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Effect of RhD and RhE sample phenotypic blood transfusion on the prognosis of hepatocellular carcinoma

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Abstract

Objective: This study aimed to analyze the therapeutic effects and clinical outcomes of HCC patients, who received both RhD and RhE same phenotypic blood transfusion during perioperative period.

Methods: Microcolumn gel technology (MGT) was used to detect Rh blood group phenotyping in 98 HCC patients. Patients received RhD and RhE same phenotypic transfusion were defined experimental group, and those received only RhD same phenotypic but RhE different phenotypic transfusion were included in control group. Hemoglobin (Hb) and hematocrit (HCT) before and after perioperative transfusion were analyzed. The occurrence of adverse transfusion reactions were observed. Survival analysis was performed using the Kaplan–Meier method.

Results: After the transfusion treatment, the Hb (118.9 ± 34.8 g/L vs 99.6 ± 26.9 g/L) and HCT [(34.0 ± 7.6)% vs (29.9 ± 8.8)%] of experimental group and the Hb (104.3 ± 36.2 g/L vs 94.8 ± 25.0 g/L) of control group were significantly higher than those before blood transfusion, respectively (all $P < .05$). In addition, Hb and HCT in experimental group were significantly higher than those in the control group after transfusion ($P < .05$). For the adverse blood transfusion reactions, the incidence of backache was reduced in the patients received Rh same phenotypic transfusion compared with those in control group (1.9% vs 15.2%, $P = .024$). The overall survival of patients in experimental group was better than that in control group (log-rank $P = .036$).

Conclusion: Our study indicated that both RhD and RhE same phenotypic transfusion significantly increased Hb and HCT and reduced backache incidence than RhE different phenotypic transfusion in HCC patients. The overall survival of patients was improved by RhD and RhE same phenotypic transfusion.

Abbreviations: Hb = hemoglobin, HBV = hepatitis B, HCC = hepatocellular carcinoma, HCT = hematocrit, HCV = hepatitis C, MET = microcolumn gel technology, MGT = microcolumn gel technique.

Keywords: blood transfusion, different phonotype, hepatocellular carcinoma, isophenotype, Rh

1. Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor and is one of the leading causes of cancer-related death worldwide.[1] Additionally, HCC is the major histological type of liver cancer and accounts for approximately 80% of the total liver cancer burden worldwide.[2] It is estimated that 80%–90% of HCC cases are caused by chronic hepatitis B (HBV) or hepatitis C (HCV) infection, and chronic HBV/HCV infection, alcoholic liver disease, metabolic syndrome and some rare autoimmune or genetic diseases may also be risk factors for HCC.[3] The hepatectomy is still the most effective treatments for some patients with early HCC.[4] Therefore, increasing awareness of optimal surgery and perioperative management can reduce perioperative morbidity and mortality in patients with hepatocellular carcinoma undergoing hepatectomy.[5] Modified surgical techniques have been found to reduce bleeding during hepatectomy, with transfusion rates falling from 62% to 22% over the past 20 years.[6] Prior to surgery, many patients have a weakened physical condition, and the added blood loss during surgery necessitates perioperative blood transfusion for some patients to insure surgery success.[7]

Previous studies indicated that perioperative transfusion increased hemoglobin (Hb) concentration and improved therapeutic efficiency in HCC patients.[8] Rh blood group system is the most complex of the erythrocyte blood group systems, second only to the ABO blood group system in clinical significance.[9] In the Rh blood group system, the sequence of antigen

A signed written informed consent was obtained from each patient.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The experimental procedures were all in accordance with the guideline of the Ethics Committee of Zibo Central Hospital and has approved by the Ethics Committee of Zibo Central Hospital. This study complies with the Declaration of Helsinki.

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intensity is D, E, c, C, e. Currently, only the detection of RhD antigen is listed as a routine detection item before clinical transfusion treatment, which reduces the production of immune antibodies in RhD antigen-negative patients due to input of RhD antigen-positive blood.[10] Thus, the incidence of immune blood transfusion reactions induced by RhD antigen were decreased.[11] RhE antigen is the Rh phenotype second only to RhD antigen, and is one of the important causes of adverse transfusion outcomes such as immune transfusion reaction and hemolytic disease of newborns.[12]

In view of the large number of diseases requiring blood transfusion treatment in clinic, the adverse transfusion outcome caused by transfusion with different Rh phenotypes will certainly affect the treatment and recovery of diseases. Therefore, the purpose this study was to analyze the therapeutic effects and clinical outcomes of HCC patients who received RhD and RhE same phenotypic transfusion during perioperative period, and to explore the necessary of routine examination of Rh blood group phenotype in clinical transfusion.

