Hepatol Int (2013) 7:901–909
DOI 10.1007/s12072-013-9457-9

ORIGINAL ARTICLE

The effects of intraoperative cryoprecipitate transfusion on acute renal failure following orthotropic liver transplantation

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Received: 15 April 2013 / Accepted: 29 June 2013 / Published online: 2 August 2013

Abstract
Purpose The definition of risk factors associated with acute renal failure (ARF) following orthotropic liver transplantation (OLT) is still controversial. Cryoprecipitate, which can supply fibrinogen and other coagulation factors, is widely used in OLT. However, the effects of intraoperative cryoprecipitate transfusion on ARF following OLT remain unclear.
Methods In a series of 389 adult patients who received grafts from deceased donors and underwent their first OLT, the clinical correlation between intraoperative cryoprecipitate transfusion and ARF following OLT was retrospectively studied after adjusting for potential confounders. The distribution of ARF and the causes of death within the first year after OLT were also compared separately in patients with and without cryoprecipitate transfusion.
Results The incidence of ARF in patients with cryoprecipitate transfusion was significantly higher than in patients without cryoprecipitate transfusion (15.9 vs. 7.8 %, $p = 0.012$). A nonlinear relationship between intraoperative cryoprecipitate transfusion and ARF following OLT was observed. The risk of ARF increased with the cryoprecipitate transfusion level up to the turning point (16 U) (adjusted OR 1.1, 95 % CI 1.1–1.2; $p < 0.001$). When the cryoprecipitate level exceeded 16 U, the level of cryoprecipitate transfusion was not associated with the risk of ARF (OR 0.95, 95 % CI 0.85–1.1; $p = 0.319$). Deaths within the first year after the operation occurred more frequently in cases with cryoprecipitate transfusion (22.9 vs. 14.2 %, $p = 0.029$).
Conclusions These findings suggested that intraoperative cryoprecipitate transfusion is associated with ARF following OLT. Cryoprecipitate transfusion during OLT should be performed carefully until more convincing evidence has been found.

Keywords Transfusion · Cryoprecipitate · Acute renal failure · Liver transplantation

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Introduction

Acute renal failure (ARF) is a common complication following liver transplantation (OLT). In 1990, the incidence of ARF following OLT reached 94.2 % [1]. More recently, there was a decline in incidence to 30–60 % between 2003 and 2007 [2–4]. It has been estimated that between 8 and 17 % of patients with ARF following OLT require replacement therapy [5, 6]. Patients developing ARF are at increased risk of mortality [7–9], and their management results in a significant economic burden [10].

The etiology of ARF following OLT is usually multifactorial. Various factors may influence the occurrence of ARF to varying degrees [11]. Preoperative renal impairment, blood loss and sepsis may all contribute to ARF following OLT [3, 5, 12]. Although the many complications following OLT caused by blood product transfusion have increasingly been attracting attention recently [13–15], few researchers are concerned about the effects of intraoperative blood product transfusion on ARF following OLT.

Intraoperative cryoprecipitate transfusion, which supplies fibrinogen and other coagulation factors, can effectively stop bleeding and promote wound healing. Moreover, it does not require cross-matching and is convenient to obtain. Therefore, cryoprecipitation has been widely adopted in OLT, particularly in developing countries. However, no uniform criteria for the application of its complex components during OLT are available. As far as we know, no preceding work or report has considered the effects of intraoperative cryoprecipitate transfusion on ARF following OLT.

In this study, we applied a set of consensus criteria—risk, injury, failure, loss and end stage (RIFLE)—published by the Acute Dialysis Quality Initiative (ADQI) to define ARF following OLT [16]. Then we retrospectively collected perioperative variables of patients undergoing OLT in a single center to explore the clinical correlation between intraoperative cryoprecipitate transfusion and ARF following OLT. We also investigated the effect of cryoprecipitate transfusion on post-transplant survival. It was hoped that these data would provide experimental evidence to decrease the occurrence of ARF following OLT.

Materials and methods

Study population

A total of 459 consecutive patients underwent OLT at Shanghai First People's Hospital between 1 January 2003 and 31 December 2010. All grafts were from deceased donors. We excluded data from children ($n = 3$), patients with renal dysfunction pre-transplantation ($n = 40$) and patients who had received re-transplantation ($n = 27$), and the remaining 389 cases formed the analysis population.

