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ORIGINAL ARTICLE

Study of the Protective Effects of Dexamethasone on Multiple Organ Injury in Rats with Severe Acute Pancreatitis

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ABSTRACT

Context Pancreas, lung, kidney and liver injury has been proven to play an important role in severe acute pancreatitis.

Objective To observe the protective effects of dexamethasone on multiple organs (pancreas, lung, kidney and liver) in rats with severe acute pancreatitis.

Animals One hundred and thirty-five Sprague-Dawley rats.

Design Ninety rats were prepared as severe acute pancreatitis models and were randomly divided into a control group and the dexamethasone treatment group (45 rats in each group). Another 45 rats were selected to be the sham operation group. Each group was randomly subdivided into 3 subgroups which were observed at 3, 6, and 12 h after surgery (15 rats in each subgroup).

Main outcome measures The survival, gross and pathological findings under the light microscope, and the pathological scores of multiple organs in each group were recorded.

Results There was no significant difference in survival between the dexamethasone treatment group and the control group (P=0.494). The pancreas pathological score was significantly lower in the dexamethasone treatment group than in the control group at the various time intervals (overall: P<0.001; 3 h: P=0.019; 6 h: P=0.010, 12 h: P<0.001). The lung pathological score was significantly lower in the dexamethasone treatment group than in the control group at 6 and 12 h (P=0.023 and P<0.001, respectively). The kidney (P<0.001) and liver (P=0.009) pathological scores were also significantly lower in the overall dexamethasone treatment group than in the overall control group, but significant differences were found only in some time intervals (kidney: 6 and 12 h, P=0.006 and P=0.044, respectively; liver: 12 h, P=0.046).

Conclusion Intravenous injection of dexamethasone can alleviate pancreas, lung, kidney and liver injury of rats with severe acute pancreatitis and may have protective effects on multiple organ injury.

INTRODUCTION

Severe acute pancreatitis is one of the most common acute abdomens in clinical practice. Owing to its acute onset, rapid progress and high mortality, it has become a hot clinical study spot and one of the toughest medical problems [1, 2]. Pancreas, lung, kidney and liver injury has been proven to play an

important role in severe acute pancreatitis multiple organ injury. As a long acting glucocorticoid, dexamethasone having effects which include anti-inflammation (its most powerful effect), anti-virus, antishock and anti-immunization can inhibit the inflammatory reactions caused by manifold factors and has been extensively applied to the treatment of severe infections. This experiment studied the protective effects of dexamethasone on severe acute pancreatitis multiple organ injuries by observing the pathological findings of the pancreas, lung, kidney and liver after dexamethasone treatment of rats with severe acute pancreatitis.

MATERIALS AND METHODS

Animals

A total of 135 healthy male Sprague-Dawley rats (250-300 g of body weight) were purchased from the Experimental Animal Center of the Medical School of Zhejiang University.

Experimental Design

Ninety rats were prepared as severe acute pancreatitis models via the improved Aho *et al*. method [3] and were randomly divided into the treatment group (45 rats) and the control group (45 rats). Another 45 rats were selected to be used for the sham operation group. Then each of these groups were randomly divided into three subgroups (observed at 3, 6, and 12 h after operation) with 15 rats in each subgroup.

