Treatment Experience of Severe Abdominal Infection after Orthotopic Liver Transplantation

Y-G Wang, J-S Wu, B Jiang, J-H Wang, C-P Liu, C Peng, B-Z Tian

ABSTRACT

This study aims to investigate the causes and treatment experience of severe abdominal infection after orthotopic liver transplantation. Clinical data were retrospectively analysed in perioperative severe abdominal infection of 186 orthotopic liver transplantation cases from March 2004 to November 2011. Among the 186 patients, 16 cases had severe abdominal infection: five cases had bile duct anastomotic leakage-inducing massive hydrops and infection under liver interstice, 10 cases had extensive bleeding of surgical wound leading to massive haematocele and infection around the liver, and one case had postoperative lower oesophageal fistula leakage causing massive hydrops and infection under the left diaphragm. After definite diagnosis, 12 cases underwent surgery within three days, with no death. Among the four cases that underwent surgery three days after diagnosis, one case died of multiple-organ failure five days after abdominal cavity exploration, which was performed 21 days after liver transplantation. Severe abdominal infections after liver transplantation were the most common causes of death in perioperative liver transplantation. Comprehensive treatment with efficacious antibiotics, multiple-organ support, controlled surgical removal of the lesion, and adequate drainage establishment was the key to the entire treatment.

Keywords: Abdominal infection, liver transplantation, treatment experience

Experiencia en el Tratamiento de la Infección Abdominal Severa después del Trasplante Ortotópico de Hígado

Y-G Wang, J-S Wu, B Jiang, J-H Wang, C-P Liu, C Peng, B-Z Tian

RESUMEN

Este estudio persigue investigar las causas y la experiencia en el tratamiento de la infección abdominal severa después del trasplante ortotópico de hígado. Se analizaron retrospectivamente los datos clínicos de la infección abdominal severa perioperatoria en 186 casos de trasplante ortotópico de hígado, de marzo de 2004 a noviembre de 2011. De los 186 pacientes, 16 casos tuvieron infección abdominal grave; cinco casos tuvieron hidropesía masiva con fuga anastomótica del conducto biliar e infección debajo del intersticio del hígado; 10 casos tuvieron sangrado profuso de la herida quirúrgica que condujo a un hematocele masivo e infección en el hígado; y un caso tuvo una fuga postoperatoria de la fístula esofágica inferior que le causó hidropesía masiva e infección bajo el diafragma izquierdo. Después del diagnóstico definitivo, 12 casos recibieron intervención quirúrgica en tres días, sin que se produjeran muertes. Entre los cuatro casos que experimentaron cirugía tres días después del diagnóstico, un caso murió de fallo orgánico múltiple cinco días después de la exploración de la cavidad abdominal, que le fue realizada 21 días después del trasplante hepático. Las infecciones abdominales graves tras el trasplante hepático fueron las causas más comunes de muerte en el trasplante perioperatorio del hígado. El manejo integral con antibióticos eficaces, el soporte multiorgánico, el retiro quirúrgico controlado de la lesión, y el establecimiento de un drenaje adecuado fueron la clave del tratamiento completo.

Palabras claves: Infección abdominal, trasplante de hígado, experiencia en el tratamiento

From: Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, Changsha 41005, China.

Correspondence: Dr J-S Wu, Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, 253 Jiefangzhong Road, Changsha 41005, China. Fax: +86 731 83929012; e-mail: jinsuwu@yeah.net

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INTRODUCTION

Organ transplantation is "one of the greatest progresses in the 20th century's medicine history" and is expected to be the only treatment for end-stage organ diseases. Large-organ transplantation, primarily liver transplantation, is a technology associated with a high degree of difficulty and fully reflects the overall strength of a hospital. The continuous development of liver transplantation has made this procedure an important treatment for end-stage liver disease (1). Severe abdominal infection after liver transplantation refers to abdominal infection with a wide infection range, long duration, and multiple-organ dysfunction. Such infection is rare and has complex aetiology and thus significantly complicates diagnosis and treatment and often leads to uncontrolled inflammation, systemic inflammatory response syndrome (SIRS), and sepsis. If handled inappropriately or managed late, such infection causes organ dysfunction and poor prognosis and becomes a common cause of death in perioperative liver transplantation. From March 2004 to November 2011, the author participated in the orthotopic liver transplantation of 186 cases, 16 of whom had perioperative severe abdominal infection. The use of sensitive antibiotics, multiple-organ function maintenance, immune regulation, controlled surgical removal of the lesion, adequate drainage establishment and other comprehensive treatments increased clinical efficacy.

