Video Article

Continuous Manual Exchange Transfusion for Patients with Sickle Cell Disease: An Efficient Method to Avoid Iron Overload

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URL: <https://www.jove.com/video/55172>

DOI: [doi:10.3791/55172](https://doi.org/10.3791/55172)

Keywords: Medicine, Issue 121, transfusion, sickle cell disease, exchange transfusion, children, iron overload, red blood cell

Date Published: 3/14/2017

Citation: Koehl, B., Missud, F., Holvoet, L., Ithier, G., Sakalian-Black, O., Haouari, Z., Lesprit, E., Baruchel, A., Benkerrou, M. Continuous Manual Exchange Transfusion for Patients with Sickle Cell Disease: An Efficient Method to Avoid Iron Overload. *J. Vis. Exp.* (121), e55172, doi:10.3791/55172 (2017).

Abstract

Children with sickle cell anemia (SCA) may be at risk of cerebral vasculopathy and strokes, which can be prevented by chronic transfusion programs. Repeated transfusions of packed red blood cells (PRBCs) is currently the simplest and most used technique for chronic transfusion programs. However, iron overload is one of the major side effects of this therapy. More developed methods exist, notably the apheresis of RBC (erythrapheresis), which is currently the safest and most efficient method. However, it is costly, complicated, and cannot be implemented everywhere, nor is it suitable for all patients. Manual exchange transfusions combine one or more manual phlebotomies with a PRBC transfusion.

At the Reference Center of Sickle Cell Disease, we set up a continuous method of manual exchange transfusion that is feasible for all hospital settings, demands no specific equipment, and is widely applicable. In terms of HbS decrease, stroke prevention, and iron overload prevention, this method showed comparable efficiency to erythrapheresis. In cases where erythrapheresis is not available, this method can be a good alternative for patients and care centers.

Video Link

The video component of this article can be found at <https://www.jove.com/video/55172/>

Introduction

A single point mutation in the β -globin gene is responsible for the production of abnormal hemoglobin (hemoglobin S, HbS). This causes sickle cell anemia (SCA), one of the most common diseases worldwide¹. SCA patients' acute symptoms and some chronic complications can be treated by the transfusion of packed red blood cells (PRBCs). Indeed, the transfusion of normal RBCs corrects the anemia while diluting the sickle RBCs. As a result, it can increase the oxygen transport capacity while decreasing hemolysis and vaso-occlusive events. To avoid chronic complications or to treat patients with acute complications, transfusion combined with the depletion of sickle RBCs, either by phlebotomy or by erythrapheresis, is an effective way to limit the dangerous increase in hemoglobin and blood viscosity while reducing the number of circulating SS RBCs².

One of the main causes of psychomotor handicaps and neurocognitive deficiencies in children with SCA³ is cerebral vasculopathy, a devastating complication of this disease. In SCA children with abnormally high velocities on transcranial Doppler, chronic transfusions are effective in preventing the occurrence of the first stroke⁴. To reduce the risk of recurrence in patients that have already suffered from an ischemic stroke, transfusion therapy is the most adequate method⁵. In the case of chronic therapy, RBC exchange transfusion is better than simple RBC transfusion, as it removes sickle cells and adds normal cells while reducing blood viscosity and limiting iron overload. Nonetheless, simple RBC transfusion is still widely used as a treatment for cerebral macro-vasculopathy. While it rapidly leads to iron overload⁴, this choice is often made because it is technically simple and maximizes the number of patients in transfusion care. Indeed, even if erythrapheresis has been reported to be the most efficient method for the chronic transfusion of SCA patients, it cannot be implemented everywhere; it is not suitable for all patients, especially young children; and it necessitates specific and expensive equipment.

For more than 20 years now, we have been treating SCA children demonstrating cerebral vasculopathy and who were temporarily ineligible for erythrapheresis with a continuous manual exchange transfusion (MET) method. In 2016, our team published a follow-up of patients that had undergone continuous manual transfusion for several years, showing that our method is associated with a satisfactory HbS decrease, efficient stroke prevention, and a limitation of iron overload comparable to that of erythrapheresis⁶. A session of MET can be carried out in any hospital

environment without specific apparatuses and by using the same volume needed for erythrapheresis. A notable advantage of this technique is that it could help prevent, or at least diminish, side effects (particularly iron overload) linked to repeated transfusions in patients who are not able to undergo erythrapheresis. The aim of this article is to describe, step by step, how to perform a session of continuous MET in order to allow the medical centers that do not have any apheresis machines, or that have patients who are not eligible for erythrapheresis, to use this method for their SCD patients, especially children.

