Effect of early endoscopic therapy and therapeutic laparotomy on serum markers of severe acute biliary pancreatitis patients

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Objective: To study the effects of early endoscopic therapy and therapeutic laparotomy on serum markers of severe acute biliary pancreatitis patients. Methods: 80 cases of patients with severe acute biliary pancreatitis in our hospital were retrospectively analyzed and divided into endoscopic group and open group. 3 d after treatment, serum was collected and contents of inflammation related molecules, liver and kidney function indicators and signaling pathway molecules were detected. Results: (1) inflammation related molecules: compared with open group, contents of pro-inflammatory cytokines TNF-α, PCT, HMGB-1 and MCP-1 in serum of endoscopic group were lower; contents of anti-inflammatory cytokines sTNF-1R and sTNF-2R were higher; (2) liver and kidney function indicators: compared with open group, contents of ALT, AST, OCT, GLDH, Cys C and Hcy in serum of endoscopic group were lower; (3) pancreatitis related signaling pathways: compared with open group, mRNA contents of JNK2, SAPK, c-Jun, Elk-1, Smad2, Smad3, ERK and p38 in serum of endoscopic group were lower. Conclusion: Early endoscopic therapy is helpful to relieve inflammatory response, prevent liver and kidney function injury and inhibit activation of pancreatitis related signaling pathways; it’s an ideal method in treating severe acute biliary pancreatitis.

1. Introduction

Severe acute biliary pancreatitis (SABP) is a more critical acute abdominal disease of general surgery. Anatomic basis of the changes is that there is a common anatomic channel between bile duct and pancreatic duct: the two merging into a common channel before entering the duodenum; stones or inflammation in bile duct will cause edema of Oddi sphincter, pancreatic juice in pancreatic duct cannot be smoothly drained into duodenum and flows back to digest its own tissue, thus forming pancreatitis. For most patients for whom conservative treatment fails, open surgery is needed, but it will cause more trauma to both local tissues and body functions and is not conducive for postoperative recovery. Endoscopic therapy is a minimally invasive treatment method developed in recent years. It uses endoscopic retrograde cholangio-pancreatography (ERCP) to know about local obstruction situation, uses endoscopic sphincterotomy and endoscopic nasobiliary drainage to relieve obstruction and enable smooth drain age[1]. In the following research, effects of early endoscopic therapy and therapeutic laparotomy on serum markers of severe acute biliary pancreatitis patients were analyzed.

2. Objects and methods

2.1 Objects

80 cases of patients with severe acute biliary pancreatitis in our hospital were retrospectively analyzed, time range from May 2012 to August 2014. All patients met the diagnosis of severe acute biliary pancreatitis and CT scan showed that Balthazar grading was above grade II. They were divided into endoscopic group and open group. Endoscopic group received ERCP+endoscopic sphincterotomy+endoscopic nasobiliary drainage. Total 38 cases were enrolled, including males/females: 23/15 cases with age range of (52.34±6.23); open group received lithotomy of common bile duct+T tube drainage. Total 42 cases were enrolled, including...
males/females: 26/16 cases with age range of (52.85±6.41). There were no differences between two groups’ general data (P>0.05).

2.2 Treatment methods

Endoscopic group: they received endoscopic therapy immediately after hospitalized in emergency. Endoscope was placed in duodenum to find the open position of oddis sphincter. Then ERCP was conducted to show local lesions and confirm obstruction site. At the same time, endoscopic sphincterotomy was conducted, using reticular basket or air-sac to remove the stones. Then nasobiliary catheter was placed for drainage. Open group: after hospitalized in emergency, they received fasting, water deprivation, fluid infusion, antibiotics, spasmylosis and other conservative treatment. If illness further developed, open surgery was conducted. Under general anesthesia, ventral midline incision was made into the abdominal cavity, tissues were separated to reveal and incise the common bile duct to remove the stones and T tube was placed for drainage.

2.3 Serum markers evaluating methods

3 d after surgery, peripheral venous blood was collected and centrifuged. Upper serum specimen was collected and transferred into 1.5 mL EP tube and preserved at low temperature. When testing, Elisa was used to detect contents of TNF-α, PCT, HMGB-1, MCP-1, sTNF-1R, sTNF-2R and Cys C; RIP was used to detect contents of ALT, AST, OCT and GLDH; fluorescence quantitative PCR was used to amplify JNKK2, SAPK, c-Jun, Elk-1, Smad2, Smad3, ERK and p38; mRNA contents were analyzed.