We defined pre-transplantation renal dysfunction as when the serum creatinine (Scr) level was greater than 133 mmol/l in two consecutive examinations performed within a 48-h period. Intraoperative blood product transfusion included whole blood, red blood cells, cryoprecipitate, fresh frozen plasma and cell saver. In our center, the indication for use of cryoprecipitate to compensate fibrinogen or coagulation factors in OLT was a plasma fibrinogen level of <1.0 g/l. As another procoagulant product, fresh frozen plasma was used in (1) cases of excessive microvascular bleeding in the presence of a PT greater than 1.5 times normal or INR greater than 2.0, or an APTT greater than two times normal; (2) patients transfused with more than one blood volume and when PT or INR and APTT could not be obtained in a timely fashion. We stopped transfusing these procoagulant products when bleeding had been significantly improved as judged by the surgeon's experience and the parameters of coagulation and fibrolysis had reached the cutoff value from the following blood test report. In our center, each unit of cryoprecipitate is made from 400 ml whole blood; the volume of each unit is 25 ± 5 ml and contains ≥80 IU factor VIII, ≥150 mg fibrinogen and other proteins in the concentrate including fibronectin (20–25 %), albumin (5–8 %), IgG (5–8 %), IgM (1–2 %), von Willebrand factor and coagulation factor XIII.

After transplantation, hepatic and renal functions as well as the concentration of immunosuppressive drugs were monitored daily in the hospitalization period. If the patient's SCR level became obviously abnormally elevated, we paused the procedure to give CNIs for 72 h. During this period, the patient was maintained on a regimen containing only steroids and mycophenolate mofetil. If the patient's SCR level remained elevated despite good urine output, the patient was maintained on a low-dose CNI to allow for renal recovery. For patients who remained oliguric, sirolimus was sometimes substituted for a CNI in the regimen. This regimen has also been adopted in other transplant centers [12]. In addition, we defined postoperative infections as hemodynamic instability accompanied with positive blood cultures, and in this study we only analyzed infections occurring before ARF. All infections were treated with appropriate therapy.

According to the RIFLE classification, ARF following OLT was classified into three groups (risk, injury and failure) based on relative changes of Scr or urine output [16]. We defined ARF as renal function reaching the level of failure (an increase in Scr ≥3.0 × baseline or decrease in GFR ≥75 % or an absolute Scr ≥354 μmol/l with an acute increase of at least 44 μmol/l and/or urine output <0.3 ml/kg/h ≥24 h or anuria ≥12 h or anuria ≥12 h) within their hospital stay period. According to these criteria, a total of 43 patients experienced ARF following OLT.

Outpatient follow-up was performed once a week for the first 3 months and every 2 weeks within the first year after the operation. The causes of death for each patient were recorded. All follow-up data were collected until 31 December 2011.

Clinical and surgical data for the cases reviewed were obtained from the China Liver Transplant Registry (CLTR) and by the checking of original medical records. National legislation and the ethics committee of Shanghai First People's Hospital approved this retrospective study.

Table 1 Demographic and clinical characteristics of the cases included in the study