Animal Model Preparation

All rats received neither food nor water for 12 hours prior to the operation. The shaving, disinfection and draping were performed after the rats were anesthetized by an intraperitoneal injection of 0.25 mL/100 g of 2% sodium pentobarbital (Sigma-Aldrich, St. Louis, MO, USA). In the sham operation group, the pancreas and the duodenum were visualized after laparotomy and then the abdomen was closed. In the severe acute pancreatitis groups (treatment and controls), after entering the abdomen by means of a median epigastrium incision, we confirmed the presence of the bile-pancreatic duct and hepatic hilus common hepatic duct, identified the pancreas and the duodenal papilla inside the duodenum duct wall; we then used a No. 5 needle to drill a hole in the mesenterium avascular area. After inserting a segmental epidural catheter into the duodenum cavity via the hole and from there into the bile-pancreatic duct in the direction of the papilla in a retrograde manner, we then used the microvascular clamp to nip the catheter head temporarily and, at the same time, used another microvascular clamp to temporarily occlude the common hepatic duct at the confluence with the hepatic duct. After connecting the epidural catheter end with the transfusion converter, we transfused 0.1 mL/100 g of 3.5% sodium taurocholate (Sigma-Aldrich, St. Louis, MO, USA) by retrograde transfusion via the microinjection pump at a speed of 0.2 mL/minute. It remained for 4 minutes after injection and then the microvascular clamp and epidural catheter were removed. After checking for bile leakage, we sutured the hole in the duodenum lateral wall, used the disinfected cotton ball to absorb the anesthetic in the abdominal cavity and closed the abdomen. The treatment group was injected with dexamethasone (Zhejiang Xinchang Pharmaceutical Co., Xinchang, Zhejiang Province, China) 0.5 mg/100 g body weight via vena caudalis, in a single administration 15 minutes after the successful preparation of the severe acute pancreatitis model. The sham operation and the control group were injected with saline of the same volume via vena caudalis 15 minutes after the operation.

Main Outcome Measures

Survival

We examined rat mortality at 3 h, 6 h and 12 h after surgery and we calculated the frequency of survival.

Pathological Findings

The rats were sacrificed in batches and samples were collected followed by observation of the gross findings of the pancreas, lung, kidney and liver. The samples

Table 1. Pathological score of the pancreas (modified according to Schmidt's pathological score system [4, 5]). The pancreas score is the sum of the four subscores (edema, acinar, inflammation, and hemorrhage).

Edema

Subscore	*Definition*
0	Absent
1	Focal expansion of interlobular septae
2	Same as 1 plus diffuse expansion of interlobar septae
3	Same as 2 plus expansion of interacinar septae
4	Same as 3 plus expansion of intercellular spaces

Acinar necrosis

Subscore	*Necrotic cells*
0	Absent
1	1-4 necrotic cells/HPF
2	5-10 necrotic cells/HPF
3	11-16 necrotic cells/HPF
4	More than 16 necrotic cells/HPF

Inflammation and perivascular infiltrate

Subscore	*Intralobular or perivascular leukocyte*
0	0-1 necrotic cells/HPF
1	2-10 necrotic cells/HPF
2	11-20 necrotic cells/HPF
3	21-30 necrotic cells/HPF
4	More than 30 necrotic cells/HPF

Hemorrhage and fat necrosis

Subscore	*Focus*
0	Absent
1	1-2 foci
2	3-4 foci
3	5-6 foci
4	7 foci or more

HPF: high power fields

were fixed according to the relevant requirements which were followed by H&E staining to observe the pathological findings of the pancreas, lung, kidney, and liver under the light microscope.

Pathological Scores

A modified Schmidt's pathological score system [4, 5] was used for the evaluation of pancreatic tissue severity (Table 1). Quantitative scoring standards have been made based on the standards for patho-histological scores of the lung (Table 2) [6] as well as the kidney (Table 3) and liver (Table 4) [7].

ETHICS

We adhered to the ethical standards in this animal experiment study. The approval of the ethics committee of our hospital was obtained for the animal study reported. The rats were not abused and were sacrificed when this study was completed.

STATISTICS

The values were presented as medians and interquartile ranges together with mean±SD values. The significance of differences among the three time subgroups within the main groups was tested using the Kruskal-Wallis test while the Mann-Whitney and the Fisher's exact tests were used to compare pairs of groups and subgroups. Two-tailed P values less than 0.05 were considered to be statistical significant; all statistical analyses were

Table 2. Pathological score of lung injury [6].

Score	Pathohistological findings	Score
0	Normal lung vessel (bronchus A and V), alveolar interstitium and capillary, alveolar epithelium lobule interstitium and bronchus	
1	Edema and inflammatory cell infiltration of the interstitium and alveolar space	Five high power fields are observed in each case and the above pathological findings are present in 1.25 HPF out of 5 HPF
2	Edema and inflammatory cell infiltration of the interstitium and alveolar space, telangiectasis and congestion of the alveolar wall, or fibroplasias and broadening of the alveolar wall	The above pathological findings are present in 1.25-2.5 HPF out of 5 HPF
3	Edema, bleeding and inflammatory cell infiltration of interstitium and alveolar space, broadened alveolar wall interstitium	The above pathological findings are present in 2.5-2.75 HPF out of 5 HPF

Table 3. Pathological score of renal injury [7].

