PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• BASIC RESEARCH •

Dexamethasone and dextran 40 treatment of 32 patients with severe acute pancreatitis

Zi-Fa Wang, Chang Liu, Yi Lu, Rui Dong, Jun Xu, Liang Yu, Ying-Min Yao, Qing-Guang Liu, Cheng-En Pan

Zi-Fa Wang, Chang Liu, Yi Lu, Rui Dong, Jun Xu, Liang Yu, Ying-Min Yao, Qing-Guang Liu, Cheng-En Pan, Department of Surgery, First Hospital, Xi' an Jiaotong University, Xi' an 710061, Shaanxi Province, China
Zi-Fa Wang, Now is in the Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA
Correspondence to: Dr. Zi-Fa Wang, Department of Surgery, University of Pittsburgh, NW607, Montefiore University Hospital, 3459 Fifth Avenue, Pittsburgh, PA 15213, United States. ziw3@pitt.edu
Telephone: +1-412-343-9407 **Fax:** +1-412-647-5959
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Abstract

AIM: Based on the pathogenesis of severe acute pancreatitis and our experimental studies, to investigate the effect of dexamethasone and dextran in treatment of patients with severe acute pancreatitis.

METHODS: Thirty-two patients with severe acute pancreatitis were treated with 0.5-1 mg/kg per day dexamethasone for 3-5 d, and 500-1 000 mL/d of dextran 40 for 7 d, besides the routine therapy.

RESULTS: After 4-8 h of treatment, abdominal pain began to be relieved; range of tenderness began to be localized in 27 patients. They were cured with nonsurgical treatment. Five of them were deteriorated, and treated with surgery. Four patients in this group died.

CONCLUSION: Dexamethasone and dextran 40 block the pathologic process of severe acute pancreatitis through inhibition of inflammatory mediators and improvement of microcirculation disorders respectively.

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INTRODUCTION

Acute pancreatitis (AP) is usually mild and self-limiting. However, 15-20% of cases deteriorate and develop organ failure or local complications (including necrosis, pseudocyst and abscess)[1]. Many patients with severe AP develop organ failure during the first few days of illness, and this accounts for the majority of early deaths[2]. The rate of severe AP approaches 40 per cent[3]. Although a number of treatments are currently available to treat AP, they have failed to have a significant impact on the overall disease progression[1,4-6]. It is known that the activation of trypsin is the trigger of AP. The key to understand the pathophysiology of AP lies in discovering why a proportion of patients progress from a limited local inflammation to a potentially dangerous systemic inflammatory response. Recent studies[6-21] showed that inflammatory mediators and microcirculation disorders (MCD) play very important roles in the pathogenesis of severe acute pancreatitis. It has been proposed that the systemic sequelae of AP arise from excessive leukocyte activation with the release of secondary inflammatory mediators, such as interleukin (IL)-1α, IL-6, IL-8, IL-10; tumor necrosis factor-α (TNF-α); platelet-activating factor (PAF); nitric oxide (NO); and phospholipase A_2[6-14]. Excessive production of these mediators contributes to the induction of the systemic inflammatory response syndrome, acute phase response, and multiple organ failure[7,14]. On the other hand, the pancreatic microcirculation is impaired in acute pancreatitis[15]. Local release of acinar enzyme, vasoactive mediators, vasoconstriction, increase in vascular permeability, ischaemia, intravascular coagulation, and capillary stasis result in pancreatic edema and hemoconcentration, and impaired capillary and venous drainage consequently lead to hemorrhagic pancreatic necrosis[16-21]. Furthermore, MCD in severe AP are not confined to the pancreas but can also be found in the colon, liver, and lungs; they extend beyond the early stage of AP and persist for 48 h or longer. They not only affect capillary blood flow but also involve prolonged changes of capillary permeability and leukocyte endothelial interaction[22]. There is no strict correlation between necrosis and organ failure in AP. Patients with pancreatic necrosis are not necessarily at risk of having initial organ failure or later organ failure during the total hospital stay and *vice versa*[23].

Therefore, the therapeutic strategy for severe AP should focus on inhibiting inflammatory mediators and improving systemic MCD. Based on our previous experimental studies[24,25], 32 patients with severe AP were treated with the new therapeutic approach.

