Original Article

DOI: 10.7860/JCDR/2016/13427.7809

Study of Twenty One Cases of Red Cell Exchange in a Tertiary Care Hospital in Southern India

Pathology Section

M. JOSHUA DANIEL[1], PRAKASH H MUDDEGOWDA[2], CHEZHIANSUBASH[3], JYOTHI B LINGEGOWDA[4], NIRANJAN GOPAL[5], KRISHNA PRASAD[6]

ABSTRACT

Introduction: Red Cell Exchange (RCE) is removal of a patient's red blood cells while replacing with donor red blood cells either manually or using automated systems. RCE is beneficial in patients with Sickle Cell Disease (SCD) either during sickling crisis or prior to major surgical procedures to bring down the sickling percentage as high sickling percentage during prolonged anaesthesia may lead to vaso-occlusive crisis. It is also employed in patients infested with malaria and babesiosis where parasitic index remain high despite medical management. RCE is also tried as an adjuvant therapy in certain poisons like nitrobenzene and carbon monoxide when first line management fails.

Aim: To study the effectiveness, clinical outcome, challenges and complications of RCE in various clinical scenario and to understand how this procedure can be effectively utilized in the management of patients in Indian scenario.

Materials and Methods: This retro prospective study was conducted in tertiary care center in southern India which analyzed 21 RCE procedures performed on patients with different clinical conditions. Of the 21 RCE performed, 18 procedures were performed on patients with case of sickle cell disease, Two procedures were performed on patients infested with severe falciparum malaria and one procedure was performed on a patient with nitrobenzene poisoning. All procedures were performed using Spectra Optia® Apheresis System - Terumo BCT.

Results: All the 18 patients who underwent the RCE for sickle cell anaemia were admitted for hemi-arthroplasty for avascular necrosis of the head of femur. The average initial HbS levels were between 73-85% and post RCE it was brought down to 22-29% and was achieved in a single sitting in all the cases.

Among the two patients infested with severe falciparum malaria, RCE helped in reducing the infestation rate. In case of nitrobenzene poisoning, RCE helped in improvement of oxygen saturation and patient showed significant improvement.

Conclusion: RCE is a safe and clinically effective therapeutic modality with very minimal to nil side effects. RCE is possibly underutilized therapy in developing world like India due to various reasons like inadequate awareness/ technical expertise, lack of equipments and facilities to identify the clinical conditions per se etc.

Keywords: Abnormal red blood cells, Malaria, Sickle cell disease

INTRODUCTION

Red Cell Exchange (RCE) is removal of abnormal red blood cells from the patient's blood and replacing them by normal donor red blood cells either manually or using an automated cell separator. Though this procedure is most commonly employed in removing sickle cells in patients with sickle cell disease with complications, it is also useful to reduce the disease burden in severe cases of babesiosis, malaria and in certain types of overdose or poisoning. RCE is helpful to reduce iron overload due to top up transfusion in thalassaemia major [1-4]. RCE can be lifesaving if employed early in ABO mismatch transfusions. In SCD, RCE prevents new vaso-occlusive events by removing HBSS and HBSβcells and provides added oxygen carrying capacity without increasing viscosity of blood. RCE can also be employed as a long term therapy to maintain a low level of HbS in primary and secondary stroke prevention in patients with homozygous Sickle Cell Disease (SCD) [5-7].

RCE offers adjunct and rapid approach in acute severe malaria with high parasitic index. RCE in severe cases of malaria is said to reduce parasitic load, remove toxic substances and also reduce microcirculatory sludging. Pregnant women, patients with renal, pulmonary and cerebral complications are most benefitted by RCE. Isolated parasitic index of 10% or above associated with clinical severity is an indication for RCE as per World health Organization – 2000, criteria in management of acute severe malaria [1,8-10]. RCE has been used in poisonings like carbon monoxide, nitrobenzene, arsenic and sodium hypochlorite, etc when the first line of management fails [1,11-13]. Only very few centers are performing RCE in India, here we present a study involving 21 RCE cases.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary care center in southern India between April 2012 and December 2013. The study analyzed the clinical outcome, effectiveness, the challenges, and side effects of this procedure on 21 patients during the study period. Amongst the 21 patients who underwent the procedure, 18 patients underwent RCE for complicated sickle cell anaemia (avascular necrosis) with high sickle cell percentage, Two patients for acute severe malaria with high parasitic index and one procedure was done on a patient with nitrobenzene poisoning with high methhaemoglobinemia. Spectra Optia® Apheresis System from Terumo-BCT Pvt Ltd was used to perform all the 21 RCE procedures. Packed red cell suspensions (SAGM) that are leukoreduced by pre-storage leuko-filtration, that are less than one week old were used during RCE. Care was taken that these red cell units transfused were all negative for sickle cells (heterozygous) using High Performance Liquid Chromatography (HPLC). The number and volume of red cell units transfused was calculated based on the patients' blood volume, haemoglobin percentage, sickling cell percentage and target haemoglobin percentage etc.

