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BRIEF ARTICLE

Individualized peri-operative fluid therapy facilitating early-phase recovery after liver transplantation

Guo-Qing Jiang, Ping Chen, Dou-Sheng Bai, Jing-Wang Tan, Hao Su, Min-Hao Peng

Guo-Qing Jiang, Ping Chen, Dou-Sheng Bai, Jing-Wang Tan, Department of Hepatobiliary Surgery, Clinical Medical College of Yangzhou University, Yangzhou 225000, Jiangsu Province, China

Hao Su, Min-Hao Peng, Department of Hepatobiliary Surgery, First Affiliated Hospital, Guangxi Medial University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Author contributions: Jiang GQ and Chen P contributed equally to this work; Jiang GQ, Chen P, Bai DS and Peng MH designed the research; Jiang GQ, Bai DS and Chen P performed the research; Jiang GQ, Tan JW and Su H analyzed the data; Jiang GQ and Chen P wrote the paper.

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Correspondence to: Min-Hao Peng, Professor, Department of Hepatobiliary Surgery, First Affiliated Hospital, Guangxi Medial University, Nanning 530021, Guangxi Zhuang Autonomous Region, China. minhaopeng@hotmail.com

Telephone: +86-771-5356799 Fax: +86-771-5356799

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Abstract

AIM: To investigate the correlation between peri-operative fluid therapy and early-phase recovery after liver transplantation (LT) by retrospectively reviewing 102 consecutive recipients.

METHODS: Based on whether or not the patients had pulmonary complications, the patients were categorized into non-pulmonary and pulmonary groups. Twenty-eight peri-operative variables were analyzed in both groups to screen for the factors related to the occurrence of early pulmonary complications.

RESULTS: The starting hemoglobin (Hb) value, an intra-operative transfusion > 100 mL/kg, and a fluid balance ≤ -14 mL/kg on the first day and the second or third day post-operatively were significant factors for early pulmonary complications. The extubation time, time to initial passage of flatus, or intensive care unit length of stay were significantly prolonged in patients who had not received an intra-operative transfusion ≤ 100 mL/kg or a fluid balance ≤ -14 mL/kg on the first day and the second or the third day post-operatively. Moreover, these patients had poorer results in arterial blood gas analysis.

CONCLUSION: It is important to offer a precise and individualized fluid therapy during the peri-operative period to the patients undergoing LT for cirrhosis-associated hepatocellular carcinoma.

Key words: Fluid therapy; Liver transplantation; Early-phase recovery; Pulmonary complications; Hemoglobin

Peer reviewer: Dr. Roberto Ballarin, Liver and Multivisceral Transplant Center, University of Modena and Reggio Emilia, No. 71, Via del Pozzo, 41100 Modena, Italy

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INTRODUCTION

Liver transplantation (LT) is the optimal therapy for end-stage liver diseases. Although LT has undergone a rapid progress, early pulmonary complications are common and known to contribute significantly to the morbidity and mortality of the patients[1-4]. Post-operative pulmonary complications may be caused by many factors during the patient's recovery, and fluid therapy is an important factor[5,6]. Individualized fluid therapy during the peri-operative period may be a significant strategy to achieve a better early-phase recovery after LT. In this study, early-phase refers to the first month after LT.

In a previous study, we investigated and assessed the use of fluid therapy in all the patients undergoing LT[7]. This study focused on the patients with cirrhosis-associated hepatocellular carcinoma (HCC), and fluid transfusion was administered based on the body weight of the patients per kg.

The purpose of this study was to investigate the clinical significance of the correlation between peri-operative fluid therapy and early-phase recovery after LT in an attempt to establish a precise and individualized fluid therapeutic strategy in the peri-operative period of LT.

MATERIALS AND METHODS

The medical records of all consecutive patients with cirrhosis-associated HCC who underwent orthotopic LT at the First Affiliated Hospital of Guangxi Medial University between July 1996 and July 2009 were retrospectively reviewed. Patients aged from 23-72 years with a mean ± SD of 45.26 ± 9.54 years. This series represents the first 102 consecutive LT recipients with cirrhosis-associated HCC in our cohort study.