Characteristics	Without cryoprecipitate transfusion ($n = 232$)	With cryoprecipitate transfusion ($n = 157$)	p value
Age, mean (SD), years	47.7 (9.2)	47.8 (9.4)	0.924
Gender, n (%)			
Male	189 (81.5)	120 (76.4)	0.228
Female	43 (18.5)	37 (23.6)	
Etiology, n (%)			
Cirrhosis	151 (65.1)	115 (73.2)	0.002*
Carcinoma	62 (26.7)	19 (12.1)	
Fulminant hepatic failure	12 (5.2)	18 (11.5)	
Others	7 (3.0)	5 (3.2)	
ABO blood group, n (%)			
Incompatibility	31 (13.4)	24 (15.3)	0.593
Compatibility	201 (86.6)	133 (84.7)	
Child-Pugh grade, n (%)			
Grade A	41 (17.7)	13 (8.3)	<0. 001*
Grade B	28 (12.1)	5 (3.2)	
Grade C	163 (70.2)	139 (88.5)	
Preoperation Scr, mean (SD), μmol/l	83.7 (9.4)	82.5 (11.4)	0.273
Warm ischemia time, mean (SD), min	3.5 (1.2)	3.4 (1.0)	0.237
Cold ischemia time, mean (SD), h	9.2 (2.0)	9.3 (2.3)	0.514
Anhepatic phase, mean (SD), min	60.8 (12.7)	63.0 (32.8)	0.362
Operation time, mean (SD), h	7.3 (1.0)	7.4 (1.2)	0.192
Blood loss, mean (SD), ml	3418 (2,555)	3482 (2,107)	0.796
Transfusion of blood products			
Whole blood, mean (SD), U	1.4 (3.5)	1.9 (4.0)	0.229
Red blood cells, mean (SD), U	9.8 (7.5)	10.0 (6.4)	0.295
Fresh frozen plasma, mean (SD), U	1.5 (3.1)	2.1 (5.0)	0.667
Platelet, mean (SD), U	0.6 (1.0)	0.6 (1.0)	0.900
Cell saver, mean (SD), ml	584 (1309)	508 (1246)	0.385
Immunosuppressive protocol, n (%)			
Including cyclosporine A	164 (70.7)	109 (69.4)	0.846
Including FK506	62 (26.7)	45 (28.7)	
Steroid, n (%)			
Used after OLT	203 (87.5)	134 (85.4)	0.541
Not used after OLT	29 (12.5)	23 (14.6)	
Infections, n (%)			
Occurred before ARF	34 (14.7)	21 (13.4)	0.722
Did not occur or occurred after ARF	198 (85.3)	136 (86.6)	

Cirrhotic patients and patients with Child-Pugh grade C were more frequently found in the cryoprecipitate transfusion group

* p <0.05 indicates a significant difference between the two groups

Statistical analysis

We first compared the data distribution of each covariate between the exposed and the non-exposed groups, using the t test (normal distribution) or Kruskal-Wallis rank sum test (non-normal distribution) for continuous variables and χ^2 tests for categorical data (Table 1). Next, univariate logistic regression (Table 2) and multivariate logistic regression models (Table 3) were used to examine whether intraoperative cryoprecipitate transfusion and other covariates had an independent effect on ARF following OLT separately. Then, Pearson's test and two-way ANOVA analysis were performed to discover the correlation between blood loss, Child-Pugh grade and cryoprecipitate transfusion (Figs. 1, 2). The χ^2 test was used to analyze the distribution of ARF in patients with and without cryoprecipitate transfusion. Then we explored the relationship between intraoperative cryoprecipitate transfusion and ARF following OLT by the smoothing plot, with an adjustment for potential confounders (Fig. 3). We further applied a two-piecewise linear regression model to examine the threshold effect of the cryoprecipitate transfusion

Table 2 Effects of risk factors on acute renal failure following OLT by univariate analysis

Variables	Total	Odds ratio (95 % CI)	*p* value
Etiology, *n* (%)			
Others	12 (3.1 %)	0.74 (0.093, 6.0)	0.780
Fulminant hepatic failure	30 (7.7)	0.28 (0.037, 2.1)	0.221
Carcinoma	81 (20.8)	1.4 (0.69, 2.9)	0.341
Cirrhosis	266 (68.4)	1	
ABO blood group, *n* (%)			
Compatible	334 (85.9)	0.37 (0.18, 0.77)	0.008*
Incompatibility	55 (14.1)	1	
Child-Pugh grade, *n* (%)			
Grade C	302 (77.6)	0.94 (0.45, 2.0)	0.882
Grade A/B	87 (22.4)	1	
Blood loss, mean (SD), 500 ml	6.9 (4.8)	1.1 (1.0, 1.1)	0.008*
Transfusion of blood products			
Whole blood, mean (SD), U	1.6 (3.7)	1.0 (0.97, 1.1)	0.277
Red blood cells, mean (SD), U	9.9 (7.1)	1.0 (0.98, 1.1)	0.384
Fresh frozen plasma, mean (SD), U	1.7 (4.0)	0.99 (0.9, 1.1)	0.804
Platelet, mean (SD), U	0.6 (1.0)	0.92 (0.65, 1.3)	0.628
Cryoprecipitate, mean (SD), U	5.2 (7.9)	1.1 (1.0, 1,1)	0.002*
Cell saver, mean (SD), ml	554 (1,283)	1.0 (1.0, 1.0)	0.561
Immunosuppressive protocol, *n* (%)			
Including cyclosporine A	107 (27.5)	1.0 (0.51, 2.0)	0.950
Including FK506	273 (70.2)	1	
Steroid, *n* (%)			
Used after OLT	337 (86.6)	3.5 (0.81, 14.8)	0.093
Not used after OLT	52 (13.4)	1	
Infections, *n* (%)			
Occurred before ARF	55 (14.1)	3.1 (1.5, 6.5)	0.002*
Did not occur or occurred after ARF	334 (85.9)	1	

