Erythrocytapheresis vs continuous Manual Exchange Transfusion to treat cerebral macrovasculopathy in children with sickle cell anemia

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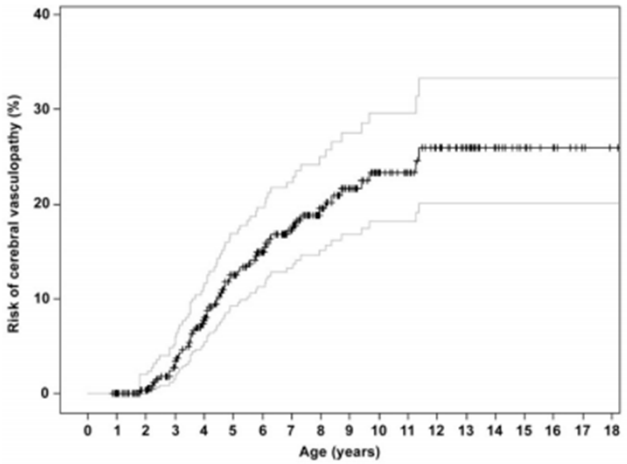
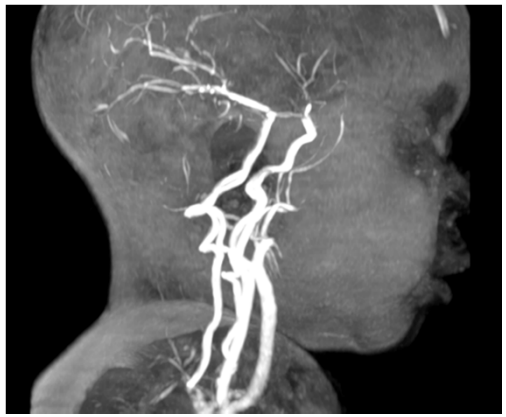
Cerebral vasculopathy in children with SCA

- Cumulative risk of **cerebral vasculopathy** is **26%** by the age of 18 years
- Cumulative risk of **stroke** is **11,5%** by the age of 18 years
- Major source of psychomotor handicap in children with SCA



Cumulative risk of cerebral vasculopathy in children with SCA (Sommet et al, 2016)

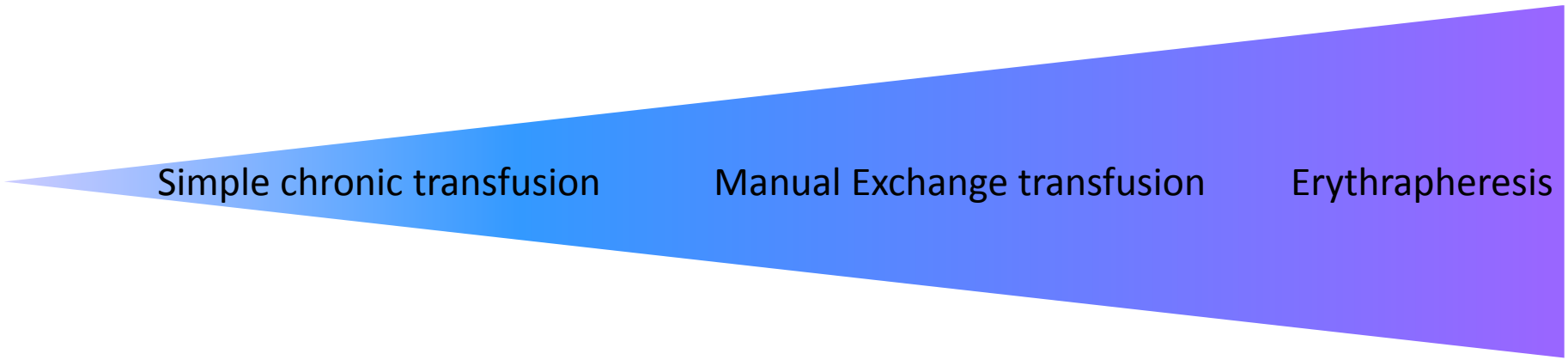
- Abnormally high blood flow velocities detected by Transcranial Doppler Ultrasonography (TCD) are predictive of high primary ischemic stroke risk.
- In 1998, the Stroke Prevention (STOP) trial demonstrated that **monthly blood transfusions**, with the objective to maintain **HbS level between 30-40%**, could **reduce the risk of ischemic stroke by 90%** in SCD children with abnormal TCD velocities.