Protocol

The protocol follows the guidelines of the hospital ethics committee. There are 3 steps in the exchange sessions: patient preparation; initial isovolemic phlebotomy (if appropriate); and whole-blood exchange, consisting of several cycles, or continuous whole-blood phlebotomy, which is associated with the infusion of diluted PRBCs. Depending of the Hb level of the patient, a fourth step of intermediary isovolemic phlebotomy can be added midway through the exchange stage. At the start of the session, all of the necessary material (packed RBCs and 5% serum albumin) must be ready. Also, each step must be prepared in advance. Other than a precision scale and double venous access, no specific equipment is required. However, it is imperative to have **constant medical supervision** over the whole procedure, and even more so if the exchange volume is high.

1. Patient Installation

1. Carry out laboratory tests prior to starting the exchange transfusion session. Perform them on the same day, less than 24 h before the session. Do not perform the tests before a physician checks the results of the following tests.
NOTE: The tests include a complete blood count, reticulocyte count, HbS rate measurement, indirect antiglobulin test (IAT), calcemia and electrolytes measurement, and liver function and coagulation tests, routinely performed by the hospital's hematology and biochemistry units.
2. Have the physician perform a thorough and complete physical examination of the patient, and pay specific attention to hemodynamic parameters such as heart rate, blood pressure, respiratory rate, and oxygen saturation. Obtain a recent body weight. Maintain an oxygen saturation >98% throughout the exchange session. To do so, administer patients with 1 L of oxygen via a nasal cannula while in supine position with the feet slightly raised.

2. Blood Product Preparation

1. Calculate and obtain the initial phlebotomy volume (see **Table 1**). For example, if the initial Hb rate of the patient for the session is 10 g/dL, bleed 12 mL/kg of blood in 60 min. For a patient of 30 kg, bleed 360 mL of blood (these are appropriate volumes).
NOTE: An Hb rate of around 8 g/dL prior to the exchange transfusion must be reached because the initial phlebotomy volume is calculated based on the patient's Hb level (**Table 1**).
No prior phlebotomy is required if the Hb level is below 8.5 g/dL. The initial phlebotomy must not exceed 5 mL/kg of body weight in the case of patients who have suffered from a recent stroke (within the last 3 months).

Initial Hb level (g/dL)	10	9.5	9	8.5
Volume to be bled (mL/kg)	12	10	8	5
Minimal duration of phlebotomy (min)	60	60	45	20

Table 1. Calculation of the Volume of the Initial Phlebotomy During Manual Exchange Transfusion.

The initial phlebotomy volume is calculated based on the patient's initial Hb level, with the goal of reaching an Hb rate around 8 g/dL prior to the exchange transfusion. The duration of the initial bleeding depends on the volume of the phlebotomy. No prior phlebotomy is required if the Hb level is below 8.5 g/dL. The initial phlebotomy must not exceed 5 mL/kg of body weight in the case of patients who have suffered from a recent stroke.

2. Calculate the exchange volume; the total exchange volume is 35 - 45 mL/kg of body weight (e.g., if the patient is a child of 30 kg, the volume of the exchange transfusion will be around 1,200 mL).
NOTE: This volume is both the volume of blood that will bleed during the exchange step and the volume of diluted PRBCs that will be transfused to the patient during the exchange step. The final volume depends on the volume of the exchange transfusion, calculated with the body weight of the patient.
3. Obtain the appropriate volume of 5% serum albumin solution (from the pharmacy) so that it is ready for use at the beginning of the session. Calculate the required volume: 50 - 100 mL to infuse prior to initiating the phlebotomy, plus the same volume during the initial phlebotomy to compensate for bleeding, plus 1/3 of the exchange volume to dilute the PRBCs.
4. Obtain the appropriate volume of phenotypically matched PRBCs (i.e., 2/3 of the calculated exchange volume from the blood bank).
5. Reduce the hematocrit of the PRBCs from 60% to 40% by diluting the PRBCs with 5% serum albumin.
NOTE: The dilution must be performed at the blood bank in a new blood bag. If this is not possible, use a 3-way tap to simultaneously transfuse the PRBCs and the 5% serum albumin and respect the flow proportions of 2/3 for the PRBCs and 1/3 for the albumin solution.