RESULTS

Eighteen patients who underwent the RCE had the procedure done for sickle cell anaemia, among which seven were females

and eleven were males, the ratio being 1 to 2.6. Seventeen patients had haemoglobin SS on Hb electrophoresis while one patient had haemoglobin SC pattern. All the 18 patients were admitted for hemi-arthroplasty for avascular necrosis of the head of femur. Amongst them, 15 patients had unilateral disease, 1 patient presented with bilateral problem and remaining 2 patients were admitted for recurrent disease on the opposite hip. Age group of patients was between 12 to 28 years with a mean age of 19 years. The average initial HbS levels were between 73-85% and post RCE it was brought down to 22-29%. Hb-A levels were maintained between 75% and 88% with a target haematocrit of approximately 33%. In all cases confirmation Hb-A % was done through HPLC. Target Hb% was achieved in a single sitting in all the cases.

Among the two patients infested with malaria, first patient was a 13-year-old female who presented with 11% infestation rate (percentage of infestation rate being calculated using the formula number of infested RBCs divided by unaffected RBCs multiplied by hundred) not responding to medical management. RCE was performed on day 4 of admission as an adjuvant to anti-malarials and other supportive management. The infestation rate dropped to 6% on single RCE procedure and top up transfusions were also given on subsequent days to combat anaemia and to improve the oxygen carrying capacity. Patient expired due to acute respiratory failure and renal syndrome on day 8, despite all possible efforts. Second case was a 21-year-old male, who presented with 10% infestation rate. The patient was put on RCE along with anti-malarials and other medical management on the day of admission. The infestation rate dropped to 7% during the first exchange and to 4 % on subsequent exchange. Three units packed red blood cells were transfused post exchange to improve the haematocrit. Patient recovered without any complication haemoglobin concentration during discharge was 12 g%.

The last case in the study where RCE was used was a 25-year-old male, who was admitted into emergency ward with suspected organophosphorous poisoning. On day two, it was noted that the patient's oxygen saturation did not improve despite management and the clinical signs and symptoms did not correlate with organophosphorus poisoning. Suspicions about possibility of nitrobenzene poisoning rose as methhaemoglobinemia was present and there was a disagreement between the percentage of arterial saturation report obtained through arterial blood gas analysis and the reading in the pulse oxymeter revealed 80% saturation while pulse oximeter showed normal saturation of 96%. Haemoglobin electrophoresis was done and presence of a raised methhaemoglobin level was noted. Treatment with methylene blue to reduce methhaemoglobin levels was not promising, as the oxygen saturation was consistently low. One volume RCE was initiated on day three and oxygen saturation improved and patient showed clinical signs of improvement. One volume therapeutic plasma exchange was also performed on this patient as his serum showed the presence of free haemoglobin which is most probably due to intravascular haemolysis.

DISCUSSION

RCE is an effective treatment modality that can be used safely in a large number of conditions. Though the efficacy is well defined in many conditions in clinical trials, its clinical benefit still remain controversial certain conditions like acute severe malaria with high parasitemia and in certain poisonings [1,4,8].

Major advantage of RCE in SCD is its iron neutrality, since the removed HbS has just as much iron as the administered HbA. Several studies have demonstrated stable iron levels in RCE [6]. Treatment of patients of SCD with bone marrow necrosis and multi-organ failure is mainly supportive. RCE is effective in management of both acute and chronic complications of sickle cell disease. However, American society for apheresis advises RCE to be used as a first line or adjunctive second line therapy for cerebrovascular accidents and acute chest syndrome. The role of RCE in multi organ failure is not yet established and should be used on case to case basis [1,14,15].