Aim of the transfusion program

- Depletion of Red Blood Cells (RBCs) with HbS (Decrease of the HbS rate by phlebotomy or erythrapheresis
- Transfusion of normal RBCs

- Avoid increase of blood viscosity
- Avoid volemic variation during the exchange transfusion
- Limit iron overload



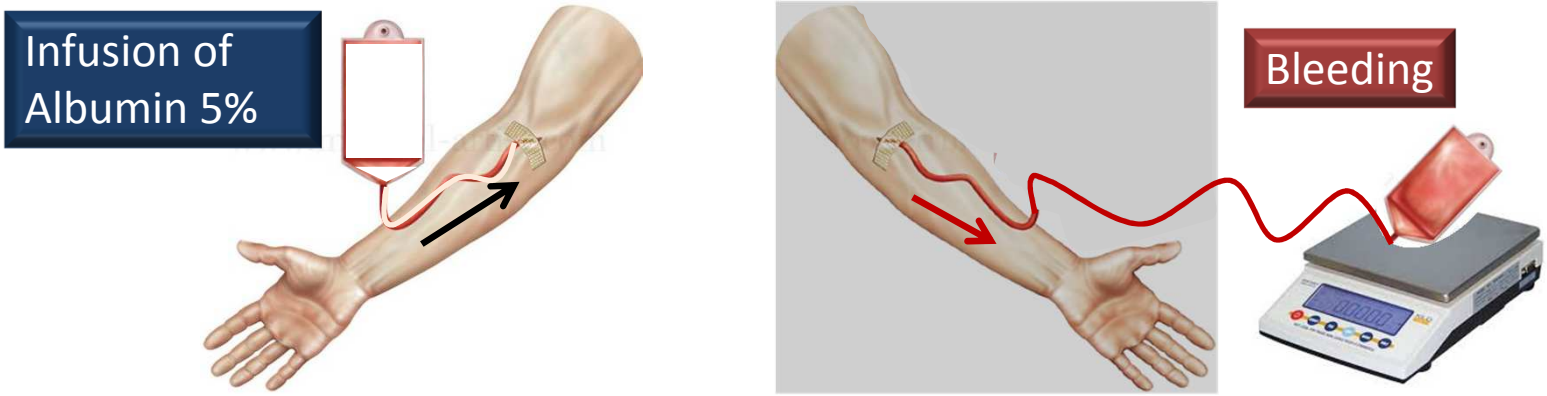
Patients & Methods

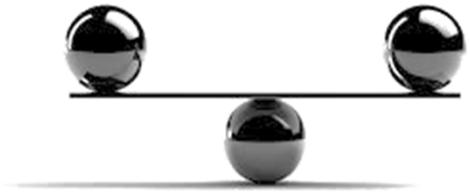
- From 2 to 16 years of age, **annual screening** by Transcranial Doppler Ultrasonography (TCD)
- If **abnormally high velocity** (>200 cm/sec) in at least one cerebral artery on TCD, and/or stroke documented by MRI/MRA: **chronic exchange transfusion program**
- Retrospectively record of all the patients in our center:
  - had cerebral macro-vasculopathy
  - underwent exchange transfusion for this indication
  - were included in the transfusion program for a **minimum of 12 months**
- Among them, some had MET, MET then Erythrapheresis or directly Erythrapheresis
- Indication for **Erythrapheresis: body weight > 25 kg + high blood flow venous access**

Continuous Manual Exchange Transfusion

1st step: **Initial phlebotomy**, to reach Hb rate=8g/dl

- Depends on the Hb rate of the patient
- **5-10 ml/kg, in 20-60 min**
- Compensated by the infusion of the same volume of Albumin 5%