3. Patient Preparation

1. Prepare two peripheral venous lines on two different limbs, one for the phlebotomy and one for the infusion of the albumin solution and PRBCs; the venous line for phlebotomy necessitates sufficient blood flow, and the one for infusion requires standard blood flow. Use a single venous access for infusion and phlebotomy with a 3-way tap if venous access is seriously limited.

- Administer 1 g of calcium per os to the patient before and after the exchange session; this prevents the occurrence of hypocalcemia due to the presence of a calcium chelating anticoagulant in the transfusion bags.

4. First Step of MET: Isovolemic Phlebotomy, if Appropriate

- Start the infusion of 5% albumin on one venous access. After infusing about 20 - 50 mL of albumin solution, begin phlebotomy on the second venous access.
- To perform the bleeding, install a peripheral intravenous access connected to an empty bleeding bag in the patient's arm. Place the bag below the level of the patient's bed. Observe the venous blood gradually fill the bleeding bag.
 - If the blood flow is too low, lift up the patient's bed (or lower the bleeding bag) in order to increase the height difference between the arm and the bleeding bag, thus increasing the blood flow. Optionally, in case of very low blood flow, have the nurse draw blood manually with a 50-mL syringe using a 3-way tap placed on the venous line.

NOTE: The flow of the phlebotomy must be the same as the flow of the infusion so as to strictly maintain the isovolemic balance.
- Weigh the bleeding bag on a precision scale during the phlebotomy in order to adapt the infusion flow in real time to compensate for the volume bled.

NOTE: If no scale is available or if there is only a single venous access, bleed 20 mL of blood each time 20 mL of albumin is infused.
- At the end of the phlebotomy step, check the Hb levels using an Hb point-of-care test according to the manufacturer's instructions and make sure that it is around 8 g/dL.
- Monitor the patients every 5 min during the initial isovolemic phlebotomy step. Stop the phlebotomy if clinical changes relevant to the patient's age are observed.

5. Second Step of MET: Isovolemic Exchange Transfusion

- For safety reasons, start the transfusion of diluted PRBCs first. Transfuse the first 20 mL of blood and then start the phlebotomy. The planned total volume of the phlebotomy at this step is the same as the volume of the transfusion (35 - 45 mL/kg of body weight).

NOTE: The rate of the phlebotomy must be the same as the infusion rate of the diluted PRBCs, following the same method as in the previous step (i.e., weigh on a precision scale or alternate 20 mL cycles).
- Midway through the exchange step, check the Hb levels, as described in step 4.3. If the level is > 9.5 g/dL, perform an additional round of phlebotomy. If not, continue the exchange transfusion.
- Monitor the patients every 15 min during the exchange transfusion step; a nurse must keep a close watch on the occurrence of any clinical and/or hemodynamic changes.

6. Additional Phlebotomy

- Perform an additional bleeding phlebotomy (see step 4.1) if the Hb levels midway through the exchange step are > 9.5 g/dL, as there is a risk of reaching a too-high level of Hb at the end of the session.

NOTE: The volume of the additional phlebotomy step depends on the Hb level (**Table 2**).
Compensate with a 5% albumin infusion, as described above, in order to keep the additional phlebotomy isovolemic, just like in the other steps.

Midway Hb level (g/dL)	10.5	10	9.5
Volume to be bled (mL/kg)	8	6	3
Minimal duration of phlebotomy (min)	30	20	15

Table 2. Calculation of the Volume of the Intermediate Phlebotomy During Manual Exchange Transfusion.

Perform an additional phlebotomy if the Hb level midway through the exchange step is higher than 9.5 g/dL, as there is a risk of reaching a too-high level of Hb at the end of the session. The duration of the initial bleeding still depends on the volume of the phlebotomy.

- Just like the initial phlebotomy, monitor the patients every 5 min. Stop the phlebotomy immediately if clinical changes occur.
- After the additional phlebotomy, check the Hb levels using an Hb point-of-care test, and then continue the exchange procedure using the same method.