Intraoperative cryoprecipitate transfusion, ABO blood group compatibility, blood loss and infections occurring before ARF might be possible risk factors for ARF following OLT

* p <0. 05 indicates a crude association between variables and ARF following OLT

on ARF according to the smoothing plot (Table 4). The threshold level of cryoprecipitate transfusion at which the relationship between ARF and the cryoprecipitate transfusion level began to change and became notable was determined using a trial method. The trial inflection point was moved along a pre-defined interval and detected the inflection point that gave the maximum model likelihood.

We ruled out ARF patients and then compared the Scr level at days 1, 3, 5 and 7 after the operation between the groups with and without cryoprecipitate transfusion by Kruskal-Wallis rank sum test separately (Fig. 4). The causes of death within the first year after liver transplantation between the exposed and non-exposed patients were also compared separately by univariate logistic regression (Table 5). All data were double entered and then exported to tab-delimited text files. All analyses were performed with R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Among the 389 patients included in the study, 157 (40.4 %) underwent cryoprecipitate transfusion during OLT, with a mean volume of 12.8 U per case. The demographic and clinical characteristics of the cases including etiology, surgical factors and intraoperative transfusion of blood products are summarized in Table 1. Cirrhotic patients were found more frequently in the cryoprecipitate transfusion group than in those who did not receive cryoprecipitate transfusion (73.2 vs. 65.1 %; $p = 0.002$). In addition, Child-Pugh grade C was also more common in the cryoprecipitate transfusion group (163/232 vs. 139/157; $p < 0.001$). Apart from these two factors, there was no noticeable difference in the basic characteristics between the two groups. Since we ruled out patients with pre-transplantation renal dysfunction, the Scr level of all transplant recipients was within the normal range before OLT in the analysis, and there was no significant difference

Table 3 Multivariate logistic regression model for risk factors associated with ARF following OLT

Variables in model	Odds ratio[a] (95 % CI)	*p* value
Cryoprecipitate, U	1.1 (1.0, 1.1)	0.002
ABO blood group compatible	0.33 (0.15, 0.73)	0.006
Infections before ARF	4.0 (1.8, 8.9)	<0.001
Blood loss, 500 ml	1.1 (1.0, 1.1)	0.018

[a] Odds ratios were derived from multivariate logistic regression analysis. These factors were adjusted in the multivariate regression analysis: age, etiology, Child-Pugh grade, ABO blood group, blood loss, infections, cryoprecipitate and steroid

Cryoprecipitate transfusion, ABO blood group incompatible, infections before ARF and blood loss were the independent risk factors associated with ARF following OLT

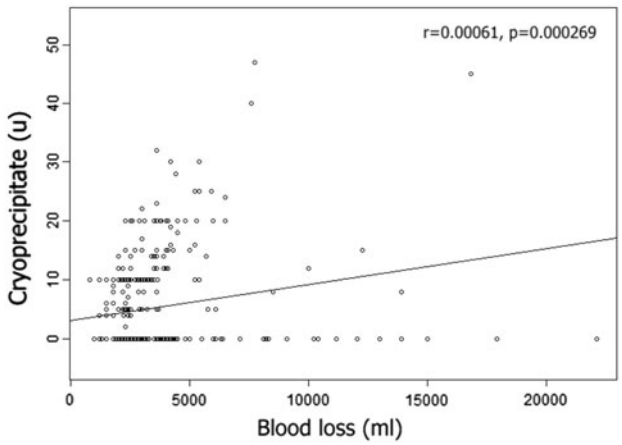

Fig. 1 Correlation between cryoprecipitate transfusion and blood loss by Pearson's test. Cryoprecipitate transfusion showed slightly positive correlation with blood loss ($r = 0.00061$, $p < 0.001$)

between the two groups (83.7 vs. 82.5; $p = 0.273$). Moreover, as the coagulation status during surgery changed constantly and the criteria for using fresh frozen plasma or cryoprecipitate were not the same, many patients received fresh frozen plasma transfusion in addition to cryoprecipitate throughout the surgical procedure. The dose of fresh frozen plasma in the cryoprecipitate transfusion group was also not significantly different from that in the group without cryoprecipitate transfusion (1.5 vs. 2.1; $p = 0.667$).