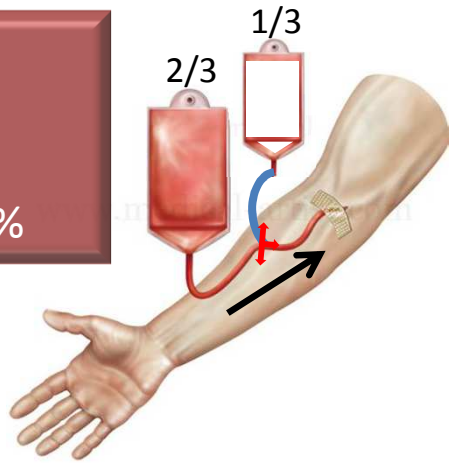


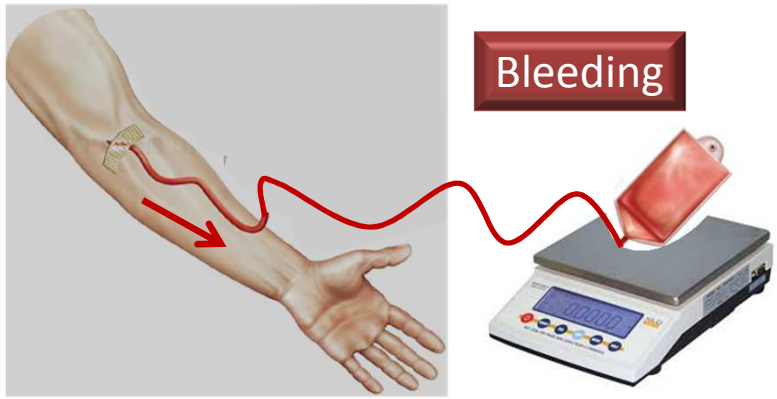
Continuous Manual Exchange Transfusion

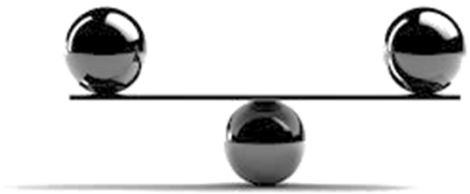
2nd step: **Continuous Manual exchange**

- Transfusion of **35-45ml/kg** of Packed Red Blood Cells **DILUTED** with Albumin 5% to reach 40% Ht
- **Simultaneous bleeding** of the same volume (35-45 ml/kg)

Infusion of
2/3 Packed Red Blood Cells
+ 1/3 Albumin 5%



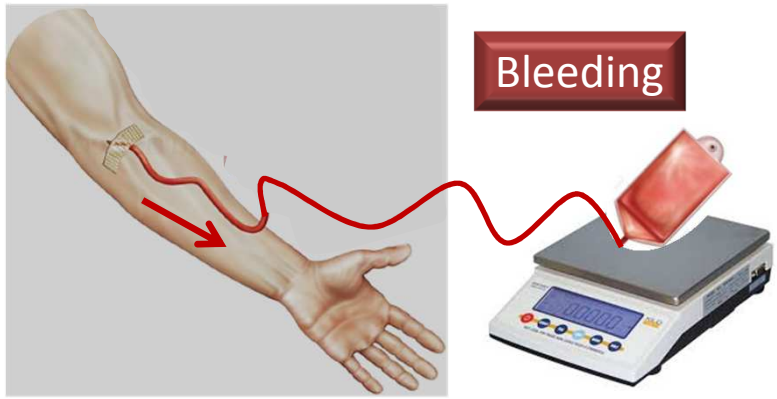


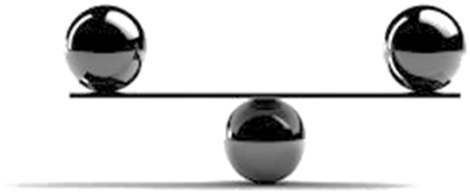


Continuous Manual Exchange Transfusion

3rd step: Supplementary bleeding

- If Hb > 9,5 g/dl at midway through the exchange step
- **Bleeding of 5-10 ml/kg, in 15-30 min**
- **Compensated** the same volume of Albumin 5%





Results

39 patients, **1353 exchange transfusion sessions (1020 MET, 333 Erythraphéresis)**