Grade	Methods
0	Normal finding
I	No cellular proliferation and fibrosis in the renal glomerulus, no congestion and microthrombus of the blood capillaries, swelling of the renal tubular epithelial cells, unclear cell margins, stenosis or atresia of the lumens, protein cast and renal interstitial edema.
II	Congestion of the glomerular capillaries, scattered necrosis of the renal tubular epithelial cells, interstitial edema and inflammatory cell infiltration
III	Grade II plus lamellar necrosis of renal tubular epithelial cells

conducted using SPSS version 11.5 for Windows.

RESULTS

Survival

Mortality in the control group was 4.4% (2/45); it was 0.0% (0/15), 0.0% (0/15) and 13.3% (2/15) at 3, 6 and 12 h, respectively. The sham operation group and dexamethasone treatment group survived at all time intervals with 100% survival and there was no significant difference (P=0.494) between the control group and both the dexamethasone treatment and the sham operated groups.

Pathological Findings of Pancreatic Tissue

Gross Findings

Sham Operation Group. No apparent abnormality of the pancreas and the peri-pancreatic epiploon were seen at any time point.

Control group. The gross pathological impairment of the pancreatic tail was more apparent than that of pancreatic head. The overall pathological change severity increased with time. At 3 h, a small number of hemorrhagic ascites could be observed by the naked eye with relatively apparent changes of pancreas hyperemia and edema, hemorrhage and necrosis. At 6 and 12 h, hemorrhagic ascites increased to a greater degree as did the edema, hemorrhage and necrosis; more saponified spots could be seen on the peripancreatic epiploon and peritoneum.

Dexamethasone Treatment Group. After 3 h, the degree of pancreas hyperemia and edema, hemorrhage and necrosis was milder than that of the control group with a decrease in ascitic fluid. At 6 and12 h, its pancreatic hemorrhage, and extent and degree of necrosis were milder than those of the control group with an apparent decrease in ascitic fluid and saponified spots.

Light Microscopy

Sham Operation Group. Mild interstitial edema occurred in very few cases; neutrophil infiltration was occasional. No acinar cells, fat necrosis or hemorrhage were observed.

Control group. The pathological change severity increased with time. At 3 h, pancreatic interstitial hyperemia, edema, a small amount of inflammatory cell infiltration, focal necrosis and interstitial hemorrhage occurred together with lamellar hemorrhage and necrosis; At 6 h, interstitial edema, hemorrhage, additional inflammatory cell infiltration, focal and lamellar hemorrhage and necrosis occurred. At 12 h, a large area of hemorrhage and necrosis, lobule outline damage and a large amount of inflammatory

Table 4. Pathological score of liver injury [7].

Grade	Methods
0	Normal finding
I	Grade I: At least two of the six items of pathological findings reported below are found in 5 random high power fields: 1. Neutrophil infiltration and edema in the portal area; 2. Swelling of the liver cells and stenosis of the sinus hepaticus; 3. Acidophilic change / acidophilic necrosis of the liver cells; 4. Focal necrosis; 5. Visible dicaryon of the liver cells; 6. Proliferation and hypertrophy of the Kupffer cells.
II	Grade I plus scattered spotty necrosis of liver cells (namely, necrosis of the liver cells only need to be found in one of 5 HPFs)
III	Grade II plus massive necrosis or two or more areas of spotty necrosis of the liver cells

cell infiltration occurred.
Dexamethasone Treatment Group. In most cases, the degree of pathological change was milder than that in the control group at the same time interval. Only a few rats had lamellar hemorrhage and necrosis, but the score of hemorrhage and necrosis decreased and the inflammatory cell infiltration was apparently alleviated.