7. Final Laboratory Test

- At the end of the exchange transfusion, perform laboratory tests for Hb, HbS, and calcemia. Do not allow the patient to leave before the results of the laboratory tests (or at least the Hb levels) have been checked by a physician.

NOTE: Overall, while the duration of the procedure varies depending on the volume to bleed and to exchange, it lasts around 4 h, on average.

Representative Results

Here, we will compare the safety, cost, and efficiency of the MET method with erythrapheresis⁶, which is the most effective method to decrease the percentage of HbS in SCD patients. To do so, we recorded 1,353 transfusion exchange sessions in the Reference Center of SCD, including 333 sessions of AET and 1,020 sessions of MET, all in SCD children suffering from cerebral vasculopathy and/or strokes. For patients, we chose MET in children with a body weight under 25 kg and/or in those lacking high blood flow venous access, which is required for erythrapheresis (sufficient size of peripheral veins, arterio-venous fistula, or indwelling central venous catheter). Conversely, AET was systematically offered to children with a body weight over 25 kg, as long as an appropriate venous access was available.

Regarding the efficiency of the exchange, we have observed a median HbS decrease of 18.8% [15.2; 23.0] after an MET session *versus* 21.5% [17.8; 25.1] after an erythrapheresis session, with a slightly higher PRBC consumption with the manual method (31.7 mL/kg [28.0; 35.2] per MET session *versus* 29.2 mL/kg [26.7; 32.7] per erythrapheresis session). Because HbS decrease is the main aim of a transfusion session for SCA patients, these results show good efficiency and allow a mean interval of 5 weeks between the transfusion sessions, both for MET and for erythrapheresis. Iron overload, a major complication of chronic transfusion, is directly linked to the transfusion method and duration. Lee *et al.* have described in the STOP study a cohort of SCA patients undergoing repeated transfusions to treat cerebral vasculopathy. In this study, iron overload was substantial, with a mean ferritin level of 1,804 µg/L after 12 months of chronic transfusions, reaching 2,509 µg/L after 24 months⁴. Erythrapheresis is recognized as an efficient method to limit iron overload for SCA patients undergoing exchange transfusion⁷. As expected, in the cohort, children who received only erythrapheresis actually had very stable ferritinemia (**Figure 1**). If we consider patients who only received MET with the continuous method, we observed a quite comparable stability of ferritinemia, witnessing an almost equivalent control of iron overload as with erythrapheresis (**Figure 1**).

Concerning the side effects of both methods, in this study, we only reported six events described as vagal fainting out of the 1,353 sessions (3 during MET and 3 during erythrapheresis). No serious hemodynamic events were reported during any session, thus making us consider both of these methods as safe for the patients.

Finally, in order to compare the costs of an erythrapheresis session with an MET session, we will consider a 30-kg child who, at the start of the session, has an Hb level of 9 g/dL. Taking into account disposable goods (including the cost of PRBCs and solutions), an MET session for this patient would cost approximately 601 euros, on top of the presence of a nurse for 4 h. On the other hand, erythrapheresis requires only half a nurse (*i.e.*, one nurse for two patients), but it necessitates closer medical supervision for a duration of 3 h and will cost approximately 628 euros. All in all, the two methods are comparable in terms of disposable goods and staff expenses. Finally, the cost of equipment is 8,886 euros per year for erythrapheresis *versus* 120 euros per year for MET (*i.e.*, 74 times higher for erythrapheresis, based on the assumption that the lifespans of the apheresis machine and other equipment (precision scale and infusion syringe) are 10 years).

