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Effect of Rapid Intravenous Albumin Infusion in Neonate with Capillary Leak Syndrome

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1. Abstract

1.1. Background: This study was intended to investigate the effect of different infusion rates of human serum albumin on 30-day survival of neonatal capillary leak syndrome.

1.2. Methods: We retrospectively retrieved data from electronic medical records at our children's hospital and we included all the term new-borns admitted between October 2017 to October 2020 with capillary leak syndrome. The patients were divided into routine infusion group and rapid infusion group according to albumin infusion rate. The primary outcome of 28-day survival and Secondary Outcomes of relative clinical data between the two groups were compared and analysed.

1.3. Results: A total of 64 children with CLS were included. They were grouped as control and (n = 42), rapid infusion group (22). There was no significant difference in rate of renal injury, the length of hospital stays and duration of mechanical ventilation and the 28-day survival rate between the two groups. After rapid infusion of albumin, the systolic blood pressure, 24-hour urine volume per kilogram of body weight and the level of urine volume were significantly increased compared with those of the routine infusion group, and the degree of weight gain was less compared with that of the routine infusion group; secondly, the ALB level was effectively increased and the CLI level was effectively decreased in the rapid infusion group compared with that of routine rate infusion; Logistic regression found that Gestational Week was related with clinical outcome.

1.4. Conclusion: Rapid albumin supplementation may speed up recovery, but the impact on the prognosis is relatively small. and further a prospective multicentre clinical study is needed to carry out.

2. Introduction

Systemic Capillary Leak Syndrome (SCLS) was characterized by stereotypic "attacks" of varying intensity of hypovolemic shock and generalized edema in association with hemoconcentration (as detected by an elevated hematocrit concentration) and hypoalbuminemia, typically occurring in the absence of albuminuria [1-5]. CLS is a devastating condition associated with various diseases, and the most common cause in newborn is sepsis induced by severe infection [6-8].

At present, CLS is becoming more and more common in neonates. Once the onset of CLS occurs in neonates, the condition is severe, the progress is fast, the treatment is contradictory, and the mortality rate is very high. There is a lack of clinical guidelines for the treatment of neonatal CLS.

Implementation of appropriate antimicrobial therapy is the basic treatment of CLS caused by sepsis. Whereas, effective fluid managements, including volume resuscitation and vasoactive drugs for stabilizing blood pressure, fluid-restrictive strategy to prevent fluid overload, and diuretic therapy to remove edema, are essential to improve the success rate of salvage [9-12].

Albumin is the colloid fluid of choice when treating edematous hypovolemic patients, the use of albumin is controversial and there are no data to support different infusion rates during fluid challenges for important outcome [13-14]. So, this study was aim to determine

whether it would result in improved 28-day-day survival in critically ill patients.

3. Methods

With Ethics approval from the Children's hospital of Chongqing medical university's Clinic Institutional Review Board (038/2021), records of all patients seen at children's hospital of Chongqing medical university, from October 1, 2017, to October 1, 2020, with a diagnosis of SCLS. The diagnosis of SCLS was based on unequivocal documentation of recurrent attacks of hypotension, elevated hematocrit concentrations, peripheral edema, and hypoalbuminemia without albuminuria. Patients whose physical signs, symptoms, and laboratory findings could be explained by an alternative diagnosis were excluded if that alternative diagnosis was confirmed with further investigations.

This research complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Parents or guardians gave their written informed consent.

This study was a factorial trial that assessed 2 different infusion speeds to be used. Patients were randomized to receive fluid challenges at 2 different infusion rates: (the rapid rate (2g/kg/h) and the control group (conventional rate 1g/kg/h) and the total albumin infusion is the same as 1.5g*kg [9].

4. Primary Outcome

4.1. The primary outcome was 28-day survival.

Secondary Outcomes

Data collection: General data such as gender, age, gestational age, birth weight, singleton or not, surgical treatment or not, and renal function were collected retrospectively for children who met the inclusion criteria for CLS. Blood pressure, body weight, 24h urine volume, Capillary leak index (CLI: Capillary leak index (CLI) was defined as C-reactive protein (CRP) (milligrams per deciliter) over albumin (grams per liter) ratio, multiplied by 100), plasma Albumin level (ALB), creatinine （6h after infusion, and hospitalization days were recorded 4 hours before and after the infusion of human serum Albumin.

4.2. Statistical Analysis

Continuous data were expressed by mean ± SD, and intergroup differences were determined by one-way analysis of variance (ANOVA) analyses. Categorical data were expressed as frequency distributions and/or percentages, and the $\chi 2$ test was used to determine intergroup differences. Combined with clinical, single factor was screened out. The factors with clinical significance were analyzed by Logistic regression analysis. Two-sided p values <0.05 were considered to indicate statistical significance.

