Is there any difference in anesthetic management of different post-OLT stage patients undergoing nontransplant organ surgery?

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BACKGROUND: **Little information is available about anesthesia management of nontransplant organ surgery of recipients after adult liver transplantation. The aim of this study was to discuss the anesthesia management of recipients for different stages after liver transplantation.**

METHODS: **The medical records of 16 patients were reviewed after OLT scheduled for elective nontransplant organ surgery at our institution from September 2002 to October 2005. The patients were divided into perioperative stage (group A) and mid-term and long-term stage (group B) groups according to post-OLT time. The data of 16 patients preoperation, intraoperation and postoperation were analyzed.**

RESULTS: **The measurements of alanine transaminase (ALT), total bilirubin (TB), prothrombin time (PT), and lung infection were significantly higher in group A than in group B ($P<0.05$). The incidence of hyperglycaemia was significantly higher in group B than in group A ($P<0.05$). During operation the incidence of hypotension was significantly higher in group A than in group B ($P<0.05$). After operation, the number of patients in ICU was significantly larger and the extubation time was longer in group A than in group B. General anesthesia was induced in 14 patients, and regional anesthesia in 2 patients.**

CONCLUSIONS: **Regional or general anesthesia can be safely delivered to adult OLT recipients except for contraindications. Special considerations include protection of the function of important organs, correction of hemodynamic instability in perioperative stage patients after OLT, and measurement of the side-effects of immunosuppression in mid-term and long-term stage patients.**

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KEY WORDS: **liver transplantation; reoperation; anesthetic management**

Introduction

For decades, improved techniques and mature experience have made liver transplantation acceptable in the treatment of end-stage liver disease. Starzl et al[1] first reported that the 1- and 5-year survival rates of patients were 85% and 65%, respectively. In 2005, Ciccarelli et al[2] reported that the actual 1-, 5-, and 10-year survival rates of 282 recipients were 76.6%, 64.9% and 52%, respectively. The same year, in our liver transplantation center, the 1-year survival rates were 92.5% in patients with end-stage liver diseases and 55.3% in those with hepatocellular carcinoma (400 liver transplants).[3]

The number and survival rate of liver transplantation continue to improve yearly, and the number of transplanted patients indicating nontransplant organ surgery is expected to increase accordingly. Subsequent anesthetic management for nontransplant procedures may be challenging. The ignorance of the main physiologic and pharmacological changes in the new grafted organ and the knowledge of high risks of rejection or infection increase the anxiety in dealing with the patients. The purpose of this study was to discuss the anesthetic issues in different post-operative stages for adult liver transplantation recipients undergoing nontransplant organ surgery.

Methods

Patients

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A total of 16 patients who had been followed up after orthotopic liver transplantation (OLT) at our institution were enrolled (14 were male and 2 female). The patients aged from 35 to 60 years were scheduled for nontransplant organ surgery from September 2002 to October 2005. We excluded patients who had undergone operation with complications of OLT such as intraabdominal bleeding, bile leakage, biliary anastomotic stenosis, vascular complications, etc. According to the time after OLT, they were divided into two groups: perioperative stage (group A) and mid-term and long-term stage (group B). The perioperative stage was defined as about one month after surgery. In group A, the time after OLT was no longer than 33 days, whereas in group B it was longer than 90 days. In group A, 5 patients were male and 2 female, with an average age of 46.7 years (range 35-57 years) and an average post-OLT period of 22.4 days (range 2-33 days). In group B, 9 patients were male, with an average age of 43.6 years (range 37-57 years) and an average post-OLT period of 301.8 days (range 91-870 days).

Anesthesia

Anesthetic methods included general anesthesia and regional block. General anesthesia was induced by midazolam 0.04-0.1 $\mu g \cdot min^{-1} \cdot kg^{-1}$, fentanyl 2-5 $\mu g \cdot min^{-1} \cdot kg^{-1}$, vecuronium 0.1 $\mu g \cdot min^{-1} \cdot kg^{-1}$ and lidocaine 1.5 $\mu g \cdot min^{-1} \cdot kg^{-1}$, and was maintained with propofol 3-5 $\mu g \cdot min^{-1} \cdot kg^{-1}$ per hour and 0.5%-1.0% isoflurane. A supplemental dose of fentanyl was given as needed throughout the procedure and neuromuscular block was achieved with vecuronium. 1.5% lidocaine and 0.5% ropivacaine were used for regional nerve block.

Monitoring included blood pressure, heart rate, electrocardiogram, pulse oximetry, and central venous pressures, capnography, rhinopharynx temperature, and urinary output. Blood gases, electrolytes and blood glucose were monitored as needed.

