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Comparison of Automated Red Cell Exchange Transfusion and Simple Transfusion for the Treatment of Children With Sickle Cell Disease Acute Chest Syndrome

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Background. Both simple transfusion (ST) of packed red blood cells and automated red cell exchange (RCE) are used in the treatment of acute chest syndrome (ACS). We report our experience using each of these modalities for the treatment of ACS. ***Methods.*** Retrospective chart review of patients with ACS treated with ST only (51 episodes, ST group) or RCE performed either at diagnosis (U-RCE group, 15 episodes) or after ST (ST + RCE group, 15 episodes). ***Results.*** The mean clinical respiratory score (CRS) at diagnosis was significantly higher in the U-RCE group than in the ST group, but there were no significant differences among the other groups. The CRS and WBC each decreased significantly after simple transfusion in the ST group and after RCE in the U-RCE group, but both the CRS and WBC increased significantly, and the mean platelet count fell significantly, after simple transfusion in the ST + RCE group. Only patients in the ST + RCE group required mechanical ventilation. There were no significant differences in length of stay (LOS) or total hospital charges among any of the groups, probably due to the small sample size. ***Conclusions.*** We conclude that the CRS identifies the patients who are most severely affected with ACS, and that upfront RCE is a safe and effective treatment for these patients. Additional work is needed to develop a method to predict which of the apparently less severely affected patients will fail to improve after simple transfusion and should receive upfront RCE. Pediatr Blood Cancer 2013;60:1952–1956.

Key words: acute chest syndrome; apheresis; automated red cell exchange; sickle cell disease

INTRODUCTION

Acute chest syndrome is defined as a new pulmonary infiltrate involving at least one complete lung segment, consistent with infiltration rather than atelectasis, and associated with at least 1 additional finding including chest pain, fever, tachypnea, wheezing, rales, cough, increased work of breathing (intracostal retractions, nasal flaring, use of accessory muscles), a >2% decrease in room air oxygen saturation, or a $PaO_2 < 60$ mm Hg in a patient with sickle cell disease [1–3]. ACS is the second most common cause of hospitalization and the most frequent cause of death in patients with sickle cell disease [1]. Although both simple transfusion (ST) and automated red cell exchange transfusion (RCE) are used in the treatment of children with ACS, particularly for patients with refractory hypoxia, multi-lobar involvement, failure to improve after ST, and need for mechanical ventilation, the appropriate indications for the use RCE in children with ACS are not clear. Since RCE has been reported to be more expensive, requires more blood, and requires central venous line insertion, data are needed to facilitate the development of evidence-based guidelines that will assist the clinician in distinguishing prospectively the patients who will benefit from RCE from those who can be treated safely with simple transfusion [4].

There are very few reports of the use of RCE in adults or children with ACS and there has been no prospective systematic comparison of RCE and ST in the treatment of adults or children with ACS [5–8]. A recent single institution retrospective cohort study reported the outcomes for 20 adult patients who received RCE for the treatment of ACS and compared the outcomes with a control group of patients who were treated with simple transfusion [8]. The authors concluded that there was no benefit for RCE in the adult ACS population and suggest that a randomized trial is indicated to determine whether RCE is beneficial in the treatment of adults with ACS [8]. In contrast, a recent single institution study reported 44 pediatric patients with 53 episodes of ACS who were treated with RCE [7]. These investigators concluded that RCE is a safe and effective treatment for ACS but this study did not include a control group of patients treated with ST [7]. This study also utilized the clinical respiratory score (CRS, Table I), an evaluation tool that was originally developed for use in asthma that has also been applied subsequently in a prospective study from the same institution using the CRS to stratify patients with ACS into groups for guideline-directed treatment [9].

We have been using RCE since 1996 for the upfront treatment of children who present with severe ACS, and for salvage therapy of children with ACS who fail to improve, or worsen, after simple transfusion. Here we report the results of a comprehensive analysis of clinical and laboratory variables in 30 patients treated with RCE for their first episode of ACS in our institution, and we include a control group of 51 patients treated with ST for their first episode of ACS. We also retrospectively applied the CRS as a tool to confirm the findings of Velasquez et al. and to determine whether the CRS, alone or in combination with other variables, would have predicted the need for RCE in our population.