5. Results

Of all patients, 64 cases were analyzed. Patients assigned to the rapid rate received a mean of 2g/kg/h on the first day vs 1g/kg/h (22 cases) for the control group (42cases).

The demographic details on the experiments are shown in Table1-4, there were no Significant difference between the two groups in the gender ratio, age, gestational age, birth weight, rate of singleton, rate of surgical treatment, and the incidence of renal damage before infusion.

Distribution of underlying diseases: 28 cases of respiratory distress syndrome, 33 cases of neonatal sepsis (16 cases were treated by abdominal surgery), 1 case of Rh blood incompatibility hemolysis, and 2 cases of severe asphyxia. There was no statistical difference in the distribution of diseases between the two groups, which was comparable.

Therapeutic effect of human albumin infusion on neonate with CLS

There were significantly increased after albumin infusion in the systolic blood pressure, diastolic blood pressure, weight and the 24-hour urine volume per kilogram of body weight and the level of ALB. while the CLI and creatinine levels were decreased. The difference was statistically significant (tab 3-4 $P<0.05$).

Comparison of therapeutic effects of different infusion rates of human serum albumin in neonate with CLS

All 64 CLS patients received albumin infusion, 22 (34.4%) received rapid human albumin infusion, and 42 (65.6%) received routine albumin infusion. The influence of different infusion rates of human serum albumin on the clinical condition of CLS is shown in Table 5. After rapid albumin infusion, the systolic blood pressure, 24-hour urine volume per kg body weight and the increased level of urine volume were significantly higher than those in the conventional infusion group, and the degree of weight gain was lower than that in the conventional infusion group. Secondly, the level of ALB was significantly increased and the CLI was significantly decreased in the rapid infusion group compare with those of routine rate infusion. However, it can be found that there were no significant differences in creatinine level, length of hospital stays and mechanical ventilation time after infusion between the two groups.

Comparison of clinical outcomes in children with CLS treated with different infusion rates of human albumin

There was no significant difference in 28-day survival rate between the two groups ($P=0.599$). As shown in table 6. By the day 28, 22 of 42 patients (47.6%) in the rapid rate group had died vs 10 of 22 (54.6%) in the control group (adjusted hazard ratio, 1.03; 95% CI, 0.96-1.11). There was no significant interaction between the two groups.

Blood pressure, body weight, 24h urine volume, CLI, CRP, plasma Albumin level (ALB), creatinine before and after albumin infusion, were included in stepwise Logistic regression model. We found that Gestational Week (B= 0.172, SE=0.063, Wald's=7.436,95%CI 1.05-1.345, OR 1.188, P =0.006) was related with clinical outcome.