SUBJECTS AND METHODS

Clinical data

The 186 cases included 118 males and 68 females. The male patients were 22 to 75 years old, with an average age of 45.62 ± 10.08 years; the female patients were 21 to 73 years old, with an average age of 45.18 ± 10.32 years. The primary diseases before transplantation were as follows: 93 cases of hepatocellular carcinoma, 63 cases of post-hepatitic cirrhosis, 19 cases of fulminant hepatitis, five cases of end-stage biliary tract disease, three cases of hepatolenticular degeneration, two cases of primary biliary cirrhosis, and one case of primary sclerosing cholangitis. A total of 165 cases underwent liver transplantation for the first time, whereas the other 21 cases underwent secondary liver transplantation. Written informed consent was obtained from all participants. The donations for 181 cases came from cadavers, three donations were provided by cardiac-death donors, and two donations came from living donors. Sixteen cases had perioperative severe abdominal infection. There were 12 males and four females, aged 42 to 75 years, with a mean age of 52.28 ± 12.56 years. The primary diseases before transplantation were one case of primary liver cancer, eight cases of post-hepatitic cirrhosis, and seven cases of severe hepatitis. Ten cases underwent liver transplantation for the first time, and the other six cases underwent secondary liver transplantation. The liver transplants came from deceased donors.

Diagnostic criteria

Severe abdominal infection was diagnosed according to the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine (2): clear abdominal infection test results and two or more signs of SIRS. Acute respiratory and circulatory dysfunction was diagnosed according to the modified Fry-MODS diagnostic criteria (3).

Persistent fever after liver transplantation

According to chest CT, liver function changes and liver biopsy pathology, pulmonary infection, and rejection after liver transplantation were excluded. The livers underwent ultrasonography and abdominal computed tomography (CT) to monitor transplanted liver size, shape, intrahepatic and extrahepatic bile ducts, intrahepatic vessels (hepatic artery, portal vein and hepatic vein), inferior vena cava, hepatic circuit, hydrop echo, fluid volume, and hydrops in the abdominal, pelvic, and chest cavities. Pulse Doppler was performed for blood flow parameters and local lesions, focussing on the number, size, shape and edge of lesions and the relation of internal echo with surrounding tissues and blood flow. The recheck situation changed several times and should thus be given attention.

Abdominal paracentesis fluid examination

Under the location guidance of B-mode ultrasonic diagnosis, an ascitic fluid sample was obtained for bacterial and fungal culture and sensitivity test. All specimens were inoculated in blood agar, cultured at 35 ˚C for 18–24 hours, smeared, separated and underwent biochemical and drug sensitivity analysis with a bacteria automatic analyzer (bioMérieux, France).

Perioperative treatment

The intestinal tract, skin and mucous membrane were routinely prepared. The basic disease status was actively improved, and preoperative invasive procedures were minimized. At the same time, patients were encouraged to blow-up balloons to exercise and improve their respiratory function. During surgery, all patients were administered intravenous and inhalation anaesthesia. Excessive intraoperative transfusion was prevented in case of pulmonary oedema, and vasoactive drugs were reasonably used. Routine basic disinfection and isolation measures were made postoperatively; aetiological information was then collected. The airway was managed thus: the ventilator tube was sterilized before use, strict aseptic operation was performed during suctioning, gastrointestinal decompression was maintained to keep the drainage unobstructed and prevent aspiration, the time of ventilator use was minimized, lung physiotherapy was administered immediately after extubation and respiratory functional exercise was intensified. Additional tacrolimus (FK506; 2 mg) was given on the second postoperative day and once every 12 hours thereafter (plasma trough concentration was maintained at 6 ng/mL to 10 ng/mL). Mycophenolate mofetil (MMF) was given 0.5 g once every 12

hours. Piperacillin or third-generation cephalosporins were properly selected and adjusted through a drug sensitivity test according to treatment efficacy. If fungal infection was suspected, treatment with antifungal agents was performed empirically or through a drug sensitivity test. Oral valaciclovir was administered routinely to prevent fungal infection. For patients with hepatitis B virus infection, 100 mg of lamivudine was given daily. For virus variation, entecavir was used. The antiviral drugs given were 100 mg of lamivudine once a day. Different symptomatic treatment measures should be performed according to different symptoms (such as hypoxaemia, respiratory failure and acute respiratory distress syndrome) with a time oxygen mask, high frequency ventilation, endotracheal intubation, and incision for auxiliary mechanical ventilation.