METHODS

We conducted a retrospective chart review of all patients who were treated with RCE during their first episode of ACS at Arkansas Children's Hospital from January 1996 through December 2010. We also identified a control group of all consecutive patients who were treated with ST during their first episode of ACS at Arkansas

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TABLE I. Clinical Respiratory Score (CRS)

Variable	Score = 0	Score = 1	Score = 2
Respiratory rate	1–5 years: <30 >5 years: <20	1–5 years: 30–40 >5 years: 20–30	1–5 years: >40 >5 years: >30
Auscultation	Good air movement, scattered wheezing (only expiratory), loose crackles	Depressed air movement, inspiratory and expiratory wheezes	Diminished or absent breath sounds, severe wheezing, or markedly prolonged expiration
Use of accessory muscles	Mild to no use of accessory muscles, mild to no retractions or nasal flaring on inspiration	Moderate intracostal retractions, mild to moderate use of accessory muscles, nasal flaring	Severe intracostal and substernal retractions, nasal flaring
Mental status	Normal to mildly irritable	Irritable, agitated, restless	Lethargic
Room air pulse oximetry	>95%	90–95%	<90%
Color change	Normal	Pale to normal	Cyanotic, dusky

The total CRS score is the sum of the values of the six individual variables. Adapted from Ref. [7].

Children's Hospital from January 2001 through December 2010 by reviewing hospital discharge and coding information. We chose to analyze only the first episode of ACS in order to avoid introducing bias by counting multiple non-independent events in the same patient. The time span for the control group was chosen to begin in 2001 since that was the earliest time that medical records were in an electronic format that could be imported into the RCE database. There were no changes in the supportive care provided to ACS patients prior to or after 2001, with the exception of the substitution of azithromycin for erythromycin when this agent became available, and no patient had been treated with hydroxyurea prior to study entry. The protocol was reviewed and approved by the Institutional Review Board of the University of Arkansas for Medical Sciences and the requirement for informed consent was waived.

Patients with sickle cell disease were determined to have ACS if they developed a new pulmonary infiltrate involving at least one complete lung segment, consistent with infiltration rather than atelectasis, and associated with at least 1 additional finding including chest pain, fever, tachypnea, wheezing, rales, cough, increased work of breathing (intracostal retractions, nasal flaring, use of accessory muscles), a >2% decrease in room air oxygen saturation, or a $PaO_2 < 60$ mm Hg [1–3]. Patients were admitted to the hospital, started on IV hydration at a rate of 1–1.5 times maintenance, and given pain control as needed, typically morphine delivered by patient controlled analgesia (PCA), and ketorolac, but other medications were used at the discretion of the attending hematologist. The respiratory care service was consulted and most patients received supplemental oxygen and incentive spirometry. Patients with a previous history of asthma were treated with inhaled beta agonists, continuation of their controller medication (typically an inhaled steroid), and in some cases systemic steroids. Patients who did not have a previous diagnosis of asthma were treated with inhaled beta agonists if they were wheezing. Antibiotic therapy consisted of an IV second (cefuroxime) or third (ceftriaxone or cefotaxime) generation cephalosporin plus a macrolide, typically azithromycin. Transfusion therapy was at the discretion of the attending pediatric hematologist and the decision to initiate RCE was made in patients with refractory hypoxia, multi-lobar involvement, failure to improve after simple transfusion, need for mechanical ventilation, or risk for hyperviscosity with simple transfusion (typically patients with SC disease or $S\text{-}B^+$ thalassemia) [4]. RCE was available immediately to patients diagnosed with ACS and was provided by the in house Arkansas Children's Hospital apheresis service. Patients treated with simple transfusion (the ST group, n = 51) received packed red blood cells sufficient to raise the hemoglobin level to a target value of 10 gm/dl. Patients were referred to the apheresis service for either upfront RCE (U-RCE group, n = 15) or when they failed to improve, or deteriorated, following ST (ST + RCE group, n = 15). Patients treated with RCE underwent deep sedation with either midazolam plus ketamine, or propofol, and then had a double lumen central venous line placed in the femoral vein. RCE was done using a Cobe Spectra and a sufficient volume of packed red blood cells to achieve a predicted post-RCE hematocrit of 34%. All blood products were irradiated, treated with a leukocyte reduction filter, and were antigen matched after January 2003.