Perioperative hypotension was defined as a mean blood pressure (MAP) that decreased by 25% from baseline, and the patient would receive a bolus of dopamine or epinephrine. After the treatment, if the MAP was decreased again by 30% from the baseline, the dose of the drug was repeated and then dopamine or epinephrine were started at a dose of 3 $\mu g \cdot min^{-1} \cdot kg^{-1}$ or 1 μg/min continuously and titrated according to the MAP. Perioperative hypertension was defined as a blood pressure more than 160/90 mmHg and the patient received a bolus of vasodilator. The dose was titrated according to the clinical effect. Corresponding measuremens were taken for acidosis or hyperglycemia.

Statistical analysis

The data were analyzed by Student's *t* test of independent samples. Numerical data were compared by Fisher's exact test because of the few cases observed. All reported *P* values were two-tailed analysed with

Table 1. Comparison of preoperative data between groups A and B

Variables	Group A	Group B
Albumin (g/L)	38.1±8.3	40.0±6.2
Glutamic pyruvic transaminase (U/L)	257.2±101.8	37.6±20.5#
Bilirubin total (μmol/L)	42.5±21.6	16.6±8.3#
Creatinine (μmol/L)	106.6±33.0	82.5±31.0
Blood platelets count ($10E^9$/L)	127.8±72.0	117.2±65.0
Hemoglobin (g/L)	104.4±30.0	115.4±21.1
WBC count ($10E^9$/L)	11.7±4.8	8.6±4.2
Fasting serum glucose (mmol/L)	6.6±2.9	5.1±1.1
Prothrombin time(s)	20.6±4.2	14.4±1.6#
Rejection (*n*)	1*	0
Pulmonary infection (*n*)	4	0#
Acid-base imbalance (*n*)	3	0
Renal insufficiency (*n*)	3	1
Hypertension (*n*)	0	3
Diabetes (*n*)	0	5#
Hypercholesterolemia (*n*)	0	2
Fungal positive in sputum culture (*n*)	1	3

#: $P<0.05$. *: one patient diagnosed as having acute rejection, which had been controlled before surgery.

Table 2. The surgical procedures and anesthesia of groups A and B

Case	Group A	Group B
1	Abdominal incision debridement and suturing (general anesthesia)	Left partial mandibulectomy(general anesthesia)
2	Abdominal incision debridement and suturing (epidural block)	Right adrenal gland tumour resection & right ureterolithotomy (general anesthesia)
3	Abdominal incision debridement and suturing (general anesthesia)	Thoracoscope lung eminectomy(general anesthesia)
4	Stomach hemostasis (general anesthesia)	T4 centrum metastatic tumorectomy(general anesthesia)
5	Abdominal incision debridement and suturing (general anesthesia)	Abdomen metastatic tylectomy (general anesthesia)
6	Abdominal incision debridement and suturing (general anesthesia)	Appendectomy# (general anesthesia)
7	Left common peroneal nerve exploration and prosthesis (nerve blockage)	Abdominal incision debridement and suturing (general anesthesia)
8		Right kidney abscess incision drainage (general anesthesia)
9		Right nephrectomy (general anesthesia)

#: A post re-OLT patient.

Table 3. Comparison of intraoperative data between groups A and B

Variables	Group A	Group B
Hypotension (*n*)	4	0#
Hypertension (*n*)	0	2
Use of inotropes (*n*)	4	0#
Acidosis (*n*)	3	0
Hypokalemia (*n*)	2	0
Use of blood products (*n*)	5	2
Time of surgery (h)	1.87±0.69	2.55±1.27

#: $P<0.05$.

Table 4. Comparison of postoperative data between groups A and B

Variables	Group A	Group B
Time to extubation >24 h (*n*)	4	1
Stay in ICU postoperation (*n*)	6	0#
Mortality (%)	2/7	0/9

#: $P<0.05$.

SPSS10.0 software. A P value less than 0.05 was considered statistically significant.

Results

Preoperative clinical and laboratory data were compared between groups A and B (Table 1). The levels of alanine transaminase (ALT), total bilirubin (TB) and prothrombin time (PT), as well as the incidence of lung infection were significantly higher in group A than those in group B ($P<0.05$). The incidence of hyperglycemia was significantly higher in group B than that in group A ($P<0.05$). The incidences of hypertension, hypercholesterolemia and fungal positive in sputum culture were higher in group B than those in group A ($P>0.05$). Three patients had acidosis in group A but none in group B. In group A, 1 patient had acute rejection, but controlled by immunosuppression before reoperation.