All LT procedures were performed using the piggyback technique without venovenous bypass. In addition to fluid transfusion given intra-operatively, small amounts of vasopressors (dopamine and noradrenaline) and shallow anesthesia were used to maintain hemodynamic stability. All patients were admitted to the intensive care unit (ICU) immediately after surgery and extubated as soon as they met standard criteria for termination of mechanical ventilation, such as the presence of adequate gas exchange function, hemodynamic stability, and ability to protect the airway. Antibiotics and anti-fungals for infection were used prophylactically.

Radiographic analysis was standardized by assessment of eight separate observations designed to determine the presence of pulmonary edema[8].Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) were defined according to the American-European Consensus Conference[9], and pneumonia was defined according to a Joint Committee of the American Thoracic Society and Infectious Diseases Society of America[10].

All variables

Twenty-five peri-operative variables affecting post-operative early-phase recovery were as follows: age; body weight index; hemoglobin (Hb); hematocrit (HCT); serum creatinine (CRE); blood urea nitrogen (BUN); serum uric acid (UA); American Society of Anesthesiologists (ASA) grade; Child-Pugh score; acute physiology and chronic health evaluation (APACHE) Ⅱ score; model for end-stage liver disease (MELD) score; warm ischemia time; cold ischemia time; anhepatic phase; operative time; diabetes; lung function; volume of intra-operative blood transfusion; volume of intra-operative packed red blood cell (RBC) transfusion; volume of intra-operative plasma transfusion; volume of intra-operative fluid transfusion; volume of intra-operative bleeding; intra-operative fluid balance; transfused volume and fluid balance on the first post-operative day. Bivariate correlation analysis for the relationship between these intra-operative variables and occurrence of pulmonary complications showed the following significant variables: blood transfusion > 30 mL/kg (P = 0.046); packed RBC transfusion > 0.05 U/kg (P = 0.041); plasma transfusion > 25 mL/kg (P = 0.042); fluid transfusion > 100 mL/kg (P = 0.014); bleeding > 10 mL/kg (P = 0.018); fluid balance > 64 mL/kg (P = 0.037); fluid transfusion volume on the first post-operative day ⩽ 44 mL/kg (P = 0.010); and fluid balance on the first post-operative day ⩽ -14 mL/kg (P = 0.018). The threshold values of these variables were obtained by bivariate correlation analysis between the volume of intra-operative transfusion and post-operative pulmonary complications. The statistically significant threshold value was 100 mL/kg. If no statistically significant threshold value was obtained, the lowest P value was recorded. The critical value of other fluid variables was determined by the same analysis.

Because of the special importance of the first 3 post-operative days for patients' recovery, the following three variables were analyzed: fluid balance ⩽ -14 mL/kg on the first day and the second or the third day after operation (P = 0.010); fluid balance ⩽ -14 mL/kg on post-operative ⩾ 1 d (P = 0.612); and fluid balance ⩽ -14 mL/kg on post-operative ⩾ 2 d (P = 0.014).

Other variables analyzed included the worst outcome of arterial blood gas analysis in the first 7 post-operative days. The outcome variables reflecting post-operative recovery included: extubation time; time to initial passage of flatus; and ICU length of stay.

In this study, fluid balance in the surgery did not include the "third space" loss, evaporative loss, and insensible loss. So far, no method has provided estimated losses for LT.

Statistical analysis

Data were presented as the mean ± SD, median/range, or percentage (%). Group means were compared using Student's t test or the Mann-Whitney U test as appropriate. The χ^2 test was used to compare percentages. Bivariate correlation was used to determine the significant threshold value of peri-operative fluid variables. Multivariate regression analysis was performed with stepwise elimination of non-significant variables. A P < 0.050 was considered significant. All analyses were performed with SPSS 12.0 software (SPSS, Chicago, IL, United States).