Chest radiograph findings were scored as positive if the pulmonary infiltrate was new, involved at least one complete lung segment, and was consistent with infiltration rather than atelectasis, in the opinion of the attending pediatric radiologist. Right-sided or left-sided pleural effusions were recorded separately. The Clinical Respiratory Score (CRS) was applied retrospectively to our dataset using the published scoring rubric (Table I) [7,9]. Retrospective scoring of mental status and color change was predicted to be difficult, and these variables were scored as zero in the event that changes in mental status or color were not noted in the medical record. The CRS was calculated for each episode of ACS at the time of diagnosis with ACS, after ST (for the ST and ST + RCE groups), and after RCE (for the U-RCE and ST + RCE groups).

Statistical Analysis

All the data were analyzed using R v2.15.0 (R Development Core Team, Vienna, Austria) and SAS v9.3 (SAS Institute, Inc., Cary, NC). Summary statistics were described as mean ± standard deviation for continuous data and frequency and percentage for categorical data. The comparisons of means among three groups (ST, U-RCE, and ST + RCE) were carried out for continuous data by fitting the linear regression models. We compared the proportions of categorical data among three groups using the Fisher's exact tests. Intragroup comparisons were also carried out to evaluate the change in the CRS and blood count parameters over time (at diagnosis, after ST and after RCE) using the paired two-sample *t*-tests. *P*-values <0.05 were considered to be statistically significant and no adjustment was made for the multiple testing.

RESULTS

We identified 81 patients who were diagnosed with ACS (Table II). Homozygous hemoglobin S (SS) was present in 63 patients, 11 were hemoglobin S and C double heterozygotes (SC), 4 were hemoglobin S and B^o thalassemia double heterozygotes (S-B^o thal), 2 were hemoglobin S and B^+ thalassemia double heterozygotes (S-B^+ thal), and one patient had hemoglobin SO Arab. Fifty-two patients were male and 29 were female. No patient had been treated with hydroxyurea prior to study entry. The average age of the patients was 8.5 years and they ranged in age from 5 months to 20 years. A majority (73%) of the RCE procedures were done between 2001 and 2010 and overlap the time period chosen for patients in the control group. The admission diagnosis was ACS in 49 episodes (61%), painful crisis in 31 episodes (38%), and one episode occurred after a laparoscopic cholecystectomy. ACS developed a mean of 1 day after admission in the episodes where ACS was not the admission diagnosis. Twelve patients had a past-history of asthma. There were no deaths during this study.

In order to study the effect of RCE on the course of ACS, we separated the episodes into a control group treated with simple transfusion only (ST group), a group treated with upfront RCE (U-RCE group), and a group treated with ST but who failed to improve or deteriorated and were treated with RCE as salvage therapy (ST + RCE group). As shown in Table III, the mean CRS at diagnosis was significantly higher in the U-RCE group than in the ST group ($P = 0.01$), but there were no significant differences in the mean CRS at diagnosis between the U-RCE and the ST + RCE ($P = 0.27$) or the ST and ST + RCE groups ($P = 0.23$). After simple transfusion, there was a significant decrease in the mean CRS in the ST group ($P < 0.001$), but the CRS in the ST + RCE group increased to a level that was significantly higher than the post-simple transfusion CRS in the ST group ($P < 0.001$). The mean CRS decreased significantly after RCE in the U-RCE ($P < 0.001$) and ST + RCE groups ($P < 0.03$), and there was no significant difference in the post-RCE CRS between these two groups ($P = 0.60$). The CRS was calculated from data recorded at a mean of 13 hours (range 5–20.5) after ST (ST and ST + RCE groups) or after RCE (U-RCE and ST + RCE groups). The mean temperature at the time of diagnosis with ACS was significantly higher in the ST group ($P = 0.02$) than in the ST + RCE group, but was not significantly different between the ST and U-RCE groups ($P = 0.11$). There were no significant differences in the past history of asthma, wheezing at diagnosis with ACS, sites of pain, days with fever, oxygen saturation at diagnosis with ACS, or chest X-ray findings among the groups (Supplementary Table I).