Table 1: Flow diagram of the patient's selection process

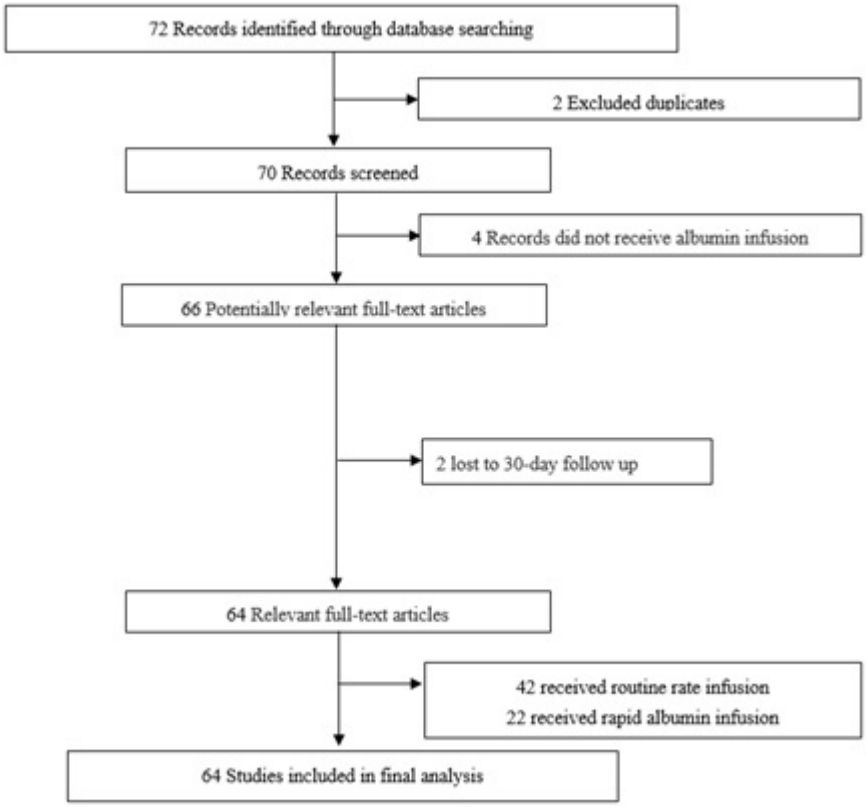

Table 2: baseline characteristics of the included patients

	Control (n=42)	rapid infusion(n=22)	z/t/X^2	P
gender, (n%)	male: 35(83.3%) female: 7 (16.7%)	male: 14(63.6%) female: 8(36.4%)	3.122	0.077
gestation (W), (X±s)	32.85±5.06	34.11±3.71	1.027	0.308
age (day), [M(QL, QU)]	0.63(0.08, 9.13)	0.42(0.06, 1.50)	0.942	0.346
birthweight (g), [M(QL, QU)]	1655(1200, 3100)	2130(1670, 2650)	0.431	0.666
Single/twin, n(%)	single: 29(69.1%) twin: 13(30.9%)	single: 16(72.7%) twin: 6(27.3%)	0.094	0.76
Surgical treatment, n(%)	9/42(21.4%)	7/22(31.8%)	0.831	0.362
Renal dysfunction, n(%)	8/42(19.0%)	6/22(27.3%)	0.572	0.45
underlying disease, n(%)				
neonatal sepsis	21/42(50.0%)	12/22(54.5%)	0.119	0.73
neonatal respiratory distress syndrome	19/42(45.2%)	9/22(40.9%)	0.11	0.74
Severe asphyxia	1/42(2.4%)	1/22(4.5%)	0.223	0.636
Rh incompatible hemolysis	1/42(2.4%)	0/22(0%)	0.532	0.466

P<0.05, there was statistically significant between the two groups.

Table 3: Comparison of clinical data before and after treatment in the routine infusion group (n=42)

	Before infusion	After infusion	z	P
SBP(mmHg), [M(QL, QU)]	58(51, 61)	65(60, 69)	-5.656	<0.001
DBP(mmHg), [M(QL, QU)]	29(24, 31)	33(32, 36)	-5.074	<0.001
24h urine volume (ml/kg), [M(QL, QU)]	52.5(40.1, 71.8)	59.8(50.3, 88.9)	-4.182	<0.001
weight (kg), [M(QL, QU)]	2.2(1.3, 3.1)	2.3(1.4, 3.3)	-5.361	<0.001
ALB(g/L), [M(QL, QU)]	22.4(19.7, 25.9)	25.5(23.3, 28.4)	-5.647	<0.001
CLI, [M(QL, QU)]	46.7(37.8, 101.5)	34.9(28.9, 60.2)	-5.645	<0.001
Creatinine(umol/L), [M(QL, QU)]	59.6(46.4, 80.5)	52.1(39.5, 71.7)	-3.002	0.003

P<0.05, there was statistically significant between the two groups.

Table 4: Comparison of clinical data before and after treatment in the rapid infusion group (n=22)

	Before infusion	After infusion	z	P
SBP(mmHg), [M(QL, QU)]	52(46, 55)	69.5(66, 75)	-4.112	<0.001
DBP(mmHg), [M(QL, QU)]	24.5(20, 26)	34(31, 38)	-4.112	<0.001
24h urine volume (ml/kg), [M(QL, QU)]	46.5(25.6, 69.2)	100.1(58.8, 119.4)	-4.107	<0.001
weight(kg), [M(QL, QU)]	2.4(1.9, 2.7)	2.5(1.9, 2.63)	-1.645	0.01
ALB(g/L), [M(QL, QU)]	24.1(21.2, 25.9)	27.9(25.6, 30.3)	-4.108	<0.001
CLI, [M(QL, QU)]	37.9(31.9, 74.9)	29.7(26.6, 35.4)	-4.107	<0.001
Creatinine (umol/L), [M(QL, QU)]	68.7(60.3, 116.7)	44.8(32.3, 87.0)	-2.868	0.004

P<0.05, there was statistically significant between the two groups.

Table 5: Comparison of clinical data after treatment with human serum albumin at different infusion rates