Figure 1. Comparison of Iron Overload During MET and Erythrapheresis Programs. Results from SCA patients undergoing chronic transfusions are taken from Adams *et al.* Results from SCA patients undergoing MET and erythrapheresis are taken from previously published work (Koehl *et al.*, 2016). Ferritinemias are expressed as mean $\pm$ SD. [Please click here to view a larger version of this figure.](#)

Discussion

The risk associated with this procedure is an unexpected misbalance between the phlebotomy and the transfusion, which can have dangerous consequences. A rapid depletion will lead to hypovolemia and acute anemia, while an excess transfusion without bleeding will lead to a dangerous increase in blood viscosity. In both cases, SCA patients could suffer from vaso-occlusive complications, as well as strokes. For this reason, one nurse must be dedicated to each patient and stay at his bedside during the whole procedure. There must also be close medical supervision, and a physician needs to be quickly available in case of any problem. Any unexpected hemodynamic modifications necessitate the intervention of the medical staff and the interruption of the procedure until the patient's condition is stable. To avoid any incidents, the calculation of the phlebotomy volume, of the albumin compensation volume, and of the exchange transfusion volume must be performed very cautiously before starting the session and should be double-checked if necessary. Everything must be ready at the patient's bedside at the beginning of the procedure (PRBC and albumin), and the venous access must be regularly checked by the nurse. Finally, the hemoglobin levels before, midway, and at the end of the session must be checked and approved by a physician.

One of the limitations of this method is the necessity of obtaining two venous accesses for each session. Even though the technique can be carried out with only one venous access (by alternating short 20-mL bleeding/transfusion cycles), the preferable scenario is to have 2 large

caliber veins, one on each arm. The other limitation of this technique is that, despite the initial control of ferritinemia, there is still a risk of iron overload in the two years following the use of this method. Indeed, by looking closely at the ferritin levels of the patients, we can observe that the manual exchanges lead, to a certain extent, to iron overload. In a previous study, we reported that after a mean duration of 51 months of erythrapheresis, the ferritin level remained stable (from 586 µg/L [491; 709] to 609 µg/L [221; 1,064]) without iron chelation therapy. However, after a mean duration of 39 months of MET, the ferritin level increased from 327 µg/L [206; 535] to 802 µg/L [146; 873]⁶ without iron chelation therapy, which remains much lower than that of repeated transfusions. Nevertheless, we must consider that the manual method should ideally be replaced by erythrapheresis if the transfusion exchange program lasts more than 2 years. While awaiting the availability of erythrapheresis, MET is highly effective and represents a solid alternative. When compared to erythrapheresis, this technique has a similar efficiency in terms of HbS decrease per session, despite a slightly higher PRBC consumption (with a difference of about 2.5 mL/kg per session). Our procedure is feasible for all patients, regardless of age or weight. For children under 10 kg, the main limitation would probably be the venous access, which can be replaced by arterial access if needed for an emergency exchange transfusion (in case of acute stroke, for example).

The most notable difference between the two techniques lies within the cost of equipment—which is much higher for erythrapheresis—the cost of human supervision and disposable goods per session being very similar. The choice of transfusion method and duration are parameters that directly influence the occurrence of iron overload⁷, which the manual method was able to limit. Preventing iron overload during transfusion programs rather than treating it is a major health goal in SCA patients undergoing a chronic transfusion program. Published data suggests that the long-term effects of iron overload can potentially be severe. These include hepatic cirrhosis (in about 1/3 of cases in adults after 4 years of transfusions)⁸, cardiac damage, diabetes, hypogonadism, and pulmonary hypertension⁹. For children, the outcome of major iron overload is yet to be determined. When chelation therapy is prescribed, only half of the patients treated are sensitive to it, as reported by us⁶ and others¹⁰. The limited efficacy of this treatment suggests poor treatment compliance¹⁰ and treatment discontinuation due to the side effects attributed to iron chelation therapy. An appropriate exchange transfusion method thus appears essential, as chelation therapy has limited efficacy.

In conclusion, while erythrapheresis appears to be the safest and most effective method for chronic transfusion therapy in SCA, its technical and financial features are not particularly advantageous. The continuous MET method is widely applicable, requires no specific equipment, and may be safe and effective in limiting iron overload, whereas chronic simple transfusions control this parameter less effectively. For children who will have to undergo a transfusion program for several years, this appears as an important challenge. The continuous MET method is a good alternative for patients awaiting erythrapheresis, and it should be preferred to simple transfusions.

Disclosures

The authors have nothing to disclose.

Acknowledgements

We would like to thank the patients and parents for their continuous support; the caregivers for their dedication; Pr Bierling, director of the French Blood Bank in the Paris area, for his support of the collaborative work between our hospital and his team to develop the continuous manual exchange transfusion method; and the University Paris Diderot and the hospital Robert-Debré for their support.

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