TABLE II. Demographic Data

	ST group	U-RCE group	ST + RCE group	Overall *P*-value[a]
Episodes	51	15	15	
Mean age (±SD)	8.0 ± 5.5	10.7 ± 5.6	8.1 ± 4.7	0.24
Gender				0.42
Male (%)	31 (61%)	9 (60%)	12 (80%)	
Female (%)	20 (39%)	6 (40%)	3 (20%)	
Hemoglobin type				0.05
SS (%)	40 (78%)	11 (73%)	12 (80%)	
SC (%)	9 (18%)	1 (7%)	1 (7%)	
SB^0 thal (%)	2 (4%)	0 (0%)	2 (13%)	
SB^+ thal (%)	0 (0%)	2 (13%)	0 (0%)	
SO Arab (%)	0 (0%)	1 (7%)	0 (0%)	

ST, group treated with simple transfusion only; U-RCE, group that received upfront RCE without prior simple transfusion; ST + RCE, group treated initially with simple transfusion followed by RCE. [a]The overall *P*-values were obtained based on the overall comparisons of three groups using the linear regression model for continuous variables and the Fisher's exact test for categorical variables.

There were no significant differences in the WBC at diagnosis among the groups. The WBC fell significantly after simple transfusion in the ST group ($P = 0.02$), and after RCE in the U-RCE group ($P < 0.01$), but rose after simple transfusion in the ST + RCE group to a level that was significantly higher than the post-simple transfusion WBC in the ST group ($P = 0.04$). Although the mean platelet count (PLT) at diagnosis was not significantly different between the groups, the PLT fell significantly after simple transfusion in the ST + RCE group ($P = 0.055$), but did not change significantly after simple transfusion in the ST group ($P = 0.35$). Consistent with previous reports, we noted significant decreases in the platelet count after RCE ($P < 0.001$) since the post-RCE blood counts were drawn immediately following completion of the RCE procedure [10]. There were no significant differences in mean hemoglobin (HGB) values between the groups at diagnosis after simple transfusion or after RCE, even though the mean volume of red cells administered in the ST group (15.9 ml/kg) was significantly greater than that administered by simple transfusion in the ST + RCE group (12.3 ml/kg, $P = 0.04$). Total blood product usage was significantly higher in both the ST + RCE ($P < 0.001$) and U-RCE groups ($P < 0.001$) than in the ST group, and was also significantly higher in the ST + RCE group than in the U-RCE group ($P < 0.001$). The mean time to initiate RCE after the decision was made that RCE was necessary was 4.5 hours, the mean post-RCE hemoglobin was 10.3 g/dl for the combined RCE groups, and the mean post-RCE hemoglobin S was 18.4%. At the time of study entry, two patients (one with anti-E and one with anti-K) who were treated with RCE and one patient (anti-C) in the ST group had pre-existing alloantibodies. Following transfusion, one patient treated with RCE developed an anti-K and one patient treated with simple transfusion developed an anti-C alloantibody.

The mean oxygen saturation at diagnosis with ACS was the lowest in the U-RCE group, was higher in the ST-RCE group, and was the highest in the ST group, but this trend did not reach statistical significance ($P = 0.09$). All patients who were treated with RCE required supplemental oxygen therapy, but only 38 of the 51 patients (75%) who were treated with simple transfusion alone required supplemental oxygen. Patients in the ST + RCE group spent significantly more days on oxygen than episodes in the ST group ($P < 0.001$); one patient in the U-RCE group, three patients in the ST + RCE group, but no patient in the ST group required treatment with bi-level positive airway pressure (BiPAP) ($P = 0.01$); and no patient in either the ST or U-RCE group, but three patients in the ST + RCE group, required treatment with mechanical ventilation. There were no complications from the deep sedation used to facilitate central venous catheter insertion, no central venous catheter-related complications, and no complications from the RCE procedure recorded in any of the patients who were treated with RCE. There were no significant differences in LOS among any of the groups. Total hospital charges were the lowest in patients in the ST group, and there was a trend toward increasing hospital charges in the patients who were treated with