RESULTS

Of the 102 patients (89 males and 13 females), 47 patients (46.08%) had pulmonary complications after LT. No hypoxia was found preoperatively. Pulmonary edema (PE; n = 8, 17.02%), acute lung injury (ALI; n = 12,

Table 1 Comparison of 25 variables between the groups with and without pulmonary complications

Variables	Non-pulmonary complication group (n = 55)	Pulmonary complication group (n = 47)	P value
Age (yr)	46.29 ± 9.14	44.06 ± 9.95	0.242
Weight index (kg/m^2)	22.78 ± 3.35	22.36 ± 3.29	0.531
Hb (g/L)	122.79 ± 21.12	109.54 ± 25.25	0.005
HCT (%)	36.21 ± 6.42	32.53 ± 7.53	0.009
CRE (mmol/L)	83.75 ± 21.35	85.96 ± 23.88	0.623
BUN (mmol/L)	4.70 ± 1.92	5.22 ± 3.09	0.323
UA (mmol/L)	303.76 ± 113.27	272.43 ± 117.94	0.175
ASA grade	2.76 ± 0.61	3.0 ± 0.75	0.082
Child-Pugh score	7.29 ± 2.40	8.38 ± 2.88	0.039
APACHE Ⅱ score	3.95 ± 2.47	4.79 ± 3.53	0.174
MELD score	14.22 ± 7.34	16.68 ± 9.39	0.140
Warm ischemia time (min)	5.80 ± 1.52	5.53 ± 1.63	0.392
Cold ischemia time (min)	710.13 ± 184.99	654.21 ± 208.25	0.154
Anhepatic phase (min)	123.04 ± 34.46	126.00 ± 47.00	0.715
Operative time (min)	423.22 ± 84.92	489.38 ± 150.00	0.009
Diabetes (%)	9.09	8.51	1.000
Lung dysfunction (%)	12.73	19.15	0.374
Volume of intra-operative blood transfusion > 30 mL/kg (%)	65.45	82.98	0.046
Volume of intra-operative packed RBC transfusion > 0.05 U/kg (%)	76.36	91.49	0.041
Volume of intra-operative plasma transfusion > 25 mL/kg (%)	43.64	63.83	0.042
Volume of intra-operative fluid transfusion > 100 mL/kg (%)	58.18	80.85	0.014
Volume of intra-operative bleeding > 10 mL/kg (%)	67.27	87.23	0.018
Intra-operative fluid balance > 64 mL/kg (%)	32.73	53.19	0.037
a (%)	21.82	4.26	0.010
b (%)	38.18	17.02	0.018
c (%)	25.45	6.38	0.010
d (%)	72.73	68.09	0.612
e (%)	36.36	14.89	0.014

Hb: Hemoglobin; HCT: Hematocrit; CRE: Creatinine; BUN: Blood urea nitrogen; UA: Serum uric acid; ASA: American Society of Anesthesiologists; APACHE: Acute physiology and chronic health evaluation; MELD: Model for end-stage liver disease. a, transfused volume on the first post-operative day ≤ 44 mL/kg; b, fluid balance on the first post-operative day ≤ -14 mL/kg; c, fluid balance ≤ -14 mL/kg on the first day and the second or the third day after operation; d, fluid balance ≤ -14 mL/kg on ≥ 1 d of the first 3 d after operation; e, fluid balance ≤ -14 mL/kg on ≥ 2 d after operation. ASA grade I was assigned a score of 1, grade Ⅱ was assigned a score of 2, grade Ⅲ was assigned a score of 3, and grade IV was assigned a score of 4. Mean ± SD was used for continuous variables, otherwise percentage was used (%).

25.53%), adult respiratory distress syndrome (ARDS; n = 6, 12.77%), and pneumonia (n = 21, 44.68%) occurred after surgery. Four patients survived no more than one month after LT.