2. Materials and methods

2.1. Study subjects

98 HCC patients who received allogeneic blood transfusion in Zibo Central Hospital from 2011 to 2015 were analyzed. All patients were identified as HCC patients by histopathology, including 59 males and 39 females, with an average age of 64.3 ± 12.2 years. All patients underwent RhD and RhE blood group identification before blood transfusion, and were divided into experimental group and control group according to the blood group difference of blood transfusion products for blood therapy. Among them, those whose blood transfusion products were consistent with ABO blood group, RhD blood group and RhE blood group of patients were experimental group (n = 52); those whose blood transfusion products were consistent with ABO blood group and RhD blood group of patients, but inconsistent with RhE blood group were defined as the control group (n = 46). Exclusion criteria: patients with severe autoimmune diseases; patients with severe infectious diseases; patients with other malignant tumors; patients during pregnancy or lactation; patients with poor compliance; patients with incomplete clinical general information. Each patients have signed informed consent and this study was approved by the Ethics Committee of Zibo Central Hospital.

2.2. Determination of Rh phenotype

Rh blood group phenotyping using microcolumn gel technique (MGT). The Rh blood group typing microcolumn gel card was taken and put into a special centrifuge. After centrifugation, the tin paper film was torn open and placed upright for future use. Then 50 microliters of 1% erythrocyte suspension were added into the D, E, e and Ctrl micropores. Finally, the test card was stationary for 3 minutes to fully react and centrifuged in a special centrifuge to observe the results. If the erythrocytes agglutinate, it indicates the formation of large particles that cannot pass through the microcolumn gel pore size, and the aggregated erythrocytes are blocked in the upper part of the microcolumn gel tube, which is a positive reaction. If there is no agglutination of red blood cells, the red blood cells deposit at the bottom of the microcolumn gel tube, which is a negative reaction.

2.3. Data collection

Automated hematology analyzer (PENTRA120; Horiba ABX, Montpellier, France) was used to analyze hemoglobin (Hb) and hematocrit (HCT) before and 2 days after receiving perioperative transfusion.

In addition, the occurrence of adverse transfusion reactions in patients after transfusion treatment was closely observed, including: fever: body temperature is higher than that before blood transfusion > 1°C, which may be accompanied by aversive cold, chills, etc; allergy: local or systemic rash occurs after blood transfusion, which can be resolved by anti-allergic treatment; other systemic symptoms: anaphylactic shock, low back pain, etc. The adverse reactions of the disease were observed to analyze whether they were related to blood transfusion.

2.4. Follow-up survey

Patients were followed up for 5 years, and survival was recorded for survival analysis, and those who died of non-neoplastic disease-related causes were excluded.

2.5. Statistical analysis

The comparison between groups was performed using T-test, chi-square test and Fisher exact test. Survival analysis was performed using the Kaplan–Meier method. Log-rank test was used to compare survival curve distribution differences.

3. Results

3.1. Baseline characteristics and Rh phenotype distribution of HCC patients

From the data of Table 1, no significant differences were found between control group and experimental group in terms of age, tumor size, gender, Cirrhosis, TNM stage, RhD and RhE phenotype (all $P > .05$).

3.2. Hb and HCT changes before and after blood transfusion in HCC patients

As shown in Table 2, there were no statistically significant differences in Hb and HCT between control group and experimental group before transfusion (all $P > .05$). In addition, the Hb (118.9 ± 34.8 g/L vs 99.6 ± 26.9 g/L) and HCT

Table 1

Baseline characteristics and Rh phenotype distribution of HCC patients.

Features	Total (n = 98)	Control group (n = 46)	Experimental group (n = 52)	*P* value
Age (yr)	64.3 ± 12.2	64.8 ± 10.6	63.9 ± 13.6	.718
Tumor size (cm)	1.55 ± 0.41	1.57 ± 0.47	1.54 ± 0.35	.796
Gender				.899
Female	59	28	31	
Male	39	18	21	
Cirrhosis				.809
No	35	17	18	
Yes	63	29	34	
TNM stage				.658
I–II	64	29	35	
III–IV	34	17	17	
RhD				.344
Negative	1	0	1	
Positive	97	46	51	
RhE				.830
Negative	50	24	26	
Positive	48	22	26	

[(34.0 ± 7.6)% vs (29.9 ± 8.8)%] of experimental group after blood transfusion were significantly higher than those before blood transfusion (all $P < .05$). The Hb of control group were significantly higher than those before blood transfusion (104.3 ± 36.2 g/L vs 94.8 ± 25.0 g/L, $P < .05$), however, no significant change was found in HCT before and after blood transfusion [(30.8 ± 8.5)% vs (29.7 ± 8.6)%, $P > .05$]. Moreover, after blood transfusion, Hb and HCT in the experimental group were significantly higher than those in the control group (all $P < .05$).