The operative categories of the two groups were markedly different (Table 2). The time of surgery was not different between the two groups (Table 3). General anesthesia was given to 14 patients and regional anesthesia to 2 patients. Two patients remained intubated and mechanically ventilated from ICU to operation room in group A but one in group B. During the operation, the incidence of profound hypotension was significantly higher in group A than that in group B ($P<0.05$). Thus, the number of patients using vasoconstrictor in group A was significantly larger than that in group B ($P<0.05$). In group A, hypotension occurred at the induction of anesthesia or during surgery. To maintain hemodynamic stability, 2 patients received dopamine and the other 2 received epinephrine continuously. In group B, 2 patients had hypertension after intubation and were treated subsequently with vasodilator. The incidences of acidosis and hypokalemia and the use of blood products were higher or more frequent in group A than in group B ($P>0.05$, Table 3). The incidence of preoperative hyperglycaemia was significantly higher in group B, but well controlled, and blood sugar was normal during surgery. There was no anesthesia-induced complication.

The number of patients in ICU after surgery was larger in group A than in group B ($P<0.05$) (Table 4). Extubation lasted for more than 24 hours for 4 patients in group A and 1 in group B. Only one patient in group B had extubation for more than 24 hours because of surgical procedures other than poor condition. In group A but not group B, two patients died in the hospital. One died of sepsis, severe pulmonary infection and multiple system organ failure (MSOF), and another died of sepsis, severe pulmonary infection and infectious-toxic

encephalopathy. The mean time for hospitalization was 39.4 days in group A and 72.2 days in group B. In general, the time of hospitalization was 7-70 days in group B, but two patients were hospitalized for 180 days and 260 days, because of renal abscess caused by fungal infection, giving a high standard deviation of group B.

Discussion

A variety of anesthetic techniques have been successfully used in patients with a history of transplant.[4] In this study, general anesthesia was given to 14 patients and regional anesthesia to 2 patients, without complications related to anesthesia. Hence the choice of anesthesia is determined by the type of surgery and the condition of the patient. If an epidural or spinal technique is planned, clotting and platelet count should be normal. Patients taking immunosuppression may have thrombocytopenia, which increases the risks associated with the block of the central nervous system.[5] If general anesthesia is scheduled no anesthetic is contradicted when hepatic and renal function is normal.[5]

The post-transplantation time can be divided into two stages: the perioperative stage, and mid-term and long-term stage.[6] Different stages have different major complications. In the perioperative stage, which is defined as one month after surgery, the major complications are intraabdominal bleeding, vascular or bile duct complications, liver dysfunction, pleural effusion, acute rejection, and infection. However, in the mid-term and long-term stage, the major problems are the side-effects of immunosuppressive drugs.[6] The complications of the perioperative stage after liver transplantation are protean, and the recipients are in poor clinical condition. In our study, in the perioperative stage the allograft function was not restored completely, and the patients suffered from severe infection, acute rejection, and acid-base imbalance. But those in the mid-term and long-term stage were better (Tables 3 and 4). We conclude that recipients in mid-term and long-term stage undergoing nontransplant surgery have a better outcome. Subsequently, anesthesia should be managed in different ways.

Hemodynamic monitoring was more instable in group A than in group B. Severe hypotension impairs graft liver function which would be normal at least 2 weeks after OLT.[7] Normal physiological mechanisms that protect liver blood flow are blunted after liver transplantation.[5, 8] The liver is an important source of blood volume in shock status via a vasoconstrictive response, and this mechanism may be impaired after liver transplantation.[9, 10] Nevertheless constrictors or catecholamines, which would reduce hepatic macrocirculation (33%-75% reduction) and microcirculation (39%-58% reduction) in a dose-dependent fashion,[11] is usually administered to correct severe hypotension during reoperation. Hence, the patients should be treated by continuous infusion of prostaglandin E, which can improve perfusion and microcirculation. The dose of the agent should be titrated according to the clinical effect. Drugs, that can impair could deteriorate liver function, should be avoided. If general anesthesia is planned, etomidate, propofol, ketamine, or fentanyl supplemented with nondepolarizing muscle relaxants has been used successfully for induction of anesthesia. Agents that do not compromise splanchnic blood flow (e.g. opioids, sevoflurane, desflurane, and isoflurane) are typically used to maintain anesthesia. Limited clinical and experimental data[12] show that intravenous anesthetics have only a modest impact on hepatic blood flow without meaningful adverse influence on postoperative liver function when blood pressure is adequately maintained.