A total of 43 patients (11.1 %) developed ARF following OLT in this study. The univariate regression analysis showed that intraoperative cryoprecipitate transfusion was significantly correlated with ARF (OR 1.1, 95 % CI 1.0–1.1, $p = 0.002$). In addition, ABO blood group compatibility (OR 0.37, 95 % CI 0.18–0.77, $p = 0.008$), intraoperative blood loss (OR 1.1, 95 % CI 1.0–1.1, $p = 0.008$) and postoperative infections (OR 3.1, 95 % CI 1.5–6.5, $p = 0.002$) might also be associated with ARF following OLT (Table 2). After multivariable risk

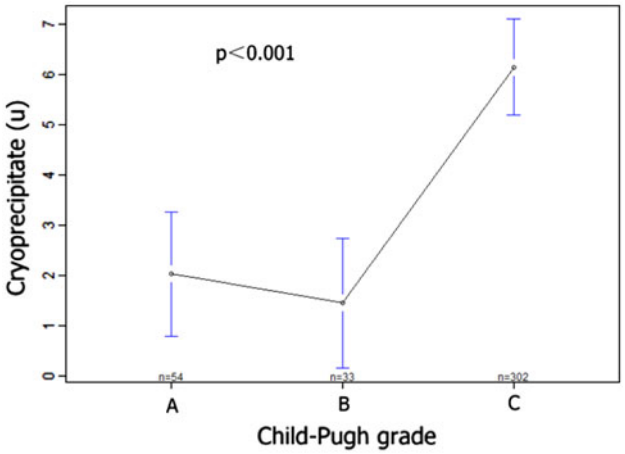

Fig. 2 Correlation between cryoprecipitate transfusion and Child-Pugh grade by two-way ANOVA analysis. There was an obvious interaction between Child-Pugh grade and cryoprecipitate transfusion ($p < 0.001$). The effect on cryoprecipitate transfusion from Child-Pugh grades A and B was not significantly different ($p = 0.938$), but the effect of Child-Pugh grade C was markedly different from that of Child-Pugh A\B ($p = 0.001$, $p = 0.003$, separately)

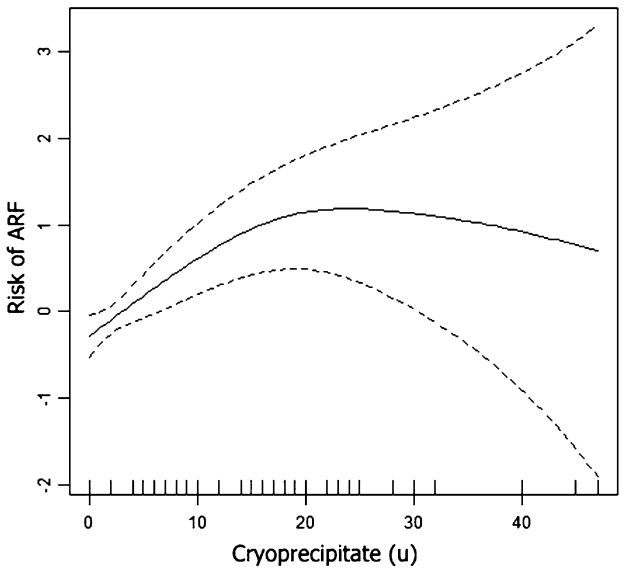

Fig. 3 The relationship between cryoprecipitate transfusion volume and the risk of ARF following liver transplantation. A nonlinear relationship between the cryoprecipitate transfusion volume and risk of ARF was observed after adjusting for age, etiology, ABO blood group, Child-Pugh grade, intraoperative blood loss and postoperative infections

adjustment for potential confounding factors (Table 3), cryoprecipitate transfusion (OR 1.1, 95 % CI 1.0–1.1, $p = 0.002$), infections before ARF (OR 4.0, 95 % CI 1.8–8.9, $p < 0.001$) and blood loss (OR 1.1, 95 % CI 1.0–1.1, $p = 0.018$) were still positively associated with ARF following OLT. Meanwhile, ABO blood group