Table 2

Hb and HCT changes before and after blood transfusion in HCC patients.

	Control group (n = 46)		Experimental group (n = 52)	
Indicators	**Before**	**After**	**Before**	**After**
Hb (g/L)	94.8 ± 25.0	104.3 ± 36.2a	99.6 ± 26.9[ns]	118.9 ± 34.8a[b]
HCT (%)	29.7 ± 8.6	30.8 ± 8.5	29.9 ± 8.8[ns]	34.0 ± 7.6a[b]

Hb, hemoglobin; HCT, hematocrit; [ns], no significant differences compared to the control group before blood transfusion.

[a] $P < .05$, compared to the data before blood transfusion in each group.

[b] $P < .05$, compared to the data in control group after blood transfusion.

Table 3

Adverse blood transfusion reaction after blood transfusion.

Reactions	Control group (n = 46)	Experimental group (n = 52)	*P* value
Fever (%)	5 (10.9%)	2 (3.8%)	.248
Allergy (%)	1 (2.2%)	0 (0)	.469
Backache (%)	7 (15.2%)	1 (1.9%)	.024

3.3. Adverse blood transfusion reaction after blood transfusion

No significant differences in the fever and allergy were found between the control group and experimental group (all $P > .05$), while, the HCC patients in experimental group had less backache cases than the HCC patients in control group (1.9% vs 15.2%, $P = .024$) (Table 3).

3.4. Evaluation of survival outcomes in HCC patients (Fig. 1)

The 5-year follow-up records showed that there were 63 deaths in 98 HCC patients, including 34 deaths in the control group with a median survival of 35 months, and 29 deaths in the experimental group with a median survival of 47 months. We plotted the Kaplan–Meier survival curves (Fig. 1) and the results indicated that patients in experimental group had significantly better overall survival than the patients in control group (log-rank $P = .036$).

4. Discussion

Considering the importance of blood transfusion for the prognosis of patients with HCC, this study collected and analyzed the data from HCC patients who received blood transfusion with RhE same phenotype. The results of this study showed that HCC patients receiving ABO, RhD and RhE same phenotypic transfusion (experimental group) had significantly increased Hb and HCT than those receiving ABO and RhD same phenotypic but RhE different phenotypic transfusion (control group). More cases with backache were found in the control group compared to the experimental group. In addition, the 5-year follow up survival revealed that RhE same phenotypic transfusion improved

