrhagic or lytic necrosis. In the 6 h group pancreas interstitial edema and hemorrhage, focal, or lamellar necrosis was visible; a comparatively large area of inflammatory cell infiltration was observed around. In the 12 h group obvious pancreas interstitial edema, interstitial hemorrhage, a large area of visible necrosis, lobule contour damage and a large amount of inflammatory cell infiltration were observed.

Treatment group

Gross changes

In the 3 h group pancreatic tissue with hyperemia and edema changes, there was milder hemorrhage and necrosis than in the model group. In the 6 and 12 h groups there was relatively limited pancreas hemorrhage and necrosis, lighter ascitic fluid color, an obviously smaller amount of ascitic fluid than in the model group, a decreased distribution and area of the saponified spot than in the model group, milder pancreas hemorrhage and necrosis than in the model group, with a relatively integrated overall pancreas structure. The pathological changes in the pancreatic tissue in the Octreotide treatment group resembled those of the Baicalin treatment group.

Changes under light microscoy

The pathological changes of most cases in the treatment group were milder than those in the model group at the corresponding time point, including a decreased degree of interstitial edema, reduced inflammatory cell infiltration, clearer cell structure than in the model group, reduced pancreas interstitial erythrocyte exudation, a small amount of focal hemorrhage and necrosis with little lamellar hemorrhage and necrosis, and reduced hemorrhage and necrosis range. The pathological changes in the pancreatic tissue of the Octreotide treatment group resembled those of the Baicalin treatment group [14].

Liver pathological changes in all groups

Model group

Gross changes

In the 3 h group mild swelling of the liver, local gray plaques in the liver of individual rats with an obscure boundary were observed; at 6 and 12 h a pale, muddy liver color or haemostasis change, a part with scattered gray plaques or necrosis manifestation in irregular shapes, was observed, especially at the edge of the liver.

Changes under light microscopy

In the 3 h group swelling and apomorphosis of liver cells, inflammatory cell infiltration in the portal area, dilation and hyperemia of sinus hepaticus, scattered focal or punctate necrosis in the hepatic lobules was observed. In the 6 h group obvious swelling of liver cells, collapse of the liver cell cord within hepatic lobules caused by integrality damage due to the relatively large area of focal necrosis of liver cells, local narrowing or vanishing sinus hepaticus, increased range and area of liver cell necrosis, visible focal or large lamellar necrosis, mainly hemorrhage necrosis and some coagulation necrosis, inflammatory cell infiltration within necrosis focus, and obvious congestion in partial sinus hepaticus were observed. In the 12 h group obviously damaged hepatic lobule structure, a further increased range and area of cell necrosis, residual metamorphic liver cells only at the periphery of the partial hepatic lobules, a relatively large area of inflammatory cell infiltration within lobules or portal area, and obvious congestion in sinus hepaticus were observed.

Baicalin and Octreotide treatment groups

Gross changes

The gross liver, pathological changes in the Baicalin and Octreotide treatment groups were milder than those in the model group.

Changes under light microscopy

In the Baicalin treatment group, at all time points, mild swelling of liver cells, mild dilation and a hyperemia change of sinus hepaticus, and scattered inflammatory cell infiltration in the portal area were observed. In the 6 and 12 h groups punctate necrosis and/or mild focal necrosis of liver cells, no obvious lamellar necrosis, and inflammatory cell infiltration in portal area were observed. The gross pathological changes in all groups were milder than those of the model group, and there was no obvious difference between the Baicalin and Octreotide treatment groups, although the Baicalin treatment group had milder pathological manifestations.

Gross changes and changes under light microscopy of kidney

Sham operation group

Gross changes

No swelling of kidney, normal morphous, and no bleeding point on the cortex renis surface.

Changes under light microscopy

Normal structures of renal glomerulus, renal tubule, and renal interstitium without obvious pathological changes were observed in most rats. Swelling of renal tubular epithelial cell was observed in a very few rats, with unclear cell boundaries, and narrowed lumens.