Pathological Findings of Lung Tissue

Gross Findings
Sham Operation Group. There was normal color and structure of the lung on both sides; no bleeding point on surface and no effusion in the thoracic cavity.
Control group. Obvious hyperemia and edema of the pulmonary lobes on both sides, dark red bleeding points on local pulmonary lobe surface, small amount of amber and dilute effusion in the thoracic cavity were observed after 3 h. Aggravated pathological changes of the lung on both sides with as the time increased, lump-like prunosus plaque on the lung surface, increased effusion in the thoracic cavity and some hemorrhages were seen after 6 and 12 h.
Dexamethasone Treatment Group. No objective bleeding point on the pulmonary lobe surface, sound elasticity of the pulmonary lobes and no objective effusion in the thoracic cavity was seen; the gross lung pathological changes were milder than those of the control group at all time intervals indicating objective therapeutic effects.

Light Microscopy
Sham Operation Group. There was normal function of most lung tissues, a notable number having slight edema and inflammatory cell infiltration of the interstitium.
Control group. At 6 h, there was edema of the lung interstitium and alveolar space, a widened interstitium of the alveolar wall, visible inflammatory cell infiltration, telangiectasis and congestion of alveolar wall and a widened alveolar septum. In the 6 and 12 h groups, a wider range of pathological changes of the pulmonary lobes, obviously increased effusion in the alveolar space, edema and bleeding of the interstitium and alveolar space, a significantly widened alveolar septum, more inflammatory cell infiltration visible and lucent kytoplasm of local tunica mucosa bronchiorum epithelium were seen.
Dexamethasone Treatment Group. There were objective therapeutic effects; most lung tissue was restored, and there was slight edema of the interstitium and alveolar space.

Pathological Findings of Kidney Tissue

Gross Findings
Sham Operation Group. There was no swelling of the kidney with normal structure, no bleeding on the renal cortex surface.
Control group. There were no obvious gross kidney changes in the 3 h group. In the 6 and 12 h groups, kidney swelling, tension of the kidney envelope, scattered bleeding on the surface of the kidney envelope in some rats and slight hemorrhagic urine within the pelvis in severe cases were found.
Dexamethasone Treatment Group. The gross pathological changes of the dexamethasone treatment group were milder than those of the control group at 6 and 12 h.

Light Microscopy
Sham Operation Group. There were normal structures of the renal glomerulus, renal tubule and renal interstitium and no obvious pathological changes in most rats; unclear margins of the renal tubular epithelial cells (especially the proximal tubule), stenosis and atresia of the lumens, congestion of the renal glomerulus and interstitial edema in a small number of rats were found.
Control group. In the 3 h group, there was congestion of the glomerular capillary, swelling of the renal tubular epithelial cells, scattered necrosis, unclear cell margins, stenosis or atresia of the lumens, a visible protein cast, interstitial edema and inflammatory cell infiltration. In the 6 and 12 h groups, there was obvious congestion of the glomerular capillary, swelling of the renal tubular epithelial cells, scattered necrosis, interstitial edema and inflammatory cell infiltration. There was eosinophilic staining floss, red cells and also eosinophilic staining homogen casts or red cell casts in the

glomerular capsule. There was expansion of the medulla renal tubule lumens and atrophy of the endothelial cells; the pathological changes worsened with time and lamellar necrosis of the renal tubular epithelial cells in a small number of rats was found.
Dexamethasone Treatment Group. There was milder congestion of the glomerular capillary, swelling of the renal tubular epithelial cells as well as less eosinophilic staining floss and red cells in the renal capsule and less inflammatory cell infiltration than that of the control group; edema of the renal interstitium and scattered necrosis in a small number of the renal tubular epithelial cells was seen.

Pathological Findings of Liver Tissue

Gross Findings
Sham Operation Group. There was no obvious swelling of the liver which had normal coloration in all time groups.
Control group. The 3 h group showed a slight swelling of the liver, some rats with local grey plaque on the liver and unclear margins while the 6 and 12 h groups showed a pale, turbid color or congestion of the liver, some with scattered grey plaque with an irregular shape or necrosis.
Dexamethasone Treatment Group. The gross liver pathological changes of the dexamethasone treatment group were milder than those of the control group at 6 and 12 h; these changes were most obvious at 12 h.