Table 1 shows the comparison of 28 variables between the non-pulmonary and pulmonary complication groups. The following variables were found significant: Hb; HCT; Child-Pugh score; operative time; intra-operative blood transfusion > 30 mL/kg; intra-operative packed RBC transfusion > 0.05 U/kg; intra-operative plasma transfusion > 25 mL/kg; intra-operative fluid transfusion > 100 mL/kg; intra-operative bleeding > 10 mL/kg; intra-operative fluid balance > 64 mL/kg; fluid transfusion volume on the first post-operative day ≤ 44 mL/kg; fluid balance ≤ -14 mL/kg on the first post-operative day; fluid balance ≤ -14 mL/kg on the first day and the second or the third day after operation; and fluid balance ≤ -14 mL/kg ≥ 2 d after operation.

Table 2 Summary of the logistic regression model and odds ratios

Variables	Beta	SE	Sig	Exp (B)	95% CI
Hb	-0.025	0.010	0.11	0.975	0.956-0.994
Volume of intra-operative transfusion	1.097	0.496	0.27	2.995	1.132-7.922
c	2.037	0.722	0.05	7.670	1.862-31.603

SE: Standard error; Sig: Statistical significance; CI: Confidence interval; Hb: Hemoglobin. c, fluid balance ≤ -14 mL/kg on the first day and the second or the third after operation. When the volume of intra-operative transfusion ≤ 100 mL/kg, the variable was assigned a score of 0, and when the variable > 100 g/L, the variable was assigned a score of 1.

Table 3 Comparison of outcome variables reflecting post-operative recovery between groups A and B

	Group A (n = 32)	Group B (n = 70)	Z or t	P value
Extubation time (h)	12/8-99	16.5/5-504	-2.779	0.005
Time to initial passage of flatus (h)	78.66 ± 21.05	90.51 ± 45.28	-1.411	0.161
ICU length of stay (h)	36.5/8-144	62/14-600	-4.173	0.000

Values are given as the mean ± SD (median/range). ICU: Intensive care unit.

The statistically significant variables were regarded as independent variables, and post-operative pulmonary complications were regarded as dependent variables. Multivariate regression analysis was performed to screen out the variables related to early pulmonary complications. Table 2 shows the statistically significant variables: Hb; intra-operative transfusion > 100 mL/kg; and fluid balance ≤ -14 mL/kg on the first day and the second or the third day after operation.

The 32 patients who received an intra-operative transfusion ≤ 100 mL/kg were referred to as group A and the other 70 patients who received an intra-operative transfusion > 100 mL/kg were as group B. Table 3 shows the comparison of outcome variables reflecting post-operative recovery between the two groups. As expected, both the extubation time and ICU length of stay in group A were shorter than in group B (P < 0.01). A comparison of the worst outcome of arterial blood gas in the first 7 post-operative days between the two groups showed that both PaO_2 and arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio in group A were higher than in group B (110.422 ± 28.305 *vs* 90.641 ± 31.169, P < 0.01 for PaO_2; and 272.355 ±

Table 4 Comparison of outcome variables reflecting post-operative recovery between groups A and B

	Group A (n = 17)	Group B (n = 85)	Z or t	P value
Extubation time (h)	12/7-32	15/5-504	-2.708	0.007
Time to initial passage of flatus (h)	59.71 ± 12.17	92.21 ± 40.96	-6.094	0.000
ICU length of stay (h)	40/13-219	60/8-600	-1.590	0.112

Values are given as the mean ± SD (median/range). ICU: Intensive care unit.

Table 5 Comparison of the worst outcome of arterial blood gas in the first 7 post-operative days between groups A and B

	Group A (n = 17)	Group B (n = 85)	t	P value
PH	7.436 ± 0.041	7.437 ± 0.055	-0.108	0.914
PaO_2	117.471 ± 31.283	92.722 ± 30.105	3.075	0.003
$PaCO_2$	44.094 ± 7.168	44.787 ± 12.038	-0.229	0.819
BE	4.459 ± 4.207	4.789 ± 4.062	-0.305	0.761
PaO_2/FiO_2	295.891 ± 92.741	224.243 ± 81.820	3.223	0.002

Values are given as the mean ± SD. PH: Power of hydrogen; PaO_2: Arterial partial pressure of oxygen; $PaCO_2$: Arterial pressure of carbon dioxide; BE: Base excess.