- SR=1,4
- median age = 5,9 yo
- median follow-up = 41 months
- genotype HbSS

	MET sessions	AET sessions	p (univariate analysis)	p (multivariate analysis)
Nombre of sessions recorded	1020	333		
Packed-RBC volume transfused per session (ml/kg)	31.7 [28.0 ; 35.2]	29.2 [26.7 ; 32.7]	0.01	0.02
Interval beetween 2 transfusionnal sessions (days)	35 [29;39]	36 [33;42]	0,45	-
Decrease of HbS rate per session (%)	18.8 [15.2 ; 23.0]	21.5 [17.8 ; 25.1]	0.04	< 0.0001

Comparison of cost

	MET	AET
Nurse	1 for 1 patient	1 for 2 patients
Physician	1 for 4 patients	1 for 3 patients
Approximative duration of a session	4 hours	3 hours
precision scale	45,00 €	-
COBE® Spectra Apheresis System	-	43 450,00 €
Annual maintenance		4 541,00 €
Infusion Syringe Pump System (Grasby™)	1 152,00 €	-
Packed-RBC	550,00 €	507,00 €
5% albumine solution	18,90 €	-
Saline solution	-	1,40 €
Calcium (per os), 2x1g	0,84 €	-
Calcium gluconate (intravenous), 2g	-	0,80 €
Cannula (x2)	1,66 €	1,66 €
Transfusion tubing (x2)	4,90 €	-
Bleeding bag (x4)	19,82 €	-
3 Way tap	0,33 €	-
Apheresis kit for COBE® Spectra	-	116,95 €
Syringe (x4)	0,52 €	-
Hemoglobin test (HemoCue®)	3,84 €	-
Estimated Cost by session (without material investment)	**600,81 €**	**627,81 €**

- Investment and maintenance **74x higher for Erythrapheresis**
- Similar cost by session

Iron overload

In the « STOP » study (SCA patients with abnormal TCD undergoing chronic transfusion- *Lee MT, 2006*)

→ **100% patients had iron overload after 12 months**

→ **Mean ferritinemia after 12 months= 1804 µg/L**

→ **Mean ferritinemia after 24 months =2509 µg/L**

Median duration of the program (months)	**39** [25 ; 53]	**55** [42 ; 72]
Mean ferritinaemia (µg/L)	**Exclusive MET**	**Exclusive Erythrapheresis**
At the onset of the program	**327** [206 ; 535]	**586** [491 ; 709]
After 12 months of program	**310** [156 ; 873]	**547** [250 ; 951]
After 24 months of program	**312** [152 ; 994]	**638** [227 ; 1233]
At the end of the follow-up	**802** [146 ; 873]	**609** [221 ; 1064]

- Overall, **38%** (n=15) developed **iron overload** (ferritin> 1000 µg/L)
- Efficiency of chelation therapy (ferritin< 1000 µg/L) in **50% of the patients**

Discussion

- Our continuous MET is comparable to Erythrapheresis in terms of **HbS decrease by session** (21,5 vs18,8%)
- Our method of continuous MET needs **slightly more PRBC than Erythrapheresis** (+2.5 mL/kg per session).
- Both methods **minimize allo-immunization** (8% IAT positive in the all cohort)
- **Good clinical tolerance** with very few adverse events recorded in both methods.
- Iron overload, directly linked to the transfusion method and its duration, is mostly controlled with our continuous method of MET: **median ferritin almost unchanged after 24 months.**
  - ✓ Preventing iron overload during transfusion programs is crucial for SCA patients
  - ✓ Appropriate exchange transfusion method can **protect children** against **long-term side effects** of **transfusion-induced hemochromatosis**.
  - ✓ Especially since the iron **chelation therapy** has **limited efficiency**: side effects, poor treatment compliance

Conclusion

Erythrocytapheresis is probably the safest and most effective method for chronic transfusion therapy in SCA

BUT…

…For technical and financial reasons, it is not widely implemented.

Our continuous MET method can be widely utilizable for **all children** with **no specific equipment** and that may be **efficient, safe** and effective in **limiting iron overload.**

It should be **preferred to simple transfusions** and is a good alternative for patients awaiting initiation of AET.

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Venous access in the Erythrapheresis group:

- 41% (n=16/39) on peripheral venous access
- 59% of patients (n=23/39) on Central Venous Catheter or Arteriovenous Fistula

Venous access in the MET group:

- 50% (n=15/39) on peripheral venous access
- 50% of patients (n=14/39) on Central Venous Catheter or Arteriovenous Fistula