Model group

Gross changes

No obvious gross change in kidney in the 3 h group. In the 6 and 12 h groups kidney swelling, kidney capsule tension, scattered bleeding points on the kidney capsule surface of partial rats, and slightly hemorrhagic urine in pelvis in severe cases, were observed.

Changes under light microscopy

In the 3 h group glomerular capillary congestion, swelling of renal tubular epithelial cells, scattered necrosis, unclear cell boundaries, narrowed or imperforate lumens, visible protein cast, interstitial edema, and inflammatory cell infiltration were observed. In the 6 h and 12 h groups obvious congestion of glomerular capillary, swelling of renal tubular epithelial cells, scattered necrosis, interstitial edema, inflammatory cell infiltration, visible eosinophilic staining floss and red cells in glomerular capsule, as well as eosinophilic staining homogen cast or red cell cast in renal tubule, and lamellar necrosis in renal tubular epithelial cells in a small number of rats, were observed.

Baicalin and Octreotide treatment groups

Gross changes

The gross kidney pathological changes of the Baicalin and Octreotide treatment groups were milder than those of the model group at 6 and 12 h.

Changes under light microscopy

Obviously less glomerular capillary congestion, renal tubular epithelial cell swelling, eosinophilic staining floss and red cells in renal capsule, and inflammatory cell infiltration than those of the model group, occasional small amount of red cell cast in renal tubule; renal interstitial edema, scattered necrosis in a small part of renal tubular epithelial cells; no obvious difference between Baicalin and Octreotide treatment group; Octreotide treatment group with better manifestations.

Gross pathological changes and changes under light microscope of lung

Sham operation group

Gross changes

Normal color and morphous of lung on both sides, no bleeding points on surface, and no effusion in thoracic cavity were observed.

Changes under light microscopy

Basically normal structures of most lung tissues, mild edema of a very small part of interstitial and alveolar wall, and mild inflammatory cell infiltration were observed.

Model group

Gross changes

In the 3 h group hyperemia and edema of pulmonary lobes on both sides, pink lung, dark-red bleeding points on the local pulmonary lobe surface, and a small amount of dilute amber effusion in the thoracic cavity were observed. In the 6 and 12 h groups aggravated pathological changes of lung on both sides, lump-like prunosus plaque on the lung surface, dark-red pulmonary lobes, increased effusion in thoracic cavity, and some hemorrhage was observed.

Changes under light microscopy

Lung interstitial and alveolar space edema, widened interstitial substance of alveolar wall, inflammatory cell infiltration around small lung vessels, telangiectasis and congestion, and widened alveolar septum were observed. In the 6 and 12 h groups a further increased range of pathological changes of pulmonary lobes, obviously increased effusion and more red cell spill in alveolar space, telangiectasis and congestion, obviously widened alveolar septum, and more inflammatory cell infiltration were visible.

Baicalin and Octreotide treatment groups

Gross changes

Mild hyperemia of pulmonary lobes on both sides, whitish lung surface, no obvious bleeding point on the pulmonary lobe surface, sound elasticity of pulmonary lobes, and no obvious effusion in thoracic cavity were observed. The gross lung pathological changes were milder than those of the model group at 6 and 12 h.

Changes under light microscopy

The pathological changes of the treatment groups were alleviated to varying extents, more obviously at 6 and 12 h. Mild telangiectasis and congestion of alveolar wall, edema of a small part of the lung interstitial substance and alveolar space, obviously less effusions such as red cells in the alveolar space than those of the control group, slightly widened alveolar septum, slight inflammatory cell infiltration were observed. There was no obvious difference between the Baicalin and Octreotide treatment groups, although the Octreotide treatment group had better manifestations.