79.486 *vs* 219.649 ± 86.462, $P < 0.01$ for PaO_2/FiO_2).

The 17 patients who received a fluid balance ≤ -14 mL/kg on the first day and the second or the third day after operation served as group A and the other 85 patients who did not receive a fluid balance ≤ -14 mL/kg served as group B. Table 4 shows a comparison of outcome variables reflecting post-operative recovery between the two groups. As expected, both the extubation time and the time to initial passage of flatus in group A were shorter than in group B ($P < 0.01$). Table 5 shows the comparison of the worst outcome of arterial blood gas in the first 7 post-operative days between the two groups. Both PaO_2 and PaO_2/FiO_2 in group A were higher than in group B ($P < 0.01$).

DISCUSSION

The LT recipients in this study presented the following characteristics: (1) All had chronic liver cirrhosis with water-sodium retention to some degree; (2) Because of the operative injury for LT, the capillary leak syndrome (CLS) created a "third space" effect; (3) Intra-operative fluid overload was common in order to maintain stable hemodynamics; and (4) A large-dose methylprednisolone was used to avoid reject reaction during and after surgery. All these factors contributed to aggravated water-sodium retention. Therefore, a precise and individualized fluid therapy is strongly recommended.

Collective studies demonstrated the importance of intra-operative fluid management to maintain body fluid equilibrium by restricting the volume of fluid infusion. Excessive fluid administration was associated with a higher risk of post-operative complications[11-14]. Aduen *et al*[15] reported that pulmonary complications interfered with the peri-operative course of patients undergoing LT and portended a worse outcome. Meanwhile, the time for extubation, ICU stay and hospital stay were significantly prolonged.

The restrictive intra-operative fluid management may be advantageous because it reduces morbidity and mortality and shortens mechanical ventilation, the time to initial passage of flatus, intensive care, and hospital stay[16-21].

In this study, binary logistic regression revealed that an intra-operative transfusion > 100 mL/kg (Table 2) was an independent risk factor for post-operative pulmonary complications. The incidence of post-operative pulmonary complications in group A was significantly lower than in group B (28.13% *vs* 54.29%, $P = 0.014$). The extubation time and ICU length of stay were also significantly shorter than in group B (Table 3). Group A had higher PaO_2 and PaO_2/FiO_2 than group B. These outcomes demonstrated that intra-operative fluid therapy was very important, which was associated with the incidence of pulmonary complications and the post-operative recovery.

Post-operative fluid overload is an independent risk factor for post-operative pulmonary complications after LT. Alsous *et al*[22] demonstrated that a fluid balance ≤ -500 mL on ≥ 1 d of the first 3 d of septic shock was associated with fewer pulmonary complications and better recovery. Our results demonstrated that it is a significant means to keep a fluid balance ≤ -14 mL/kg on the first day and the second or the third day after LT (Table 2). The incidence of post-operative early pulmonary complications in group A was lower than in group B (17.65% *vs* 51.76%, $P = 0.01$). This fluid therapy contributed to a better recovery (Tables 4 and 5) possibly because a fluid balance at ≤ -14 mL/kg within 3 d after LT could prevent edema, thus improving the blood supply and promoting recovery.

Of the four variables (fluid balance on the first post-operative day ≤ -14 mL/kg, fluid balance ≤ -14 mL/kg on the first day and the second or the third day after surgery, fluid balance ≤ -14 mL/kg on ≥ 1 d after surgery, and fluid balance ≤ -14 mL/kg on ≥ 2 d after surgery), only the fluid balance ≤ -14 mL/kg on the first day and the second or the third day after operation was included in the logistic regression analysis of outcome. It suggested that precise and individualized fluid balance in the peri-operative period should be accomplished as early as possible. In contrast, a negative fluid balance in the peri-operative period should be achieved to some extent.