Comprehensive treatment

Active recovery and multiple-organ support should be performed, the amount of liquid should be strictly controlled and maintained, a low central venous pressure (< 10 cmH_20) should be maintained to prevent pulmonary oedema and cardiac dysfunction and protect liver and kidney function, in case of catheter-related infections in other parts. Ulinastatin (50×10^4 U) was intravenously infused once a day for three to five consecutive days, and then growth hormone 4U was subcutaneously injected once a day. The sources of infection were controlled, infected lesions were cleaned and rinsed under subphrenic spaces while obeying damage control principles, and postoperative continuous rinsing and negative pressure drainage were performed. Once patients presented with persistent high fever, purulent drainage exceeding 100 mL per day or significant digestive juice outflow, and apparent signs and symptoms of peritonitis, the time for surgery was ripe. The surgical procedure included control of the source of infection, consecutive subphrenic space probing on the principle of controlling damage, subphrenic space lesion clearance, washing with physiological saline and diluted fortified iodine solution, low-set drainage from each subphrenic space, and postoperative continuous negative pressure washing and drainage.

Based on bacterial culture and sensitivity test results, sensitive antibiotics were selected. Considering that *Colibacillus* combined with other bacteria was the most common abdominal infection, treatment with carbapenems was empirically performed before drug sensitivity tests.

Parenteral nutritional support was provided, and enteral nutrition was actively repeated. Immunosuppressive agents were adjusted according to blood $CD_4^+CD_8^+$ results. In severe abdominal infection, immunosuppressive agents were withheld. After infection was controlled, the use of immunosuppressive agents was gradually resumed. Immunoglobulin was supplemented.

Main observation indices

Blood immune inhibitor and blood $CD_4^+CD_8^+$ concentration were detected twice a week. Liver transplantation blood flow condition, resistance index, transplanted liver texture, and surrounding haemorrhage were detected by liver and kidney function, blood routine, coagulation function and abdominal ultrasound. We also observed the traffic of the abdominal cavity drainage tube, drain colour, body temperature and breathing, and heart rate changes.

RESULTS

Among the 16 cases of severe abdominal infections, five cases had bile duct anastomotic leakage-inducing massive hydrops and infection under the liver interstice, 10 cases had extensive bleeding of surgical wound leading to massive hematocele and infection around the liver and one case had postoperative lower oesophageal fistula leakage causing massive hydrops and infection under the left diaphragm.

There were different degrees of symptoms: mania (5/16) or apathy (11/16), dyspneoa (3/16) or shortness of breath (13/16), different degrees of fever (16/16), bloody or purulent secretions in the abdominal drainage tube (13/16) or discharge from the incision (3/16) more than 800 mL/day flow from the postoperative abdominal drainage tube, progressively deepening yellowing of the skin and sclera (12/16), persistent or paroxysmal abdominal pain (16/16), no significant relief of symptoms or brief remission of symptoms but a repeated increase after broad-spectrum anti-infective therapy.

Six cases had severe abdominal infection in the first week after surgery, seven cases had it after the second week, and three cases had it within the third week. The average time of occurrence after surgery was 8.56 ± 3.25 days.

The fluid cultured from abdominal paracentesis was positive in 16 cases for bacteria: six cases of *Escherichia coli*, three cases of *E coli* and *Enterobacter cloacae*, three cases of *E coli* and *Pseudomonas aeruginosa*, two cases of *E coli* and *Acinetobacter baumannii*, one case of *E coli* and *Enterococcus feces*, and one case of *E coli* and methicillin-resistant *Staphylococcus aureus*.

Treatment and prognosis

All 16 cases of severe abdominal infection underwent surgical exploration. Intra-abdominal infections were cleared with controlling measures, and a double-lumen suction tube was placed for postoperative continuous suction. Twelve cases underwent surgery within three days after diagnosis, with no deaths. Four cases underwent surgery three days after diagnosis. One case underwent liver transplantation on the 21st day and then died because of multiple-organ failure five days after abdominal exploration.