2.4 Statistical methods

Detected data was input into computer by SPSS 19.0 software, analysis of differences between two groups for t test. Differences were considered to be statistically significant at a level of P<0.05.

3. Results

3.1 Changes of serum inflammation related cytokines

Activation of inflammatory response is the most important change in patients with pancreatitis. Abnormal contents of serum pro-inflammatory cytokines and anti-inflammatory cytokines are the most direct embodiment of activation of inflammatory response. In the research, 3 d after treatment, serum specimen was collected and Elisa was used to detect contents of pro-inflammatory cytokines TNF-α, PCT, HMGB-1 and MCP-1 as well as anti-inflammatory cytokines sTNF-1R and sTNF-2R. T test analysis showed that compared with open group, contents of pro-inflammatory cytokines TNF-α, PCT, HMGB-1 and MCP-1 in serum of endoscopic group were lower; contents of anti-inflammatory cytokines sTNF-1R and sTNF-2R were higher.

3.2 Liver and kidney function indicators

There is systemic inflammatory response hyperthyroidism in patients with severe acute biliary pancreatitis. It will lead to liver and kidney function damage. Serum ALT, AST and GLDH contents can reflect changes of liver function; Cys C and Hcy

Table 1.
Changes of Liver and kidney function indicators in serum.

<table>
<thead>
<tr>
<th></th>
<th>Liver function</th>
<th>Kidney function</th>
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<tbody>
<tr>
<td></td>
<td>AST (U/L)</td>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>Endoscopic group</td>
<td>31.42±4.42</td>
<td>33.58±4.71</td>
</tr>
<tr>
<td>Open group</td>
<td>45.63±5.93</td>
<td>50.13±6.28</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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Figure 1. Changes of serum inflammation related cytokines. (Left) compared with open group, contents of anti-inflammatory cytokines sTNF-1R and sTNF-2R in serum of endoscopic group were higher; (Right) compared with open group, contents of pro-inflammatory cytokines TNF-α, PCT, HMGB-1 and MCP-1 in serum of endoscopic group were lower.
contents can reflect changes of kidney function. In the research, 3 d after treatment, serum specimen was collected and liver and kidney function indicators were detected. T test analysis showed that compared with open group, contents of ALT, AST, OCT, GLDH, Cys C and Hcy in serum of endoscopic group were lower.

3.3 Pancreatitis related signaling pathways

Inflammatory response and target organ damage processes in patients with pancreatitis involve the activation of multiple signaling pathways, including SAPK signaling pathway, TGF-β signaling pathway, and so on. In the research, 3 d after treatment, serum specimen was collected. First total RNA was extracted for RT and then PCR was used to detect mRNA contents of signaling molecules. T test analysis showed that compared with open group, mRNA contents of JNKK2, SAPK, c-Jun, Elk-1, Smad2, Smad3, ERK and p38 in serum of endoscopic group were lower.

4. Discussions

Biliary pancreatitis develops rapidly. Mostly, there is complete obstruction in partial pancreatic duct and pancreatic juice will continuously digest its own tissue. Key measures to treat the disease are to remove obstruction in bile duct and pancreatic duct and restore normal drainage of pancreatic juice[2]. Open surgery is the most conventional treatment. It can effectively incise the bile duct, remove the stones and relieve obstruction. But due to the larger trauma from operation, duration of postoperative edema of oddis sphincter is longer, duration of pancreatitis symptoms and signs are longer and body function injury is greater[3]. Endoscopic therapy is a minimally invasive treatment method developed in recent years. It uses endoscopic retrograde cholangio-pancreatography (ERCP) to get image information of local obstruction, and then endoscopic sphincterotomy (EST) and endoscopic nasobiliary drainage (ENBD) are conducted. It can to relieve partial obstruction on the basis of reducing trauma to local tissues. Activation of inflammatory response is the most prominent change in patients with pancreatitis. Under the effects of self digestion of pancreatic juice, retrograge of biliary duct bacteria into the blood and other factors, a lot of inflammation related cytokines change and directly lead to sphincter edema and tissue damage. TNF-α is the most important pro-inflammatory cytokine. It can promote the generation of inflammatory mediators of IL-1β and IL-6, and also cause vascular endothelial permeability increase and local microcirculatory disorder[4,5]; procalcitonin PCT is a newly developed serum marker that can accurately and sensitively reflect inflammatory degree[6]; monocyte chemoattractant protein MCP-1 is an important chemokine in the body that can locally recruit inflammatory cells; high mobility group box protein 1 (HMGB1) is an inflammatory cytokine that changes in late inflammatory response[7]. sTNF-1R and sTNF-2R are anti-inflammatory cytokines that can combine with TNF- and block its function. They are constantly consumed in the progression of pancreatitis. In the research, inflammation related cytokines were detected and it was found out that compared with open group, contents of pro-inflammatory cytokines TNF-α, PCT, HMGB-1 and MCP-1 in serum of endoscopic group were lower and contents of anti-inflammatory cytokines sTNF-1R and sTNF-2R were higher, which indicated that endoscopic therapy was helpful to relieve inflammatory response in the progression of pancreatitis.