MATERIALS AND METHODS

General data of patients

According to the definition of the International Symposium on Acute Pancreatitis held in 1992 in Atlanta[26], 32 patients with severe AP were treated in our hospital. Eighteen of them were males and fourteen females. The mean age was 42.8 (range 26-63) years. The treatment began from 8 h to 4 d after the symptoms onset.

Diagnosis

The patients had an epigastric pain of visceral nature that radiated to the back. The pain was constant and at times could be poorly localized. Other clinical findings included fever, nausea, vomiting, ileus, and abdominal distention, hyperamylasemia, and hypotension. Ultrasonography demonstrated edema of the pancreas, retroperitoneal edema, and pancreatic ascites. Sixteen patients represented biliary systemic problems (cholecystitis, cholelithiasis or biliary ductal dilatation). Findings on CT (or contrast-enhanced dynamic CT) included edema of the pancreas, peripancreatic fluid collections, and edema of the surrounding viscera and pancreatic necrosis. Twelve patients had abnormal findings on chest radiographs at the time of diagnosis, including segmental atelectasis, an elevated hemidiaphragm, pleural effusions, or the presence of

early pulmonary parenchyma infiltrates.

Treatment

After severe AP was diagnosed, the patients were treated with following routine methods: (1) Nasogastric tube decompression; (2) Supplemental oxygen, mechanical ventilation instituted in the event of respiratory insufficiency, (3) Aggressive fluid and electrolyte resuscitation to prevent hypovolemia and prerenal azotemia; and (4) Prophylactic antibiotics (Imipenem).

Besides above routine therapy, 0.5-1.0 mg/kg of dexamethasone was administered daily for 3-5 d, and 500-1 000 mL of dextran 40 was daily administered for 7 d.

RESULTS

After for 4-8 h of treatment, the abdominal pain began to be relieved, and the range of tenderness began to be localized in 27 patients. They were cured with nonsurgical treatment. Five patients were deteriorated, and 4 patients were treated with surgery (necrosectomy). The necrotic peripancreatic and pancreatic tissues were removed, and the lesser sac was drained with multiple drains (closed drainage), or lavaged with a large volume of dialysate (closed lavage). Cholecystectomy was performed in 21 patients with biliary pancreatitis, after pancreatitis was completely relieved. Operative cholangiography was performed in 18 patients. Gallstone was found in 5 cases of them, and their common bile ducts were explored. Four cases died, and 2 of them died from acute respiratory distress syndrome, 1 died from postoperative intraabdominal hemorrhage and sepsis and, 1 died from severe intraabdominal infection and organ failure.

DISCUSSION

It is now becoming much better understood that inflammatory mediators and MCD play a dominant role in the pathogenesis of systemic inflammatory response syndrome and organ dysfunction of AP. In addition, there is little doubt that inhibition or blockage of the inflammatory mediators or improvement of MCD can dramatically alter the expected course of experimental AP[30-33]. In our observation, the patients were treated with dexamethasone and dextran 40 for 4-8 h, then, their symptoms and signs began to be improved. Twenty-seven out of 32 patients were cured with this non-surgical approach. The mortality rate was lower (12.5%) compared with literature (40%)[3].