DISCUSSION

After liver transplantation, patients may suffer hypoimmunity, immunosuppressant application, long intraperitoneal exposure time during liver transplant, bacterial translocation induced by intestinal barrier dysfunction, blood oozing and accumulating in the abdominal cavity caused by a large surgical wound, diseased liver lesion resection-induced rupture of hollow viscus,

abdominal large effusion caused by poor biliary anastomosis-induced bile leakage, granulocytopaenia and preoperative usage of various broad-spectrum antibiotics. Liver transplant patients are more susceptible to severe abdominal infections than other abdominal surgery patients. Severe abdominal infections after liver transplantation often caused systemic inflammatory response syndrome and cardiopulmonary dysfunction, liver and kidney dysfunction, pyemia, or even septicaemia, which are the most common causes of death in perioperative liver transplantation (3–5).

During liver transplantation, because of massive blood transfusion and other infusions for maintaining haemodynamic stability, different degrees of water and sodium retention were observed postoperatively, even pulmonary oedema and cardiac dysfunction. Cardiac dysfunction was often accompanied by hypotension. With low blood volume and increased fluid, a vicious cycle was formed, with resultant acute abdominal compartment syndrome (6–8). The patients' intra-abdominal pressure increased sharply, and abdominal infection symptoms were aggravated, causing a secondary blow to the patient and leading to further deterioration. Thus, the amount of liquid in severe abdominal infection should be strictly controlled after liver transplantation, low central venous pressure should be maintained, pulmonary oedema and cardiac dysfunction should be prevented, liver and kidney function should be protected, and infection in other parts, such as catheter-related infections, should be avoided. These measures ultimately helped the patients withstand the first blow caused by the sudden abdominal infection, proving conditions for patients to receive damage-controlling abdominal exploration and surgical debridement of infected lesions. Of course, purely relying on repeated recovery and organ function support, even repeated usage of systemic anti-infective drugs, would make the severe damage caused by intra-abdominal infections difficult to reverse.

Severe abdominal infections after liver transplantation are normally caused by *E coli* or a mixture of *E coli* and other bacteria. Bacterial translocation caused by intestinal barrier dysfunction is the main source of *E coli* (1, 9, 10). Many bacterial toxins and inflammatory mediators are absorbed into the bloodstream, increasing multiple-organ dysfunction. Thus, once diagnosis of severe abdominal infection after liver transplantation is clear, early debridement should be performed on the infected lesions. Such debridement should be moderate, focussing on necrotic tissue and strictly complying with principles of damage control. Clearing all abdominal purulent necrotic tissue is not necessary because it would increase bacteria and toxin absorption in the blood stream and aggravate the dysfunction of the respiratory, circulatory, and other systems. Open exploration should be avoided in the already adhesive inferior abdominal cavity to avoid the further expansion of peritoneal contamination. However, effective exploration should also be performed in the subphrenic space, and preoperative abdominal CT and B-ultrasound should be performed with care, avoiding blind exploration. Abdominal purulent necrotic tissue debridement should be moderate, and extensive rinsing should cover all parts of the abdomen during surgery, including the various interstices. Thorough peritoneal lavage, supplemented by postoperative continuous active flushing and negative drainage, can clear the infection. Severe abdominal infection after liver transplantation indicates the need for positive surgical exploration after clear diagnosis, active recovery, and multiple-organ support. The lesions should be removed as soon as possible; otherwise, they would lead to organ failure, resulting in the death of the patient.

Severe abdominal infections after liver transplantation are commonly caused by extensive bleeding after liver transplant and sometimes by gastrointestinal fistulae, which are the results of surgically injured gastrointestinal tract or infection-induced enteron diabrosis (2, 3, 11, 12). It may be difficult to identify such injury in the early stage. In the re-occurrence of similar symptoms after surgical removal of infected lesions in severe abdominal infections after liver transplantation, the possibility of gastrointestinal fistulae should be considered. Methylene blue or charcoal powder should be orally administered and the blue or charcoal powder flow from the wound drainage tube can be used for diagnosis. In this experiment, one case had a combination of gastrointestinal fistulae and severe abdominal infection. In this combined gastric fistula and severe abdominal infection, ulinastatin can be used for inflammation, which can improve circulation and stabilize respiratory and circulatory function. After the patient achieved a stable condition, growth hormone was administered to improve body metabolism and immune status, protect the intestinal barrier function, and promote the recovery of the body. Better clinical results were achieved (13–17).

Severe abdominal infection after liver transplantation is the most common cause of death in perioperative liver transplantation. Comprehensive treatments, such as active recovery, multiple-organ support, controlled surgical removal of the lesion, and adequate drainage, are the key factors.

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