TABLE III. Clinical and Laboratory Data in the ST, U-RCE, and ST+RCE Groups

	ST (N = 51)	U-RCE (N = 15)	ST+RCE (N = 15)	Overall *P*-value[a]
CRS at diagnosis	3.0 ± 2.0	4.7 ± 2.0	3.8 ± 2.5	0.03
CRS after ST	2.0 ± 1.6	NA	4.9 ± 1.9	<0.001
CRS after RCE	NA	2.4 ± 1.2	2.1 ± 1.6	0.60
WBC at diagnosis (K/μl)	19.6 ± 8.0	25.1 ± 12.1	23.8 ± 15.1	0.13
WBC after ST (K/μl)	17.8 ± 7.4	NA	22.9 ± 9.9	0.04
WBC after RCE (K/μl)	NA	17.0 ± 7.1	16.0 ± 5.5	0.66
HGB at diagnosis (g/dl)	7.3 ± 1.4	8.0 ± 1.7	7.6 ± 1.6	0.22
HGB after ST (g/dl)	10.2 ± 1.2	NA	9.5 ± 2.2	0.13
HGB after RCE (g/dl)	NA	10.4 ± 1.1	10.3 ± 1.1	0.85
PLT at diagnosis (K/μl)	312 ± 140	354 ± 95	345 ± 150	0.49
PLT after ST (K/μl)	321 ± 115	NA ± NA	319 ± 160	0.97
PLT after RCE (K/μl)	NA	175 ± 55	176 ± 130	0.99
Oxygen saturation at diagnosis	92.3 ± 7.6	87.0 ± 9.5	89.5 ± 10.4	0.09
Days on oxygen	2.4 ± 2.3	3.7 ± 2.1	4.7 ± 1.8	0.001
Pre-RCE %S	NA	71.6 ± 14.9	49.2 ± 13.4	<0.001
Post-RCE %S	NA	19.5 ± 7.9	17.3 ± 9.7	0.49
LOS (days)	5.5 ± 3.9	5.7 ± 2.7	6.5 ± 2.7	0.59
Total hospital charges	$14,269 ± $11,610	$18,544 ± $9,854	$20,867 ± $8,471	0.08

All data are mean ± standard deviation. ST group, group treated with simple transfusion only; U-RCE group, group that received upfront RCE without prior simple transfusion; ST + RCE group, group treated initially with simple transfusion followed by RCE. CRS, clinical respiratory score; HGB, hemoglobin level; LOS, length of stay; NA, analysis is not applicable; PLT, platelet count; RCE, automated red cell exchange transfusion; ST, simple red blood cell transfusion; WBC, total leucocyte count. [a]The overall *P*-values were obtained based on the overall comparisons of three groups using the linear regression model for continuous variables and Fisher's exact test for categorical variables.

RCE, but none of these differences reached statistical significance ($P = 0.08$) in our study, probably due to the relatively small sample size and large variation in total charges within each group.

DISCUSSION

Although both ST and RCE are used commonly in the treatment of ACS in children, it is not clear how the clinician can distinguish prospectively the patients who will benefit from RCE from those who can be safely treated with ST. Prior pediatric studies have reported that RCE is a safe and effective treatment for ACS in children, but a study done in adult patients concluded that RCE is not beneficial in adult patients with ACS [4,7,8]. For this reason, we performed a comprehensive analysis of clinical and outcomes data on all patients treated with RCE or simple transfusion at our institution for their first episode of ACS.

