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

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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 ng/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.

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)\[3\]. Many patients with severe AP develop organ failure during the first few days of illness, and this accounts for the majority of early deaths\[3\]. 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\(_2\)\[16-14\]. 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\[19\]. 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\[19-21\]. 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\[28\], 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 (cholecytitis, 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[33-40]. 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%)[33].

It has been shown in recent studies that inflammatory mediators, including IL-1, IL-6, PAF, and arachidonic acid metabolites were excessively produced during AP. These mediators play an active role in initiating or amplifying the cytokines cascade[41,42]. The principal effect of dextran 40 is plasma volume expansion, 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 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.

REFERENCES

1. Beger HG, Rau B, Issenmann R. Prevention of severe change in acute pancreatitis: prediction and prevention. J Hepatobiliary Pancreat Surg 2001; 8: 140-147

2. Makhlia R, Kingsnorth AN. Pancreatic microcirculation dysfunction during experimental acute pancreatitis. J Hepatobiliary Pancreat Surg 2002; 9: 401-410

3. Mckay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complication in acute pancreatitis. Br J Surg 1996; 83: 919-923

4. Ulh W, Schrag HJ, Schmitter N, Aufenanger J, Nevalainen TJ, Buchler MM. Experimental study of a novel phospholipase A2 inhibitor in acute pancreatitis. Br J Surg 1998; 85: 618-623

5. Chen HM, Wang ZF, Pan CE, Liu SG. Role of inflammatory mediators in acute pancreatitis. Huaren Xiaohua Zazhi 1998; 7: 170-171

6. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut 1997; 40: 1-4

7. Abe T, Shimogawa T, Satoh A, Abe R, Kikuchi Y, Koizumi M, Toyota T. Nitric oxide modulate pancreatic edema formation in ratcaerulein-induced pancreatitis. J Gastrointest Surg 1995; 30: 635-642

8. De Beauch A, Goldie AS, Ross JA, Carter DC, Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. Br J Surg 1996; 83: 349-353

9. Zhao ZG, Chen YD. Influencing factors of pancreatic microcirculatory impairment in acute pancreatitis. World J Gastroenterol 2002; 8: 406-412

10. Beger HG, Rau B, Issenmann R. Prevention of severe change in acute pancreatitis: prediction and prevention. J Hepatobiliary Pancreat Surg 2001; 8: 140-147

11. Chen HM, Wang ZF, Pan CE, Liu SG. Role of inflammatory mediators in acute pancreatitis. Huaren Xiaohua Zazhi 1998; 7: 170-171

12. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut 1997; 40: 1-4

13. Mckay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complication in acute pancreatitis. Br J Surg 1996; 83: 919-923

14. Ulh W, Schrag HJ, Schmitter N, Aufenanger J, Nevalainen TJ, Buchler MM. Experimental study of a novel phospholipase A2 inhibitor in acute pancreatitis. Br J Surg 1998; 85: 618-623

15. Chen HM, Wang ZF, Pan CE, Liu SG. Role of inflammatory mediators in acute pancreatitis. Huaren Xiaohua Zazhi 1998; 7: 170-171

16. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut 1997; 40: 1-4

17. Mckay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complication in acute pancreatitis. Br J Surg 1996; 83: 919-923

18. Ulh W, Schrag HJ, Schmitter N, Aufenanger J, Nevalainen TJ, Buchler MM. Experimental study of a novel phospholipase A2 inhibitor in acute pancreatitis. Br J Surg 1998; 85: 618-623

19. Chen HM, Wang ZF, Pan CE, Liu SG. Role of inflammatory mediators in acute pancreatitis. Huaren Xiaohua Zazhi 1998; 7: 170-171

20. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut 1997; 40: 1-4
Yao XL, Cowan MJ, Gladwin MT, Lawrence MM, Angus CW, Shelhamer JH. Dexamethasone alters arachidonate release from human epithelial cells by induction of p11 protein synthesis and inhibition of phospholipase A2 activity. J Biol Chem 1999; 274: 17202-17208

Wang ZF, Pan CE, Lu Y, Liu SG, Zhang GJ, Zhang XB. The role of inflammatory mediators in severe acute pancreatitis and regulation of glucocorticoids. Hepatobil Pancreas Dis Int 2003; 2: 458-462

Takaoka K, Kataoka K, Sakagami J. The effect of steroid pulse therapy on the development of acute pancreatitis induced by closed duodenal loop in rats. J Gastroenterol 2002; 37: 537-542

Rakonczay Z, Duda E, Kaszaki J, Ivanyi B, Boros I, Lonovics J, Takacs T. The anti-inflammatory effect of methylprednisolone occurs downstream of nuclear factor-kappaB DNA binding in acute pancreatitis. Eur J Pharmacol 2003; 464: 217-227

Osman MO, Jacobsen NO, Kristensen JU, Larsen CG, Jensen SL. Beneficial effects of hydrocortisone in a model of experimental acute pancreatitis. Dig Surg 1999; 16: 214-221

Gloor B, Uhl W, Tcholakov O, Roggo A, Muller CA, Worni M, Buchler MW. Hydrocortisone treatment of early SIRS in acute experimental pancreatitis. Dig Dis Sci 2001; 46: 2154-2161

Gomez G, Townsend CMJ, Green D, Rajaraman S, Uchida T, Thompson JC. Involvement of cholecystokinin receptors in the adverse effect of glucocorticoids on diet-induced necrotizing pancreatitis. Surgery 1999; 106: 230-236

Gullo A, Beriot G. Ingredients of organ dysfunction or failure.