Light Microscopy
Sham Operation Group. There was generally normal hepatic tissue, slight inflammatory cell infiltration in the portal area; a normal structure for most liver cells, some with acidophilia apomorphosis or slight expansion and congestion of the sinus hepaticus.
Control group. In the 3 h group, there was swelling or acidophilia apomorphosis of the liver cells, inflammatory cell infiltration in the portal area, expansion and congestion of the sinus hepaticus and scattered spotty necrosis in the hepatic lobule. In the 6 h group, there was obvious swelling of the liver cells, an increased area of liver cell necrosis, visible focal or massive hemorrhagic necrosis, inflammatory cell infiltration in necrosis area, obvious congestion of the partial sinus hepaticus, bile duct proliferation and scattered necrosis of individual cells in the portal area (concentration and fragmentation of the nucleus). In the 12 h group, there was a visibly damaged structure of the hepatic lobule, an increased area of liver cell necrosis, more inflammatory cell infiltration in the lobule and/or portal area, and obvious congestion of the sinus hepaticus.
Dexamethasone Treatment Group. In the 3 h group, there was a slight swelling of the liver cells, slight expansion and congestion of the sinus hepaticus, scattered inflammatory cell infiltration but on a notably lesser scale in the portal area at all time intervals in the dexamethasone treatment group. In the 6 and 12 h groups, the necrosis area of liver cells was more limited and there was no obvious lamellar necrosis. The gross pathological changes of the dexamethasone treatment group were milder than those of the control group at 6 and 12 h, and were most obvious at 12 h.

Pathological Scores of Multiple Organs

The median and interquartile range of the pathological scores of multiple organs, together with the mean and SD, are shown in Table 5. The data of the two rats who died in the control group at 12 h were not available for this evaluation.

Pancreas
The score significantly increased with time both in the dexamethasone ($P=0.017$) and the control ($P<0.001$) group. Both the dexamethasone and the control groups significantly exceeded the sham operation group at all time intervals ($P<0.001$). The score in the dexamethasone group was significantly less than that of the control group ($P<0.001$) and an increase in the level of significance as time increased (3 h: $P=0.019$; 6 h: $P=0.010$; 12 h: $P<0.001$) was observed.

Lung
No significant differences of the score were observed among the different time intervals within the three groups of treatment. At all

Table 5. Pathological scores of multiple organs (median and interquartile range are reported together with mean±SD). Fifteen rats were evaluated in each subgroup.

	Groups			P values [a]		
	Dexamethasone treatment	**Control group**	**Sham operation**	**Dexamethasone *vs.* Controls**	**Dexamethasone *vs.* Sham**	**Controls *vs.* Sham**
Pancreas						
3 h	7 (6-8) 6.73±1.22	8 (7-9) 7.87±1.13	0 (0-1) 0.40±0.51	P=0.019	P<0.001	P<0.001
6 h	8 (6-8) 7.33±1.92	9 (8-10) 8.93±1.10	0 (0-1) 0.40±0.63	P=0.010	P<0.001	P<0.001
12 h	8 (8-9) 8.20±1.15	11 (10-11.5) 10.69±1.32 [c]	0 (0-1) 0.47±0.64	P<0.001	P<0.001	P<0.001
P value [b]	*0.017*	*<0.001*	*0.939*			
Overall	**8 (6-8.5) 7.42±1.56**	**9 (8-10) 9.09±1.63 [d]**	**0 (0-1) 0.42±0.58**	**P<0.001**	**P<0.001**	**P<0.001**
Lung						
3 h	1 (0-1) 0.67±0.49	1 (1-2) 1.07±0.70	0 (0-0) 0.07±0.26	P=0.097	P=0.001	P<0.001
6 h	1 (0-1) 0.60±0.51	1 (1-2) 1.33±0.90	0 (0-0) 0±0	P=0.023	P<0.001	P<0.001
12 h	0 (0-1) 0.53±0.64	2 (1-2) 1.77±0.60 [c]	0 (0-0) 0.07±0.26	P<0.001	P=0.014	P<0.001
P value [b]	*0.695*	*0.058*	*0.600*			
Overall	**0 (0-1) 0.60±0.54**	**1 (1-2) [d] 1.37±0.79**	**0 (0-0) 0.04±0.21**	**P<0.001**	**P<0.001**	**P<0.001**
Kidney						
3 h	1 (1-2) 1.27±0.59	2 (1-2) 1.67±0.62	0 (0-0) 0.20±0.41	P=0.099	P<0.001	P<0.001
6 h	1 (1-1) 1.20±0.56	2 (1-2) 1.87±0.74	0 (0-1) 0.27±0.46	P=0.006	P<0.001	P<0.001
12 h	1 (1-2) 1.47±1.31	2 (1.5-2.5) 2.00±0.71 [c]	0 (0-0) 0.20±0.41	P=0.044	P<0.001	P<0.001
P value [b]	*0.355*	*0.450*	*0.882*			
Overall	**1 (1-2) 1.31±0.60**	**2 (1-2) 1.84±0.69 [d]**	**0 (0-0) 0.22±0.42**	**P<0.001**	**P<0.001**	**P<0.001**
Liver						
3 h	1 (1-2) 1.60±0.91	2 (1-3) 1.93±0.80	0 (0-0) 0.07±0.26	P=0.291	P<0.001	P<0.001
6 h	1 (1-3) 1.73±0.88	2 (2-3) 2.20±0.68	0 (0-0) 0.13±0.35	P=0.108	P<0.001	P<0.001
12 h	2 (1-3) 1.71±0.87	3 (2-3) 2.46±0.78 [c]	0 (0-0) 0.07±0.26	P=0.046	P<0.001	P<0.001
P value [b]	*0.841*	*0.176*	*0.765*			
Overall	**1 (1-2.5) 1.71±0.87**	**2 (2-3) 2.19±0.76 [d]**	**0 (0-0) 0.09±0.29**	**P=0.009**	**P<0.001**	**P<0.001**