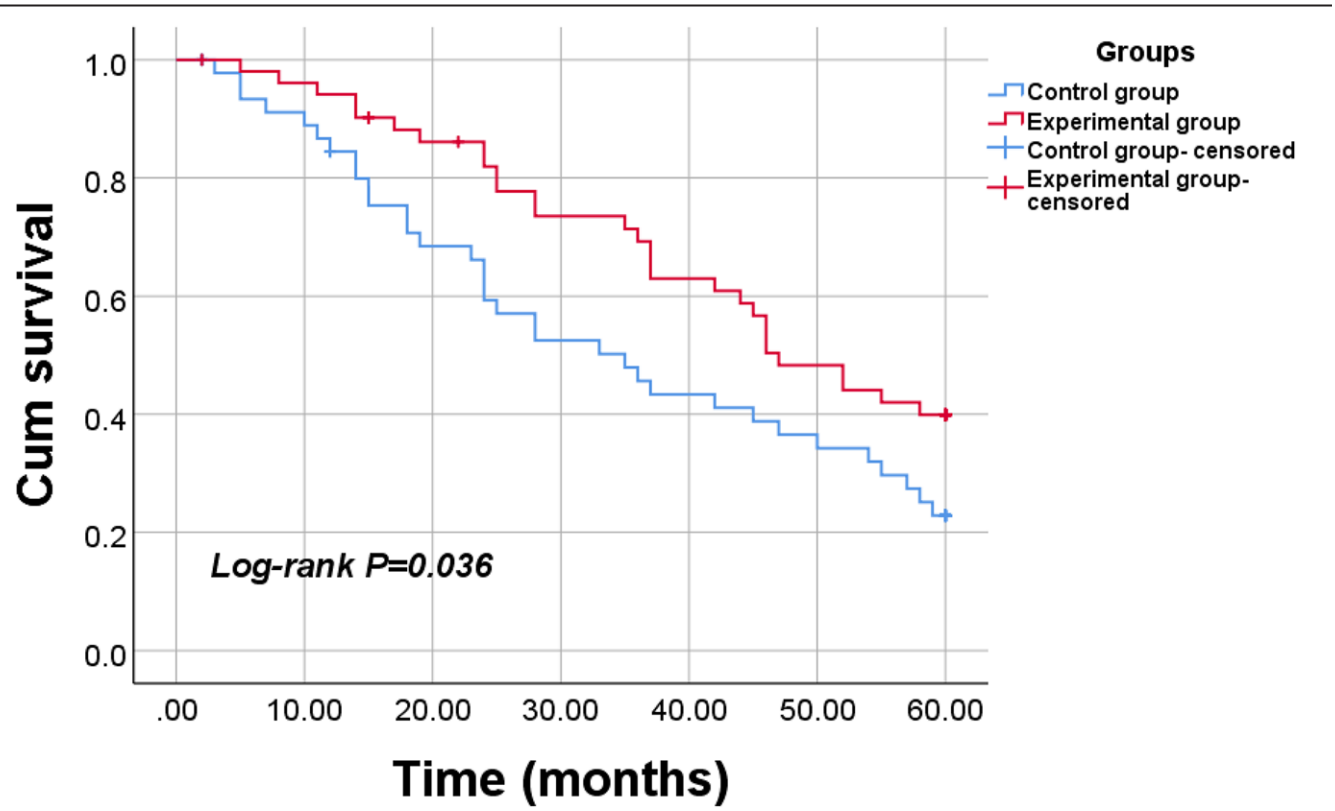

Figure 1. Survival curves of HCC patients receiving different blood transfusion methods. Experimental group: patients receiving ABO, RhD, and RhE same phenotypic blood transfusion; control group: patients receiving ABO and RhD same phenotypic blood transfusion.

the overall survival than RhE different phenotypic transfusion in patients with HCC.

At present, glucan gel immunoassay was widely used in the detection of Rh blood group antigen, which effectively makes up for the deficiency caused by only RhD antigen detection in the past.[13,14] Therefore, it is very important to strengthen the determination of RhE antigen in blood donors, and try to achieve same phenotypic blood transfusion in clinical practices, which will improve the safety of blood transfusion.[15,16] The body will produce immune antibodies when receiving RhE antigen-negative patients receive RhE antigen-positive blood products, especially red blood cells.[17] After receiving RhE antigen-positive blood products, the heterologous red blood cells well be destroyed by the induced immune responses, inducing noneffective blood transfusion and even hemolytic reaction.[12] Studies have reported that the negative rate of RhE antigen reached closely 50% in human, indicating the importance of RhE antigen detection when matching the blood of patients.[12] However, because of the weak immunogenicity of RhE than that of RhD, the detection of RhE antigen has not be highlighted in clinical practices. RhE antigen-negative is still the cause of hemolytic transfusion reaction and hemolytic diseases of newborns, and leads to difficulties in blood type identification and cross matching.[18] Thus, attention should be paid to RhE antigen detection.

For blood cross matching test, in addition to saline medium method, coagglutamine method should also been applied. If conditions allow, enzyme method, anti-human globulin test and gel method are also needed.[19–21] In the present study, there were 52 patients received ABO, RhD and RhE same phenotypic blood transfusion, which were included experimental group, and 46 cases received blood transfusion only considering ABO and RhD phenotype, but RhE phenotype was different, which were included in control group. By detecting the Hb and HCT values of patients, it was found that only Hb concentration was increased after blood transfusion in control group, while both Hb and HCT were significantly increased after transfusion in experimental group, indicating that both RhD and RhE same phenotypic transfusion improved the transfusion efficiency significantly. Regarding adverse reactions led by blood transfusion, the incidence of backache, which is one of the major adverse reactions after transfusion,[22,23] was significantly reduced in patients received RhE same phenotypic transfusion. Importantly, this study followed up the survival information of patients in 5 years after treatment, and found that HCC patients, who received RhE same phenotypic transfusion, had better survival outcomes than those in control group. Therefore, the detection of ABO, RhD, and RhE antigen when blood transfusion is important, which may assist with the improvement of overall survival in patients with HCC.

In conclusion, RhD and RhE same phenotypic blood transfusion increased Hb and HCT and reduced backache incidence after transfusion in HCC patients, and the patients with this blood transfusion method had better survival prognosis than those receiving transfusion only considering RhD antigen condition. Therefore, we suggest that for blood transfusion, especially for patients with blood transfusion history and pregnancy history, blood donor institutions should be advised to conduct RhE blood type identification and matching, so as to better improve the effectiveness, safety and prognosis of blood transfusion.

Author contributions

Conceptualization: Feng Guo.
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Writing – original draft: Ling Zhang, Feng Guo.
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