Table 4 Threshold effect analysis of cryoprecipitate transfusion on ARF using piecewise linear regression

Inflection point of cryoprecipitate transfusion (U)	Odds ratio[a] (95 % CI)	*p* value
<16	1.1 (1.1, 1.2)	<0.001
≥16	0.95 (0.85, 1.1)	0.319

A 16-U threshold for the cryoprecipitate transfusion volume existed for risk of ARF

[a] Adjusted: age, etiology, Child-Pugh grade, blood loss, ABO blood group and infections

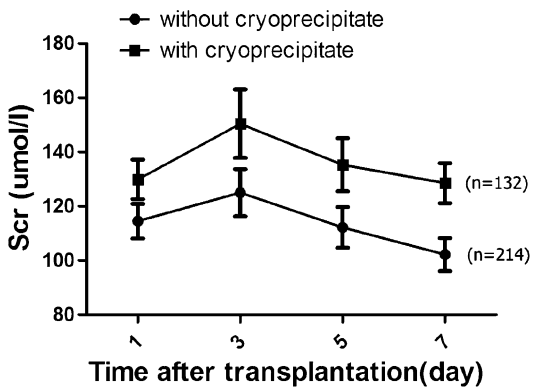

Fig. 4 Mean Scr levels over time. The Scr level reached a peak at postoperative day 3 and then began to decline gradually. After ruling out all of the ARF patients, the level of Scr in the group of patients with cryoprecipitate transfusion ($n = 132$) at day 1, 3, 5 and 7 was significantly higher than in patients without cryoprecipitate transfusion ($n = 214$) separately ($p < 0.01$)

compatibility could significantly reduce the risk of ARF (OR 0.33, 95 % CI 0.15–0.73, $p = 0.006$). Furthermore, we found that cryoprecipitate transfusion was obviously correlated with the Child-Pugh grade ($p < 0.001$), but slightly positively correlated with blood loss ($r = 0.00061$) (Figs. 1, 2).

Twenty-five patients developed ARF in the cryoprecipitate transfusion group, and 18 patients developed ARF in the no-cryoprecipitate transfusion group. The distribution of ARF in patients with cryoprecipitate transfusion was significantly higher than in patients without cryoprecipitate transfusion (15.9 vs. 7.8 %, $p = 0.012$). After adjusting for these possible factors related to ARF, including age, etiology, ABO blood group, Child-Pugh grade, intraoperative blood loss and postoperative infections, a nonlinear relationship between cryoprecipitate transfusion and ARF was observed (Fig. 3). The risk of ARF increased with the cryoprecipitate transfusion level up to the turning point (16 U) (OR 1.1, 95 % CI 1.1–1.2; $p < 0.001$). When the cryoprecipitate level was ≥16 U, the level of cryoprecipitate transfusion was not associated with the risk of ARF (OR 0.95, 95 % CI 0.85–1.1; $p = 0.319$) (Table 4).

Although there was no significant difference in the Scr level between the two groups before OLT, this situation changed obviously after transplantation. After excluding all ARF patients from the analysis, in the cryoprecipitate transfusion group, the level of Scr at postoperative day 1, 3, 5 and 7 was significantly higher than in patients without cryoprecipitate transfusion group, respectively ($p < 0.01$) (Fig. 4).