Most of the RCE in the present study were uneventful except for few allergic and febrile reactions. None of the patients had any reactions due to citrate toxicity, as the anticoagulant used during these procedures gets metabolized in the liver within minutes and the ratio of anticoagulant used is generally 1:10, which is very low. None of these patients showed the presence of any allo or auto antibodies during antibody type and screen except one sickle cell patient who had anti-D allo-antibody. Studies suggest that SCD patients may benefit from extended antigen matching, especially in patients who have already made allo-antibodies or patients with warm reacting auto-antibodies [16,17]. No comparable studies regarding RCE and avascular necrosis of the head of femur in SCD was found in pubmed literature search. Most of the studies have advocated RCE in acute chest syndrome and SCD [3,4]. None of the patients who underwent the procedure presented with acute chest syndrome either during or after RCE.

RCE is frequently used as adjunctive treatment in management of acute severe malaria with high parasitic index when first line management fails. Though its efficacy as initial therapeutic choice remains controversial, some questions based on theoretical basis of exchange transfusion note that sequestered parasites, which cause most of the pathology associated with severe malaria is not removed. Studies have shown a greater benefit from adjunct transfusion in Asia, compared with patients of Africa attributing it possibly to virulence and anti-malarial sensitivities of *Plasmodium falciparum*. Mortality in this clinical scenario remains high and studies have reported high mortality rates in RCE in patients with acute severe malaria and high parasitic index. In our study, one patient died due to multiple organ failure [2,9,18-20].

Nitrobenzene, also known as nitrobenzol, mirbane oil or essence of mirbane, when introduced into the body, is metabolized to aniline. Nitrobenzene and aniline are typical aromatic nitrocompounds and aromatic nitro amino compounds that cause methhaemoglobinemia. Nitrobenzene is commonly available in printing dyes, ether and soap industry and is used as a suicidal poison. Patient initially presents with cyanosis and progresses to dyspnoea and tachycardia. At high saturation of above 70% methhaemoglobin, it can even cause death. This patient presented with cyanosis and dyspnoea with methhaemoglobin percentage of 75%. Significant methhaemoglobinemia due to acute nitrobenzene poisoning is uncommon and is a rare life threatening emergency. Once poisoning is suspected, clinical evaluation and early effective management with methylene blue will improve the clinical outcome. Diagnosis is generally based on persistent cyanosis despite oxygen therapy. As in the present case, there will be a difference between observed (pulse oximetry) and calculated (arterial blood gas) oxygen saturation. RCE is very effective in patients who are refractory to conventional management i.e. methylene blue. This is the first reported case of RCE done on acute severe nitrobenzene poisoning in Indian scenario [11,13].

LIMITATION

The main limitation of the study could be the low number of procedures, partly limited mainly due to procedure rarity and clinicians knowledge. Larger numbers of procedures would be helpful in identifying more pro and cons of the study

CONCLUSION

RCE is safe and clinically effective procedure with minimal or no side effects when initiated at the right time by trained personnel's. The main challenges in performing RCE in developing countries

are lack of awareness, technical expertise, infrastructure, early identification of disease condition, limited supply of safe blood, etc. These things make RCE limitedly available to many needy patients across the country.

REFERENCES

[1] Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice – Evidence based approach from the writing committee of the American society of apheresis: The sixth special issue. *J Clin Apher*. 2013;28:145-284.

[2] Red blood cell exchange and depletion procedures. (internet). 2012 (cited 2014 Jun 15). Available from: http://www.terumobct.com/location/north-america/Documents/306670723B.pdf

[3] Cho G, Hambleton IR. Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. The Cochrane library. Published online: 8 Jan 2014. Available from : http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008360.pub3/pdf

[4] Draser E, Igbineweka N, Vasavda N, Free M, Awogbade M, Allman M, et al. Blood transfusion usage among adults with sickle cell disease – a single institution experience over ten years. *Br J Haemat*. 2011;152:766-70.

[5] Mahfoudhi E, Lecluse Y, Driss F, Abbes S, Flaujac C, Garcon L. Red cell exchanges in sickle cell disease lead to selective reduction of erythrocytes – derived blood microparticles. *Br J Haemat*. 2012;156:545-47.

[6] Swerdlow PS. Red cell exchange in sickle cell disease. *Haematology Am Soc Haematol Edu Program*. 2006:48-53.