We found that patients who received upfront RCE were readily identifiable by their elevated CRS scores at diagnosis, which were significantly higher in these patients than in patients who were treated successfully with simple transfusion only. Despite their significantly higher CRS scores at diagnosis, patients who received upfront RCE had no central venous catheter-related complications, never required mechanical ventilation despite the deep sedation required to insert the central venous catheter, rapidly improved after RCE, and had mean LOS and mean total hospital charges that were not significantly different than patients who were treated successfully with simple transfusion only or patients who worsened after simple transfusion and required salvage RCE. We did not find any significant differences in WBC at diagnosis among the groups, in contrast to previous reports that suggest that an elevated WBC at the time of diagnosis with ACS is associated with more severe disease [11]. We conclude that, although the highest CRS at the time of diagnosis was correlated with the most severe episodes of ACS, these patients nevertheless had a hospital course that was indistinguishable from less severely affected patients who were treated successfully with simple transfusion alone, provided that they received RCE as their primary therapy. These conclusions are in agreement with the findings of previous studies using RCE for the treatment of ACS in children, but conflict with the conclusions reached by a recent adult study [7,8]. Possible reasons for this discrepancy include the increased incidence of chronic pulmonary and cardiac disease in adult patients with sickle cell disease, and the very long time to the initiation of RCE in the adult study (mean of 17 hours), in contrast to the rapid initiation of RCE in our study (mean of 4.5 hours) and in that of Velasquez et al. (median of 5 hours) [7,8].

In contrast to the patients in the U-RCE group who presented with the most severe ACS, patients in the ST + RCE group, who either failed to improve or deteriorated after simple transfusion, were indistinguishable at diagnosis from episodes in the ST group. Although the CRS scores and blood counts in the ST + RCE group were indistinguishable from the ST group at diagnosis, after simple transfusion the patients in the ST + RCE group developed significant elevations in the CRS and WBC, and a significant fall in PLT, all of which have been shown by previous investigators to be adverse prognostic indicators [1,7,10]. In contrast, episodes that were successfully treated with simple transfusion had a significant fall in the CRS, a decrease in the WBC, and a stable PLT after simple transfusion. We conclude that the CRS, even with the addition of the WBC, is probably not sufficiently robust to allow accurate differentiation at the time of diagnosis with ACS between those patients who will improve with simple transfusion and those who will fail to improve, or will develop progressive ACS, after simple transfusion.

The primary limitations of our report derive from the small sample size and from the retrospective design of the study. Although there were clear trends for decreasing LOS with upfront RCE, and for increasing total hospital charges for the groups treated with RCE, the small sample size is the most likely explanation for our failure to demonstrate statistically significant differences in the LOS and total hospital charges among the groups, and we suggest that a larger study would provide statistical validity to the trends that we observed. The retrospective application of the CRS resulted in only 1 instance where an alteration in the patient's mental status was recorded, no instances where alterations in the patient's color was recorded, and resulted in a long interval of 13 hours (mean) in measuring the post-transfusion CRS. All previous studies of the use of RCE for the treatment of ACS in children were retrospective, and therefore share these limitations, which can only be overcome by a prospective, multi-institutional trial [5–7].

Despite the limitations shared by our study and of the study of Velasquez et al. [7], the use of the CRS has been a major advance in the study of pediatric ACS. The CRS was initially developed to determine the severity of acute asthma exacerbations and was applied to children with ACS with the rationale that airflow obstruction is common in patients with ACS [7]. Despite the correlation between an elevated CRS and the need for RCE in our study, and in the study of Velasquez et al., the use of this tool alone did not distinguish which of the apparently less severely affected episodes would eventually worsen after simple transfusion and go on to be salvaged by RCE [7]. Inflammation has been suggested to play a major role in the pathogenesis of ACS and altered levels of sVCAM-1, phospholipase A_2, leukotrienes, and other inflammatory mediators are important in the pathogenesis of ACS, which has led some investigators to suggest that treatment with glucorticoids might decrease the degree of inflammation and lessen the severity of ACS [10,12–15]. Future work incorporating additional variables, such as altered levels of inflammatory biomarkers, into the risk stratification assessment may add to the predictive power of the CRS and allow treating physicians to prospectively distinguish those patients with ACS who will do well with simple transfusion from those who may benefit from upfront RCE. Additional data to define the appropriate indications for RCE in children with ACS are needed, and we suggest that a prospective, multi-institution study be initiated to address this question.

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