Table 5 Comparison of causes of death 1 year after liver transplantation in patients with and without cryoprecipitate transfusion

Causes of death, *n* (%)	Without cryoprecipitate transfusion ($n = 232$)	With cryoprecipitate transfusion ($n = 157$)	Odds ratio (95 % CI)	*p* value
Liver related	12 (5.0)	10 (6.4)	1.2 (0.53, 3.0)	0.617
ARF related	4 (1.7)	10 (6.4)	3.9 (1.2, 12.6)	0.024*
Myocardial infarction	2 (0.9)	2 (1.3)	1.5 (0.21, 10.6)	0.695
Hypovolemic shock	2 (0.9)	4 (2.5)	3.0 (0.54, 16.6)	0.207
Acute lung injury/ARDS	3 (1.3)	1 (0.6)	0.49 (0.05, 4.7)	0.538
Pulmonary embolism	2 (0.9)	2 (1.3)	1.5 (0.21, 10.6)	0.695
Sepsis or MOF	7 (3.0)	5 (3.2)	1.1 (0.33, 3.4)	0.925
Malignancy	0 (0.0)	1 (0.6)		
Unknown	1 (0.4)	2 (1.3)	3.0 (0.27, 33.2)	0.374
Total	33 (14.2)	37 (22.9)	1.8 (1.1, 3.0)	0.029*

There was a significant difference in ARF-related deaths between the two groups. More deaths within the first year after OLT were observed in the patients with cryoprecipitate transfusion

ARDS acute respiratory distress syndrome

* *p* value <0.05 indicates a significant difference between the two groups

More deaths within the first year after OLT were also observed in patients with cryoprecipitate transfusion than in those without cryoprecipitate transfusion (22.9 vs. 14.2 %, $p = 0.029$). There was a significant difference in ARF-related deaths between the two groups (6.4 vs. 1.7 %, $p = 0.024$), but other significant differences in causes of death were not found (Table 5).

Discussion

To date, studies have investigated several risk factors for developing postoperative ARF. The impact of postoperative infection on patient's renal function has been widely accepted [5, 17]. From the perspective of pathophysiology, serious infection can result in systemic arterial vasodilation and intra-renal vasoconstriction, and it is also conducive to other kidney injuries [18, 19]. In addition, blood loss during the surgical procedure can lead to hemodynamic instability and hypotension after graft reperfusion [20, 21], so blood loss was considered another risk factor related to ARF [5]. As the current analysis found, these two factors were also associated with the occurrence of postoperative ARF. Preoperative renal dysfunction has been evaluated as a potential strong predictor of postoperative ARF [22, 23]. To minimize the influence on the results, we excluded patients with preoperative Scr levels greater than 133 mmol/l from the analysis. Moreover, the total volume of cryoprecipitate transfusion was affected by the severity of end-stage liver disease and the etiology, so Child-Pugh grade and etiology were also adjusted in the analysis. After adjusting for these potential confounders, we still found a significant correlation between intraoperative cryoprecipitate transfusion and the occurrence of ARF following OLT. Because the definition of ARF in the current study was stringent, it might also have skewed the results because of the relatively small group of patients examined. We also compared the postoperative Scr level between the groups with and without cryoprecipitate transfusion after ruling out all patients with ARF. The results indicated that the Scr level in patients receiving cryoprecipitate transfusion was significantly higher than in those who did not receive it. This led to the same conclusion, linking cryoprecipitate to renal toxicity in this setting.

Cryoprecipitate was first reported by Pool et al. [24]. Its major components include fibrinogen, factor VIII/von Willebrand factor molecular complex (FVIII/vWF), factor XIII, fibronectin, platelet microparticles and immunoglobulin [25]. Patients with end-stage liver disease are characterized by reduced levels of coagulation factors, easily leading to coagulation disorders [26]. It is commonly thought that cryoprecipitate transfusion during OLT can effectively provide fibrinogen and other coagulation factors to improve the function of blood coagulation and control intraoperative bleeding. This procedure is therefore widely applied in OLT centers. In our center, 40.4 % of patients had been transfused with cryoprecipitate at a mean volume of 12.8 U. Unfortunately, our study indicated that cryoprecipitate transfusion during OLT is associated with the occurrence of postoperative ARF. More importantly, the data further revealed that the risk of ARF increased with the increase of cryoprecipitate transfusion until the critical point (16 U) had been reached. This also demonstrated that a more accurate criterion is needed to guide the use of cryoprecipitate so as to prevent the occurrence of ARF.