Discussion

Qingyitang, which is a representative prescription of traditional Chinese medicine (TCM) for the treatment of acute pancreatitis, can alleviate endotoxemia and inhibit systemic organ and tissue injury by endotoxin in SAP pigs by promoting the secretion of motilin, enterocinesia and toxin excretion of intestines [23]. Extensive clinical practice has also shown its sound therapeutic effects on acute pancreatitis [24–28]. *Scutellaria baicalensis georgi* is the main material in Qingyitang. As one of the effective ingredients in *Scutellaria baicalensis georgi* (Labiatae) and a glucur, Baicalin, which is quite cheap, can be given by intravenous administration to overcome the shortcomings of the inconvenient administration of Qingyitang [29–34]. Baicalin can resist bacteria and inflammation, inhibit platelet aggregation, eliminate oxygen free radicals, and lower the rate of endotoxin generation. In addition, the metabolite of Baicalin in the body is baicalein, which can more effectively inhibit pancreatin [35]. All of these pharmacologic effects can antagonize many processes during SAP onset. Its many effects are similar to those of Somatostatin and its analogues such as Octreotide but it has a broader application range. It is theoretically feasible to use it for acute pancreatitis treatment.

The development of TCM monomer is the only way for TCM to realize modernization and internationalization. The intravenous administration of TCM monomer complies with the basic idea of TCM modernization. Intravenous administration features the following advantages: (1) known structure formula, molecular weight, and physical and chemical characteristics of TCM monomers are convenient for quantification and dose control; (2) during the process of preparing TCM monomer, various production technique indexes can be controlled, quality control can be applied to products, and Food and Drug Administration (FDA) standards can be easily reached; (3) appropriate drug carriers and preparation techniques can be found based on the physical and chemical characteristics of the TCM monomers; (4) it can greatly increase the concentration of TCM effective ingredients, overcome the fatal weakness of the slow effect of TCM, and enhance the absorption of the medicine in body; and (5) it can totally control the pollution of harmful substances such as heavy-metal ions and residual pesticide. The reform of the dosage form of Qingyitang, namely direct intravenous administration of its effective ingredients, can overcome its shortcomings, which make its administration inconvenient in clinical practices. Baicalin is the ingredient in many formulated Chinese products commonly used in clinical practices today, including qing kai ling injection, shuang huang lian injection, chai huang oral solution, shuang huang lian oral solution, yin huang oral solution, sanhuang tablets, and siji sanhuang soft capsules. Therefore, oral administration and intravenous injection of Baicalin could have great potential in clinical application.

Experiments prove that both Baicalin and Octreotide can inhibit pancreatin activity, reduce pancreas necrosis and plasma amylase content, lower the serum contents of TNF-α, NO, and MDA compared to those of a model group, inhibit the inflammatory reaction and change of SAP rat, inhibit lipid peroxidation, reduce organ injury, and increase the SAP rat survival rate. Experimental results show that the 12 h survival rate of the treatment groups was markedly higher than that of the model group ($P < 0.05$). The necrosis level of organs in the Baicalin treatment group was milder than that of the model group at all time points, with gross hyperemia, bleeding, edema and inflammatory cell infiltration and telangiectasis under light microscopy also milder than those of the model group. Baicalin has therapeutic effects similar to those of Octreotide. These experiments prove that Baicalin and Octreotide have protective effects on multiple organ injury of SAP rats. A discussion of the protective mechanisms for multiple organs in SAP follow.

TNF-α is the central mediator of systemic inflammatory response syndrome, which can affect angiotasis and permeability, lead to circulatory failure, shock and organ failure [36] associated with the severity and final death of acute pancreatitis [37]. For instance, endotoxemia can cause the bulk release of cytokines such as TNF-α, cause adhesion enhancement and activation of leucocytes, and result in SAP lung injury. Experiments prove that both Baicalin and Octreotide can inhibit the rise of the plasma TNF-α level to block the progression of systemic inflammatory response syndrome and avoid multiple organ dysfunction [38].