It has been shown in recent studies that inflammatory mediators, including IL-1, IL-6, PAF, and archidonic acid metabolites were excessively produced during AP. These mediators play an active role in initiating or amplifying the cytokines cascade[9,10], and a central role in the progression of AP from a local to a systemic disease[11,27-29]. It is the cumulative effect of each of these mediators that eventually leads to vascular leakage, hypovolemia, systemic inflammatory response syndrome, shock, and organ failure[27,28]. Therefore, recent advances in understanding of the pathophsiology of the early systemic illness have led to the development of a new therapeutic approach in AP. Many specific inhibitors of these mediators have beneficial effects in experimental AP[33-40]. However, few specific inhibitors can be used in clinic. A recent randomized, controlled study showed that antagonist of PAF activity is not sufficient to ameliorate systemic inflammatory response syndrome in severe AP[41]. One of main reasons is that many inflammatory mediators may be involved in the pathophysiology of AP, and any one specific antagonist can not successfully down-regulate this inflammatory response, systemic effects, and organ failure. Dexamethasone is a non-specific anti-inflammatory agent, can inhibit or block several inflammatory mediators' production, including inhibition of synthesis of TNF-α, IL-1α, IL-6, IL-8, and prostaglandins[42-44]. In our previous study, we found that dexamethasone attenuated the inflammatory mediators, 6-keto-$PGI_1\alpha$, TXB_2, and cytokine IL-6, and then improved the survival rate of experimental AP[24]. The mechanism by which dexamethasone inhibits archidonic acid and its metabolites is that dexamethasone can induce phospholipase A_2 inhibitor lipocortin. Other studies also indicated that exogenous glucocorticords have beneficial effects in experimental AP[42-47]. Now it is also clear that, the earlier glucocorticords used, the better the results obtained. However, the optimal dose of glucocorticords is not known. We used a high dose of dexamethasone short time interval, and found significant results. Although glucocorticords have a positive impact on AP, Gomez *et al*[48] found that survival rate decreased and pancreatic necrosis increased in mice after 7 d of pretreatment with hydrocortisone. Therefore, in our clinic, dexamethasone was used for 3-5 d to prevent its potential side reactions.

MCD is another important factor in the pathogenesis of multiple organ dysfunction syndromes in AP[49,50]. MCD involve a series of changes including vasoconstriction, ischaemia, increased vascular permeability, impairment of nutritive tissue perfusion, ischaemia/reperfusion, leukocyte adherence, hemorrheological changes and impaired lymphatic drainage. In addition, MCD in AP is not confined to the pancreas but appear to be a systemic disorder. Increased capillary permeability results in ascites and/or pleural effusion. Above mentioned ultrasonography demonstrated ascites in all patients with severe AP. In our previous experimental study, we found that blood viscosity, plasma viscosity, hematocrit, erythrocyte osmotic fragility elevated, while erythrocyte sedimentation rate and fibrinogen decreased significantly in AP[25]. MCD affect organs other than the pancreas and persist after pancreatic necrosis is manifested and enzyme levels have returned to normal values[22]. Therefore, MCD are not only an initiating or aggravating factor to pancreatic injury, but considered as a systemic reaction that contributes to pancreatitis-associated multiple organ dysfunction syndrome. Dextran 40 has numerous pharmacologic effects when infused intravenously: anti-platelet activity, anti-fibrin activity, and plasma volume expansion in hypovolemia, improvement of microcirculation by decreasing blood viscosity and impeding erythrocyte aggregation. The principal effect of dextran 40 is plasma volume expansion, resulting from the drug' s colloidal osmotic effect in the drawing fluid from the interstitial to the intravascular spaces. Plasma volume expansion is accompanied by an increase in central venous pressure, cardiac output, stroke volume, blood pressure, urinary output, capillary perfusion, and pulse pressure, and by a decrease in heart rate, peripheral resistance, blood viscosity, and mean transit time. Dextran 40 also enhances blood flow through correction of hypovolemia and improved microcirculation. Dextran 40 may coat erythrocytes, thus reducing bonding forces and maintaining the erythrocytes in a state of electronegativity, and mutual repellancy; dextran 40 may also coat other formed elements. In addition, the drug may decrease erythrocyte rigidity, thereby facilitating passage of erythrocytes through small blood vessels[51]. In experimental studies, it has been shown that dextran not only limited the progression of pancreatic necrosis by improving pancreatic microcirculation, reduced trypsinogen activation, prevented acinar necrosis, and improved survival in necrotizing rodent pancreatitis[52-56], but also reduced blood viscosity, hematocrit and erythrocyte osmotic fragility, and elevated fibrinogen significantly[25]. The colon, liver, and lungs affected by the AP associated systemic inflammatory response may still benefit from improved microcirculation at a time when pancreatic necrosis can no longer be reversed[22].

In conclusion, treatment of severe AP with dexamethasone and dextran is an effective and practical approach. Dexamethasone can inhibit multiple inflammatory mediators and dextran can improve MCD. We emphasize that high dose of dexamethasone should be used in a short time interval to ensure the pharmacological effect and avoid its potential side reactions. Of course, when patients represent acute respiratory distress syndrome or severe intraabdominal infection, other therapeutic approaches, such as, mechanical ventilation, surgery should be considered.

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