Recipients are generally immunocompromised secondary to immunosuppressive therapy and their poor clinical condition, and they are at high risk for postoperative infection. Infection is a major cause of morbidity and the most common cause of death in liver transplant recipients.[13-17] The reported mortality of pulmonary infection complication is about 36%-60%.[18, 19] In our study, 4 patients in group A suffered from this complication, and the incidence of acidosis secondary to infection in group A was higher than in group B. The ICU stay time was longer, and the mortality was higher. Hence, anesthesia management should focus on correction of acid-base imbalance, protection of pulmonary function and anti-infection. Perioperative invasive monitoring requires aseptic techniques and should be discussed in terms of the risk-benefit ratio.[20-22] Oral endotracheal intubation is preferred over nasal intubation because of the potential infection caused by nasal flora. The use of a laryngeal mask is acceptable.[4] Perioperative antibiotic prophylaxis should be used appropriately. Precautions must be taken to protect lung function in optimal lung inflation and tracheal suction for removal of secretion to promote tracheal and bronchial hygiene. Mechanical ventilation with positive end expiratory pressure (PEEP) is essential, and humidifier should be used routinely.

Except for reoperation, regrafts, biliary reconstruction, and transfusion are also risk factors for hepatic arterial thrombosis. Once happen, the mortality rate is high in the transplant population.[23, 24] Liver transplant recipients should have a low blood viscosity (hematocrit approximately 28%) during the perioperative period.[25] Approximately 36% of liver transplant recipients may suffer from acute rejection in the early posttransplant period and require bolus steroid therapy as a rescue agent.[13] Rejection results in a progressive deterioration in organ function tests, and is the main cause of late mortality in transplant recipients.[13-15] The presence of rejection should always be ruled out preoperatively. There is some evidence that patients who undergo surgery during a period of rejection have a higher morbidity.[20]

But the clinical condition of recipients in the mid-term and long-term stage are more stable, and the functions of the liver and other organs returns to normal. The side-effects of immunosuppressive therapy are a major problem. The immunosuppressive agents have potential side-effects, such as neurotoxicity, nephrotoxicity with hyperkalaemic renal tubular acidosis, toxicity of the central nervous system, hypertension, diabetes, thrombocytopaenia, and leucopaenia. The incidence rates of hypertension and hypercholesterolemia after transplantation are reported 77% and 62%, respectively.[26, 27] Trail et al[27] reported that 5.2% of post-OLT patients were identified as having postransplant diabetes mellitus (PTDM) within 1 month after discharge. Liver transplant recipients have a prevalence of risk factors for cardiovascular disease, higher than that of the general population, and have a higher predicted risk for developing coronary heart disease (CHD).[28] No deaths from CHD or stroke were found during the study period.[26] The side-effects of immunosuppressive agents have a direct impact on anesthetic and perioperative management.[4] Anesthesia management should focus on the reduction of blood pressure and blood glucose. It is important to monitor the blood pressure and blood glucose carefully, if necessary, insulin or vasodilator should be given and stitrated according to the clinical effect. The interactions between immunosuppressive and anesthetic agents also should be stressed.[4] Patients receiving cyclosporine as an immunosuppressive agent may require a smaller dose of nondepolarizing muscle relaxant, and the recovery time may be prolonged. Ketamine in a child immunosuppressed with cyclosporine may not be safe and alternative anesthetics need to be considered for biopsy of the liver.[29] Such procedures should be performed with a sedative technique.[30]