The first 3 d after operation comprise the stress phase. Vascular recovery time varied from 36 h to 72 h after surgery. The transition points from positive to negative fluid balance also occurred. LT recipients need a large-dose methylprednisolone after operation, especially during the first few days. However, methylprednisolone would cause and aggravate water-sodium retention which may appear post-operatively, so the transition points would be postponed. Fluid balance during the first 3 d after surgery is crucial for recovery. If a positive fluid balance lasts too long, it is difficult for patients to recover. Thus, fluid balance should be properly managed as early as possible, and the quantity and time of negative fluid balance should be assessed individually.

Under the circumstances of stable hemodynamics, we should extrude the sequestered fluid from the peripheral circulation and the "third space" back to the central circulation. Whether or not a negative fluid balance is needed, the quantity and time of a negative fluid balance should be assessed by the following measurement: blood pressure, pulse, central venous pressure, HCT, the estimated volume of transfusion on the second day, and liquid intake and output volume of the preceding day. The fluid balance on the second post-operative day could be accomplished by adjusting the urine volume per hour. With administration of diuretics and colloid, urine volume could be controlled as needed. If hemodynamics were unstable, blood volume should be supplemented and inotropic drugs, such as dopamine, should be properly used.

We also found that Hb was an independent risk factor for post-operative pulmonary complications, which may be a significant factor for early recovery. When the patients with hepatic cirrhosis developed hypersplenism, which was always parallel with a reduction of hemocytes, their immune function became obviously lower and their hepatic function was poorer than other patients without a reduction of hemocytes. A low level of Hb may result in oxygen deficiency.

It is important to keep a fluid balance during the peri-operative period of LT. The precise and individualized fluid administration at the first 3 d after surgery significantly decreased the incidence of early pulmonary complications after LT. The strategies of an intra-operative transfusion ≤ 100 mL/kg and a fluid balance ≤ -14 mL/kg on the first day and the second or the third day after LT should be recommended. This study was limited by its small sample size. The shortcomings may limit the extrapolation of these results to all LT recipients. The hypothesis should be re-examined and verified in a much larger cohort before it is used for improving the prognosis and patient management. Nonetheless, if validated by future prospective studies, the fluid therapy used in this study would provide a simple and inexpensive method of augmenting the current prognostic indicators, and would be of obvious benefit for the anxious family members and care providers as well.

COMMENTS

Background

Liver transplantation (LT) is the optimal therapy for end-stage liver disease. Early-phase complications after LT are common and known to contribute significantly to morbidity and mortality of the patients. Individualized fluid therapy during the peri-operative period may be a significant strategy to achieve a better early-phase recovery after LT.

Research frontiers

Recently, more attention has been paid to peri-operative fluid therapy. Fluid therapy is an important factor related to pulmonary complications and patient recovery.

Innovations and breakthroughs

This research focused on the LT recipients with cirrhosis-associated hepatocellular carcinoma, and fluid was administrated based on the body weight in kilograms so as to guarantee a precise and individualized fluid therapy peri-operatively.

Applications

It is important to offer a precise and individualized fluid therapy during the peri-operative period to the patients undergoing LT for cirrhosis-associated hepatocellular carcinoma. With an intra-operative transfusion > 100 mL/kg and a fluid balance ≤ 14 mL/kg on the first day and the second or the third day after LT can significantly improve the early-phase recovery after LT.

Terminology

The capillary leak syndrome is a rare condition characterized by recurrent episodes of generalized edema and severe hypotension associated with hypoproteinemia. A shift of fluid and protein from the intravascular to the interstitial space results in hypovolaemia. Attacks vary in frequency, severity, and duration, and can be fatal.

Peer review

Authors have investigated the clinical significance of the correlation between peri-operative fluid therapy and early-phase recovery after LT. The topic is interesting and offers points of reflection. The manuscript is original and may be useful to clinicians.

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