The change of MDA, which is a decomposition product of peroxide lipid, can indirectly reflect the change in free radicals in the body in disease conditions, while free radicals are one of factors that cause tissue injury. Studies

Table 5 Comparison of pharmacologic effects of Baicalin and Octreotide [47–67]

Pharmacologic effects	Baicalin	Octreotide
Anti-bacteria	+	No relevant report
Inhibit platelet aggregation	+	Inhibit the release of platelet activating factor
Anti-inflammation	Inhibit the excessive expression of plasma inflammatory factors and lower vasopermeability	Two-way regulation, maintain a low-level balance of inflammatory and anti-inflammatory reaction of body
Anti-oxidation	Remove oxygen free radicals	Indirectly inhibit the generation of oxygen free radicals
Anti-endotoxemia	+	+
Anti-tumor, immunological regulation	+	No relevant report
Inhibit pancreatin activity	Its metabolite in body, baicalein has comparatively effective pancreatin inhibiting effect	Inhibit internal and external secretion of pancreatin
Pancreas protection	No relevant report	+
Liver protection	Anti-hepatic fibrosis and treat hepatitis	Prevent hepatic fibrosis and treat primary hepatic carcinoma
Kidney protection	Treat pyelonephritis and diabetic nephropathy	Treat hepatorenal syndrome
Lung protection	Treat respiratory infection	Treat massive hemoptysis of pulmonary tuberculosis and necrotic pancreatitis lung injury; diagnose and treat lung cancer

Note: + indicates having this effect

have already proven that Baicalin can inhibit the generation of MDA, which is a lipid peroxidation product of hepatic mitochondria in rat, and the increase of liver MDA due to liver injury caused by oxygen free radicals [39, 40]. This experiment shows that the MDA content of the treatment groups was obviously lower than that of the model group at all time points, indicating the certain resisting effects of Octreotide and Baicalin on tissue lipid peroxidation in SAP rats [41].

Large doses of NO can injure tissues by continuous vasodilatation, direct toxic effect, granulocyte activiation, etc. In recent years, NO has been believed to be one of final common mediators of inflammatory mediator cascade reactions during inflammatory reaction, closely related to the onset and progression of multiple organ failure. For instance, local excessive NO after interaction with O_2 has a direct toxic effect on nephridial tissue cells [42]. The bulk generation of NO can cause lung hypoperfusion injury [43, 44]. In this experiment, the serum NO content of SAP rats was higher than that of the sham operation group, possibly because endotoxemia and inflammatory mediators such as TNF-α had activated iNOs and caused bulk release of NO to participate various pathological processes of SAP [45, 46]. Experimental data show that Baicalin and Octreotide can lower the serum NO content of SAP rats, indicating that their protective effects for multiple organs of SAP rats are related to lowering of the serum NO content and alleviating various cell damage mechanisms due to NO.

In conclusion, the manifold pharmacologic effects of Baicalin and Octreotide enable them to protect the functioning of multiple organs in SAP rats. The experiment also proves that Baicalin can replace Octreotide for the treatment of SAP, and reduce multiple organ pathological changes and complications. It is well known that Octreotide, which has been extensively applied in clinical practice for years, has marked therapeutic effects. As an analogue of Somatostatin (SS), it can inhibit the secretion of various alimentary juices such as pancreatic fluid, gastric fluid, and intestinal juice by membrane receptor regulation mediated by specific high-affinity G proteins and inhibition of the function of cholecystokinin in stimulating pancreatin secretion and release, and inhibiting acid secretion by gastrin. Studies in recent years indicate that, besides the mechanism of effectively blocking pancreas autodigestion, Octreotide can also treat acute pancreatitis by approaches including inhibition of the release of PLA_2, interleukin, TNF-α and NO in blood of pancreatitis rat, and inducing the apoptosis of pancreatic cells. Besides these pharmacologic effects, Baicalin injection also has extensive therapeutic effects including anti-bacteria, anti-tumor, anti-oxidation and immunological regulation actions. Therefore, with its cheap price and broad prospects for development, it is quite possible for Baicalin to become an effective option for the clinical treatment of SAP (see Table 5 for a comparison of the pharmacologic effects of Octreotide and Baicalin from the literature).

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