There is rapid progression in patients with severe acute biliary pancreatitis. Massive release of inflammatory cytokines will lead to the occurrence of systemic inflammatory response syndrome and at the same time cause damage to liver, kidney and other target organs. Goals of both open surgery and endoscopic therapy are to relieve obstruction and enable smooth drainage. As has been noted, advantages of endoscopic therapy are less trauma, faster recovery and shorter duration of postoperative edema of oddis sphincter, which are conducive for smooth pancreatic juice drainage and can also rapidly relieve inflammatory response and reduce the risk of target organ damage[8]. Liver is an important place for amino acid metabolism. Transaminases are important enzymes in liver cell that catalyze amino acid metabolism. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two enzymes in liver cell cytoplasm that catalyze amino acid; ornithine carbamyl transferase (OCT) and glutathione dehydrogenase (GLDH) are two enzymes in liver cell mitochondria that catalyze amino acid[9,10]. In the case of systemic inflammatory response increase, excessively generated inflammatory cytokines will directly cause liver cell injury; and bile duct obstruction and poor intrahepatic biliary drainage can also cause liver cell injury. Mutual interaction of the two result in the rupture of liver cells and the release of enzymes in cytoplasm and mitochondria into bloodstream. Kidney is the most common injured target organ except for the liver. Inflammatory cytokines can lead to endothelial injury and affect the blood perfusion of glomerulus, thus leading to abnormal filtrating function. Homocysteine Hcy is
an amino acid that can cause endothelial injury and inflammation. Its generation in the activation process of systemic inflammatory response increases. It can cause glomerular structure damage and is the cause of renal function injury; Cys C is a small-inducible protein excreted by kidney. It can accurately and sensitively reflect changes of kidney function. Serum Cys C level increase is the outcome of kidney function injury[11]. In the research, liver and kidney function indicators were detected and it was found out that compared with open group, contents of ALT, AST, OCT, GLDH, Hcy and Cys C in serum of endoscopic group were lower, which indicated that endoscopic therapy was helpful to control liver and kidney function injury caused by pancreatitis.

The progression process of severe acute biliary pancreatitis involves abnormality of multiple signaling transduction pathways. Signaling pathways in the body are composed of a variety of signaling molecules, including upstream ones that mediate activation process and downstream ones that mediate transcriptional activation function. Activation and amplification of inflammatory response, large generation of inflammatory cytokines and injury of target organ function are all related to the activation of a variety of signaling pathways. Signaling pathway mediated by stress-activated protein kinase (SAPK) is closely related to the activation of inflammatory response[12]. In the activation process of inflammatory response, JNK kinases JNKK2 function enhances and can specifically activate SAPK; activated SAPK can dislocate into nucleus and enhance the function of nucleus transcription factors c-Jun and Elk-1, thus promoting expressions of a variety of inflammation related genes[13]. TGF-β is an important molecule that causes liver tissue fibrosis. In the occurrence and development process of severe pancreatitis, it is largely generated and causes liver function injury through downstream signaling pathways. Smad is an important signaling molecule of TGF-β downstream; activated Smad2 and Smad3 can promote activation of pancreatic stellate cells and play an important role in aggravating inflammatory injury and increasing fibroblasts generation [14]. Besides, TGF-β can also increase -SMA expression through ERK and p38 of downstream mitogen activated protein kinase MAPK family, thus leading to liver function injury[15]. In the research, pancreatitis related signaling molecules were detected and it was found out that compared with open group, contents of JNKK2, SAPK, c-Jun, Elk-1, Smad2, Smad3, ERK and p38 in serum of endoscopic group were lower, which indicated that endoscopic therapy was helpful to inhibit activation of pancreatitis related signaling pathways.

To sum up, it can be concluded that early endoscopic therapy is helpful to relieve inflammatory response, prevent liver and kidney function injury and inhibit activation of pancreatitis related signaling pathways; it’s an ideal method in treating severe acute biliary pancreatitis.

References