Currently, guidelines for the use of cryoprecipitate recommend a fibrinogen cutoff value of 1.0 g/l [27–29]. However, there is no evidence base for this recommendation [30], and how to properly use cryoprecipitate transfusion in OLT for patients with end-stage liver disease remains controversial. Since there are some difficulties in real-time monitoring of the fibrinogen concentration during liver transplantation, blood test results play a lesser role in guiding the use of cryoprecipitate because of their time lag. Usually we can only determine the turnaround time for stopping the transfusion according to the surgeon's experience and the results of other tests, such as thrombelastography. Since the blood coagulation system is maintained in a state of low-level balance in patients with end-stage liver disease [31], this protocol to guide cryoprecipitate use may easily cause a coagulation imbalance. From a physiopathological point of view, microthrombosis formation caused by excessive blood clotting and hemodynamic changes caused by bleeding may both contribute to the occurrence of ARF.

Immune factors might also play an important role in the increased risk of ARF with cryoprecipitate transfusion. Cryoprecipitate contains high concentrations of platelet microparticles together with low concentrations of immunoglobulins IgG and IgM [30, 32], platelet microparticles that are strongly immunogenic [33]. In our experience, transfusion of these immunogens might be involved in the occurrence of ARF following OLT. In addition, when large doses of cryoprecipitate transfusion are required, a patient might receive cryoprecipitate made from more than one blood donor's plasma. This would increase the frequency of leukocyte system alloimmunity and might also be involved in the occurrence of ARF.

In the present study, compared with patients without cryoprecipitate transfusion, patients receiving cryoprecipitate transfusion showed significantly higher 1-year mortality after the operation. The main reason for this difference was ARF-related deaths. Renal replacement therapy (RRT) is always the only choice for the clinician if conservative treatment is ineffective. ARF patients died not only from renal failure but sometimes also from co-

morbidities induced by RRT such as sepsis and coagulopathy. It is known that the incidence of sepsis was significantly higher in OLT patients undergoing hemodialysis than in patients without hemodialysis [34]. Previous studies also have shown that ARF significantly increases mortality in OLT recipients [35, 36]. These conclusions were consistent with our findings.

Advances in immunosuppressive agents mean that ABO incompatibility is no longer an absolute contraindication for OLT [37]. Early retrospective studies have reported that the occurrence of postoperative acute rejection, biliary tract complications and hepatic artery embolism is also significantly higher in ABO blood group-incompatible cases than in ABO blood group-compatible cases [38–40]. Interestingly, our analysis indicated that ABO blood group incompatibility may be associated with an increased risk of ARF following OLT. Because of the gradual reduction in the number of OLTs in ABO blood group-incompatible cases, multicenter and larger-scale analyses are required to support and validate this conclusion.

Although our analysis suggested that cryoprecipitate transfusion during OLT is associated with postoperative ARF, this research has several limitations that should be noted. First, the best definition of pre-transplantation renal dysfunction in the setting of liver cirrhosis is controversial [41, 42]; we choose Scr greater than 133 mmol/l as the cutoff value in the study because it has been selected in several consensus conferences [43, 44]. In addition, due to the limitations of a retrospective study, possible selection bias and the sample size from a single center might have been presented in this research.

In some countries, cryoprecipitate transfusion is replaced by a virus-inactivated fibrinogen concentrate, which is thought to reduce immune-related complications [45, 46]. However, cryoprecipitate is easy to obtain. Moreover, rational use of cryoprecipitate in OLT can effectively reduce blood loss and promote wound healing, so it is still being utilized in developing countries. However, due to the specificity of the blood coagulation system in patients with end-stage liver disease, how to use it properly in OLT remains controversial. Our study has shown that cryoprecipitate transfusion during OLT is associated with postoperative ARF and might increase mortality within the first year. Cryoprecipitate transfusion during OLT should be performed cautiously until more convincing results from evidence-based medicine are available.

Acknowledgements We gratefully acknowledge Prof. Changzhong Chen from Harvard Medical School for the assistance with statistics. This work was supported by a grant from the National Natural Science Foundation of China (81170445).

Conflict of interest Shuang Liu, Xiaoliang Wang, Yuanshan Lu, Tao Li, Zijun Gong, Tao Sheng, Bin Hu, Zhihai Peng and Xing Sun declare that they have no conflicts of interest.

Compliance with Ethics Requirements All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Due to the retrospective nature of the study, this article did not involve any studies with human or animal subjects. National legislation and the ethics committee of Shanghai First People's Hospital approved this retrospective study.

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