[a] Comparison between pairs of groups (Mann-Whitney test)
[b] Comparison among the three different time intervals (Kruskal-Wallis test)
[c] Data of only 13 rats are available because two rats died in the control group at 12 h
[d] Data of only 43 rats are available because two rats died in the control group at 12 h

time intervals the control group significantly exceeded the sham operation group (P<0.001), as well as the dexamethasone treatment group significantly exceeded the sham operation group (P=0.001, P<0.001, and P=0.014, respectively). At 6 h and 12 h, the score of the dexamethasone treatment group was significantly less than that of the control group (P=0.023 and P<0.001, respectively).

Kidney

No significant differences among the different time intervals were observed within the three groups of treatment. Both the scores of the dexamethasone treatment group and the control group were significantly higher than that of the sham operation group at the different time intervals (P<0.001). The overall score of the dexamethasone treatment group was significantly lower than that of the control group (P<0.001), but significant differences were only observed at 6 and 12 h (P=0.006 and P=0.044, respectively).

Liver

No significant differences among the different time intervals were observed within the three groups of treatment. The scores of both the control group and the dexamethasone treatment group were significantly higher than those of the sham operation group at the different time intervals (P<0.001). The overall score of the dexamethasone treatment group was significantly lower than that of the control group (P=0.009). This difference was particularly significant at 12 h only (P=0.046).

DISCUSSION

Acute pancreatitis, especially severe acute pancreatitis, is a relatively hazardous acute disease among digestive system diseases and has a high mortality rate. One reason is that, at an early stage, the disease can cause a systemic inflammatory response syndrome leading to multiple organ dysfunction syndrome [2, 3, 8]. The other reason is that, until now the exact pathogenesis of acute pancreatitis is still unknown. However, people's interpretation of it has changed from the traditional "pancreatin autodigestion theory" to the "inflammatory mediator or cytokine theory", "microcirculation disturbance theory", "nitrogen monoxide (NO) and oxygen free radical injury theory", "bacteria translocation theory", "calcium overload theory", and so on. The main cause of death during severe acute pancreatitis is usually not pancreatitis itself but its complications and systemic multiple organ or systemic function insufficiency. Severe acute pancreatitis complicated by multiple organ injury will greatly increase mortality [8].