	Control (n=42)	rapid infusion(n=22)	z/X^2	P
SBP (mmHg), [M(QL, QU)]	65(60, 69)	69.5(66, 75)	2.63	0.009
DBP(mmHg), [M(QL, QU)]	33(32, 36)	34(31, 38)	0.65	0.518
24h urine volume (ml/kg), [M(QL, QU)]	59.8(50.3, 88.9)	100.1(58.8, 119.4)	2.42	0.016
24h Increment of urine (ml/kg), [M(QL, QU)]	13.8(5.9, 23.7)	45.8(32.8, 57.6)	4.85	<0.001
weight (kg), [M(QL, QU)]	2.3(1.4, 3.3)	2.5(1.9, 2.63)	0.13	0.893
Increment of weight (kg), [M(QL, QU)]	0.1(0, 0.1)	0(0, 0.1)	3.16	0.002
ALB(g/L), [M(QL, QU)]	25.5(23.3, 28.4)	27.9(25.6, 30.3)	1.99	0.046
Increment of ALB (g/L), [M(QL, QU)]	3.1(1.9, 4)	4.8(3.4, 5.9)	3.86	<0.001
CLI, [M(QL, QU)]	34.9(28.9, 60.2)	29.7(26.6, 35.4)	1.93	0.044
Creatinine (umol/L), [M(QL, QU)]	52.1(39.5, 71.7)	44.8(32.3, 87.0)	0.59	0.557
Mechanical ventilation (day), [M(QL, QU)]	8.5(5, 23)	8(3, 25)	0.04	0.966
Length of stay (day), [M(QL, QU)]	22.5(15, 43)	23(10, 34)	0.54	0.591

P<0.05, there was statistically significant between the two groups.

Table 6: Comparison of 28-day survival rate between the two groups

	n	survive	death	survival rate	X2/*P*
Control	42	20	22	47.62%	0.599※
Rapid infusion	22	12	10	54.55%	

※P>0.05, there was no statistically significant between the two groups.

6. Discussion

Clinically, the most common causes of CLS are severe infection, severe asphyxia and hypoxic-ischemic encephalopathy, acute lung injury or respiratory distress syndrome, while cold injury syndrome, hyperglycemia, post-cardiopulmonary bypass, trauma, shock, and fetal edema caused by Rh incompatibility are also related to CLS [15]. Most of the cases included in this study were children with neonatal sepsis and respiratory distress syndrome, as well as children with severe asphyxia and Rh incompatibility.

The use of albumin in neonatal CLS is controversial in terms of indications and infusion methods. there were no significant differences of 28-day survival rate, creatinine level, length of hospital stays, length of mechanical ventilation, between the two groups post-infusion, suggesting that rapid albumin infusion did not improve the clinical outcome of CLS. A meta-analysis of albumin infusion for resuscitation showed no evidence that albumin reduces mortality in critically ill patients [21].

Our study showed that albumin infusion can improve hypoproteinemia, raise blood pressure, urine volume and improve renal function. Compared with the conventional infusion group, it was found that the systolic blood pressure and urine volume in the rapid infusion group were significantly higher than those in the conventional infusion group, and the degree of weight gain in the rapid infusion group was lower than that in the conventional infusion group. Secondly, the ALB level of children in the rapid infusion group was effectively increased, and the CLI level was effectively decreased, suggesting that the clinical effect of rapid albumin infusion was better than that of conventional albumin infusion. Naijie Cui et al [18]. conducted an experiment to observe the use of isotope-labeled albumin in animals with pulmonary capillary leakage. In this study, it was found that albumin exosmosis existed at the beginning, but with the increase of the dose and the speed of the input albumin, the exosmosis slowed down relatively, indicating that high dose and rapid infusion of albumin can play a good protective role. This is consistent with the results of this study. Therefore, rapid albumin infusion can reduce albumin leakage, quickly and effectively raise plasma osmotic pressure, improve tissue perfusion, and help improve the clinical symptoms of CLS.

The in-hospital mortality rate in this cohort of patients was about 50% which was similar as the Yang's study [23] we also found that Gestational Week was related with clinical outcome. As previously reported that prematurity was associated with a continued risk of increased mortality [24]. in our study there was no acute left heart failure or acute pulmonary edema occurred.

In summary, through this study we can found that albumin infusion can improve clinical situations momentarily, but the patient's prognosis is not improved. While as the improvement of the disease process, albumin supplementation may speed up recovery, but the impact on the prognosis is relatively small. and further a prospective multicenter clinical study is needed to carry out.

The limitations of this study are as follows: (1) Critically ill children have multiple albumin infusion, but only the data before and after

one infusion were included in this study, and the other data before and after infusion were not included, and the subsequent studies need to further quantify the infusion status for comprehensive comparison;(2) This study is a retrospective, controlled study with a small sample size, which may affect the results and cause bias, and needs to be further confirmed by a prospective study with a large sample size;

7. Declarations

Ethics approval & consent to participate:

This study was approved by Institutional Review Board of Children's Hospital of Chongqing Medical University. Due to the retrospective nature of the study, the informed consent was waived off by Institutional Review Board of Children's Hospital of Chongqing Medical University because waiving off could not pose any risks, neither violate the rights and welfare of the subjects (patients).

All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board of Children's Hospital of Chongqing Medical University and conducted in accordance with the principles as defined in the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

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