[7] Cheung ATW, Miller JW, Miguelino MG, To WJ, Lin X, Chen PC, et al. Exchange transfusion therapy and its effects on real-time microcirculation in pediatric sickle cell anaemia patients: An intravital microscopic study. *J Peditr Haematol Oncol*. 2012;34(3):169-74.

[8] Udani S, Deshpande A, Kalgutkar S. Exchange transfusion for severe malaria: A comparison of red cell exchange with whole blood exchange. *IJCCM*. 2003; 7(2):124-27.

[9] Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: A meta analysis. *CID* 2002:34;1192-98.

[10] Cabrera LS, Arroyo MF, Gonzalez FR, Palacios MS. Erythrocytapheresis in the management of severe falciparum malaria. *J Emerg Trauma Shock*. 2010; 3(2):206.

[11] Srivastava A, Chaturvedi A, Gupta SK, Agarwal GR, Verma RK. Acute nitrobenzene poisoning: case fatality and importance of methylene blue. *Srilankan Journal of Anaesthesiology.* 2010;18(2):91-93.

[12] Romanovsky A, Djogogovic D, Chin D. A case of sodium chlorite toxicity managed with concurrent renal replacement therapy and red cell exchange. *J Med Toxicol*. 2013;9:67-70.

[13] Saxena H, Saxena AP. Acute methhaemoglobinemia due to ingestion of nitrobenzene (paint solvent). *Indian J Anaesth*. 2010;54(2):160-62.

[14] Adamski J, Hanna CA, Reddy VB, Litovsky S, Evans CA, Marques MB. Multiorgan failure and bone marrow necrosis in three adults with sickle cell beta thalassaemia. *Am J Haematol*. 2012;87:621-24.

[15] Stokley S. Guideline for exchange transfusions in children and adolescents with sickle cell disease. (internet) 2011 (cited 2014 Jun15). Available from: https://www.nuh.nhs.uk/handlers/downloads.ashx?id=48971.

[16] Wilkinson K, Harris S, Gaur P, Haile A, Armour R, Teramura G, et al. Molecular blood typing augments serologic testing and allows for enhanced matching of red blood cells for transfusion in patients with sickle cell disease. *Transfusion*. 2012;52:381-88.

[17] Baron JM, Baron BW. Red cell exchange is not effective for patients with sickle cell anaemia and coexisting warm autoantibody haemolysis. *Blood Transfus*. 2010;8:303-06.

[18] Hackenberg LA, Staudinger T, Bojic A, Locker G, Leitner GC, Graninger W, et al. Automated red cell exchange as an adjunctive treatment for severe Plasmodium falciparum malaria at the Vienna General Hospital in Austria: a retrospective cohort study. *Malar J.* 2012;11:158.

[19] Deshpande A, Kalgutkar S, Udani S. Red cell exchange using cell separator (Therapeutic erythrocytapheresis) in two children with acute severe malaria. *JAPI*. 2003;51:926-26.

[20] Watanaboonyongcharoen P, Park YA, Poisson JL, Brecher ME. Rapid increase in parasitemia following red cell exchange for malaria. *J Clin Apher*. 2011;26(6): 315-19.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Transfusion Medicine, Mahatma Gandhi Medical College and Research Institute, SBV, Pillaiyarkuppam, Puducherry, India.
2. Associate Professor, Department of Pathology, VMKV Medical College, Seeragapadi, Salem, Tamil Nadu, India.
3. Consultant Hematologist, MIOT International Hospital, Chennai, India.
4. Associate Professor, Department of Pathology, VMKV Medical College, Seeragapadi, Salem, Tamil Nadu, India.
5. Associate Professor, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, SBV, Pillaiyarkuppam, Puducherry, India.
6. Lt col- Graded Specialist Anesthesia, AMC, 425 FD Hospital, Poonch.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. M. Joshua Daniel,
Associate Professor, Department of Transfusion Medicine, Mahatma Gandhi Medical College and Research Institute,
SBV, Pillaiyarkuppam, Puducherry-607402, India.
E-mail: drjoshuadaniel@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 10, 2015**
Date of Peer Review: **Sep 03, 2015**
Date of Acceptance: **Feb 24, 2016**
Date of Publishing: **May 01, 2016**