Pancreas, lung, kidney and liver injury plays an important role in the onset and progression of severe acute pancreatitis. The key to aggravation or even severe acute pancreatitis occurrence is that loss of control of the manifold inflammatory mediators during acute pancreatitis can trigger cascade reactions causing massive necrosis of the pancreatic tissue complicated by systemic multiple organ failure. In this regard, the roles of cytokines have been the focus [9, 10]. For example, tumor necrosis factor-alpha (TNF-alpha) and interleukins (ILs) can mediate inflammatory reactions [11, 12, 13, 14]. The cascade reactions of manifold cytokines can mediate inflammatory injuries and interact with the digestive and lysosomal enzymes to cause systemic inflammatory response syndrome, thereby aggravating the disease condition. The key to leucocyte adhesion on endothelial cells is the interaction between the intercellular adhesive molecule (ICAM-1) and integrin on the surface of the granulocytes. Its excessive expression and activation as well as the aggregation of leucocytes, especially neutrophils, are also relevant to multiple organ injury complicated by severe acute pancreatitis [13, 15, 16, 17, 18]. The changes in vasoactive substance IL-1beta, phospholipase A2 (PLA2), nitrogen monoxide (NO), endothelin (ET), thromboxane (TXA_2), prostacyclin (PGI_2), etc. also participate in multiple organ injury during severe acute pancreatitis [14, 19, 20, 21]. The above inflammatory reactions, mediated by various inflammatory mediators, are the key causes of acute pancreatitis aggravation, injury to the lung, kidney and

liver or even severe acute pancreatitis onset. In addition, nuclear factor-kappa B (NF-kappa B) is also relevant to the onset of severe acute pancreatitis. As a multifunctional nuclear factor, NF-kappa B participates in the regulation of body immunization and inflammatory molecule expression [22, 23, 24]. NF-kappa B can participate in severe acute pancreatitis onset by up-regulating the expression of genes such as ICAM-1, TNF-alpha and IL-6 to mediate the inflammatory reactions [25, 26, 27, 28], related to multiple organ injury. Ischemia, anoxemia and ischemical reperfusion injuries due to microcirculation disturbances also play important roles in the injury of organs outside the pancreas when complicated by severe acute pancreatitis. Foitzik *et al*. [29] have obviously reduced the pathological lesions and the mortality of experimental animals by improving the microcirculation of the kidney and the lung. Apoptosis is a kind of bodily self-protective mechanism activating its autogene program under certain pathophysiol-ogical conditions to remove the unrecoverable cells which are substantially different from necrosis [30]. The degree of apoptosis is also related to the multiple organ injury of severe acute pancreatitis [31, 32, 33].

After this experiment adopted the improved Aho *et al*. method [3] of preparing severe acute pancreatitis rat models, rat survival in the dexamethasone treatment group was higher than that in the control group, but statistics showed no significant difference between the two groups (P=0.494), which might be related to the small number of cases. However, from the prospective of organ injury degree, the degree of rat pancreas, lung, kidney and liver injury in the control group are all higher than those in the dexamethasone treatment group whether they are judged by gross changes or by changes seen under a light microscope. In addition, this experiment investigated the pathological scores of multiple organs. The pathological scores of the four organs were significantly higher in both the dexamethasone treatment and control groups than in the sham operation group. Dexamethasone addiction significantly decreased all four scores in comparison to the control group; in particular, the decrease in the pancreas score was significant in all three time intervals while the decrease in the scores of the other organs were significant only in some of the longer time intervals.

According to the results of the pathological scores, injuries to the pancreas, lung, kidney, and liver of the control group worsened at all time intervals after surgery while the injuries in the dexamethasone treatment group were relatively milder at all time intervals after surgery. A progressive increase in the pathological score over time was observed for pancreas only in the dexamethasone treatment and control groups; the positive effect of the dexamethasone treatment also seemed to increase with time. Therefore, it can be hypothesized that dexamethasone has certain therapeutic effects and can protect multiple organs from injury during severe acute pancreatitis.

Dexamethasone is a kind of long-acting glucocorticoid. In 1952, Stephensen *et al*. [34] reported, for the first time, a case in which cortisone treatment for acute hemorrhage necrosis pancreatitis had had a certain treatment effect and established the milestone of glucocorticoid treatment in acute pancreatitis. Later, numerous empirical studies proved that glucocorticoid treatment could improve pancreatitis animal survival but the mechanism is still unknown. Currently most scholars support glucocorticoid treatment mainly because it has an effect on acute pancreatitis. Its mechanism includes inhibiting the inflammatory mediator [35], resisting endotoxins [36], improving micro-circulation [37], removing oxygen free radical [38], inhibiting NO [39], inhibiting NF-kappa B [40, 41], inducing apoptosis of the acinar cells [31, 42, 43] and so on. Clinical research proves dexamethasone indeed has certain therapeutic effects on severe acute pancreatitis [44].