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References

1 Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation (1). N Engl J Med 1989;321:1014-1022.
2 Ciccarelli O, Kaczmarek B, Roggen F, DeReyck C, Goffette P, Danse E, et al. Long-term medical complications and quality of life in adult recipients surviving 10 years or more after liver transplantation. Acta Gastroenterol Belg 2005; 68:323-330.
3 Zheng SS, Xu X, Liang TB, Wang WL, Shen Y, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: prognostic analysis of 89 cases. Zhonghua Wai Ke Za Zhi 2005;43:450-454.
4 Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, Theodoraki K, Papadimitriou L, Papadimitriou J. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. Anesth Analg 1999;89: 613-622.
5 Csete M, Sipher MJ. Management of the transplant patient for nontransplant procedures. Adv Anesth 1994;11:407-431.
6 Zheng SS, Wu J. We should prevent the complication of liver transplantation. Natl Med J China 2005;85:169-173.
7 Howard TK. Postoperative intensive care management of the adult. In: Busuttil RW, Klintmalm GB, eds. Transplantation of the liver. Philadelphia: WB Saunders; 1996:551-563.
8 Li XN, Benjamin IS, Alexander B. Hepato-cardiovascular response and its regulation. World J Gastroenterol 2005;11: 676-680.
9 Henderson JM, Millikan WJ, Hooks M, Noe B, Kutner MH, Warren WD. Increased galactose clearance after liver transplantation: a measure of increased blood flow through the denervated liver? Hepatology 1989;10:288-291.
10 Pedrosa ME, Montero EF, Nigro AJ. Liver microcirculation after selective denervation. Microsurgery 2001;21:163-165.
11 Mehrabi A, Golling M, Kashfi A, Boucsein T, Schemmer P, Gutt CN, et al. Negative impact of systemic catecholamine administration on hepatic blood perfusion after porcine liver transplantation. Liver Transpl 2005;11:174-187.
12 Christopher J, O'Connor, David M, Rothenberg, and Kenneth J. Tuman. Anesthesia and the hepatobiliary system. In: Ronald D. Miller eds. Miller's anesthesia, 6th Edition. Philadelphia: Natasha Andjelkovic;2005:2209-2229.
13 Papalois VE, Hakim NS. New immunosuppressive drugs in organ transplantation. In: Hakim NS, eds. Introduction to organtransplantation. London: Imperial College Press; 1997:225-236.
14 Killenberg PG, Cotton PK. Drug interactions with commonly used immunosuppressive agents. In: Killenberg PG, Clavien P-A, eds. Medical care of the liver transplant

patient. Malden, MA: Blackwell Science;1997:341-358.
15 Howard TK. Postoperative intensive care management of the adult. In: Busuttil RW, Klintmalm GB, eds. Transplantation of the liver. Philadelphia: WB Saunders; 1996:551-563.
16 McCarthy PM. Immediate postoperative care after thoracicorgan transplantation. In: Shumway SJ, Shumway NE, eds. Thoracic transplantation. Oxford: Blackwell Science;1995:205-218.
17 Duran FG, Piqueras B, Romero M, Carneros JA, de Diego A, Salcedo M, et al. Pulmonary complications following orthotopic liver transplant. Transpl Int 1998;11(Suppl 1): S255-259.
18 Golfieri R, Giampalma E, Morselli Labate AM, d'Arienzo P, Jovine E, Grazi GL, et al. Pulmonary complications of liver transplantation: radiological appearance and statistical evaluation of risk factors in 300 cases. Eur Radiol 2000;10: 1169-1183.
19 Gelb AW, Sharpe MD. Organ transplantation: anesthetic considerationsfor the previously transplanted patient. In: Benumof JL, ed. Anesthesiology Clinics of North America. Philadelphia: WB Saunders;1994:827-843.
20 Black AE. Anesthesia for pediatric patients who have had a transplant. Int Anesthesiol Clin 1995;33:107-123.
21 Johnston TD, Katz SM. Special considerations in the transplant patient requiring other surgery. Surg Clin North Am 1994;74:1211-1221.
22 Silva MA, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, et al. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. Liver Transpl 2006;12:146-151.
23 Ikegami T, Hashikura Y, Nakazawa Y, Urata K, Mita A, Ohno Y, et al. Risk factors contributing to hepatic artery thrombosis following living-donor liver transplantation. J Hepatobiliary Pancreat Surg 2006;13:105-109.
24 Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit--a contributing factor to hepatic artery thrombosis following liver transplantation. Transplantation 1988;46:162-163.
25 Neal DA, Tom BD, Luan J, Wareham NJ, Gimson AE, Delriviere LD, et al. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? Transplantation 2004;77:93-99.
26 Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. Am J Surg 2002; 183:595-599.
27 Trail KC, McCashland TM, Larsen JL, Heffron TG, Stratta RJ, Langnas AN, et al. Morbidity in patients with posttransplant diabetes mellitus following orthotopic liver transplantation. Liver Transpl Surg 1996;2:276-283.
28 Sharpe MD. Anaesthesia and the transplanted patient. Can J Anaesth 1996;43:R89-98.
29 Agarwal A, Raza M, Dhiraaj S, Saxena R, Singh PK, Pandey R. Is ketamine a safe anesthetic for percutaneous liver biopsy in a liver transplant recipient immunosuppressed with cyclosporine? Anesth Analg 2005;100:85-86.
30 Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, Contis J, Briassoulis G, Kostopanagiotou E. Anaesthetic and perioperative management of paediatric organ recipients in nontransplant surgery. Paediatr Anaesth 2003; 13:754-763.

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