Glucocorticoid can help the homeostasis of the body under stress and slow down the excessive inflammatory reactions as well as their consequences. These features, which are exactly required for clinical treatment of

severe infection and septic shock, are difficult to achieve. Excessive inflammatory reactions play important roles in the pathogenesis of severe acute pancreatitis. Kingsnorth [45] believed that the cause of acute pancreatitis progression into severe acute pancreatitis was that the massively activated pancreatin, while causing self-injury of the pancreatic tissue, also activated the inflammatory cells in the pancreas and made them release inflammatory mediators which entered the blood circulation and activated other inflammatory cells in the body to release enormous inflammatory mediators. The cascade reactions of these inflammatory mediators then promoted the systemic inflammatory response syndrome and multiple organ failure during the course of severe acute pancreatitis. Dexamethasone can improve the survival of rats with severe acute pancreatitis by lowering the serum inflammatory mediator content [46]. Currently, most empirical studies on dexamethasone treatment for severe acute pancreatitis focus on the inhibition of the inflammatory mediators [47, 48, 49]. A study by Sugiyama *et al*. [50] showed dexamethasone was more effective in severe cases of acute pancreatitis. Many empirical studies emphasize that only early use of dexamethasone can achieve the expected therapeutic efficacy [48, 51].

Even though it has so many advantages, dexamethasone also has unpleasant side effects. Some authors even believed that glucocorticoid treatment could induce the onset of acute pancreatitis [52, 53]. Therefore, the side effects of dexamethasone should be actively prevented during its clinical application. Issues such as its indications, dosage and treatment course should be identified [54] in order to realize the dosage required, the course and the application of dexamethasone in order to shorten the disease course of severe acute pancreatitis patients and lower the mortality rate.

APPENDIX

Declaration of the Chinese Medicine Association About How to Deal with Duplicate Contribution of Same Manuscript

To guarantee the reputation of Chinese Medicine Association as well as the benefits of readers, we are hereinafter to make the declaration about how to deal with duplicate contribution of same manuscript.

1. Manuscripts mentioned in this declaration include original research reports, or such two manuscripts, in which key figures and charts are the same though there could be some differences in the methods of expression and statement, but excluding Minutes of important meetings, diagnosis standard of diseases, guide of prevention and cure against diseases, agreements reached between institutes, news press, or manuscripts with abstract or introduction once published in one publication but full text contributed to another publication. In case authors of the above manuscripts intend to contribute to one more publications, they shall inform publications involved.
2. When the full text of one manuscript has been published in one publication, the manuscript shall not be contributed to other publications unless it is of different writing style, different language or different country.
3. The unit of the author shall figure out in the letter of recommendation that the manuscript is not contributed to more than one publication at the same time.
4. In case that the manuscript is not return within three months upon receipt from editorial department but the author intends to contribute it to other publications, it is necessary to contact the editorial department of this magazine and make explanation accordingly.
5. If the editorial department speculates that the manuscript could be contributed to two publications at the same time, it is necessary to collect relevant data and carefully check before informing the author. And the editorial department shall listen to the author's explanation before making decision about how to deal with the problem. In case of disputes between the author and the editorial department, it shall be submitted to senior competent departments or authorizations for final arbitration.

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Authors' declaration Some data are not original because they were previously published in the Journal of Medical Research 2006; 35(11):19-23 [7]. The authors declare and ensure that publication in JOP does not violate any existing copyright. According to the certification published by the Chinese Medical Association (the supervisor of the Chinese Medical Journals), a paper published in Chinese can be published in another foreign journal especially in English (an English translation of this certification is provided in the appendix). In addition, the authors have informed Dr. Ruiqin Zhao, the director of the Journal of Medical Research; she was pleased and faxed the declaration which agreed to the publication of this article in JOP.

Conflict of interest The authors have no potential conflicts of interest

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