Erythropoietin to Prevent Unnecessary Transfusions in Patients with Cyanotic CHD - A Prospective Control Trial

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Rady Children's Hospital – San Diego
and University of California, San Diego

Parent Informed Consent

Erythropoietin to Prevent Unnecessary Transfusions In Patients With Cyanotic Congenital Heart Disease – A Prospective Randomized Control Trial

This is a research study. Research studies include only subjects who choose to take part. You are being asked to let your child take part in this study because he/she has cyanotic congenital heart disease. Please take your time to make your decision. Discuss it with your child and family. Be sure to ask any questions that you may have.

STUDY INVESTIGATOR AND SPONSOR

Investigator(s): David Werho, MD

Sponsor: Division of Cardiology, Department of Pediatrics
Rady Children's Academic Enrichment Fund

WHY IS THIS STUDY BEING DONE?

Cyanotic congenital cardiac patients require higher hemoglobin concentrations (red blood cell levels) for optimal delivery of oxygen to the body. Erythropoietin (EPO) is a hormone that the human body makes to stimulate the production of red blood cells. It has been given to help increase red blood cell levels in patients with low counts. Giving EPO and iron may prevent and/or decrease the number of blood transfusions needed in this population. We will study if giving EPO and iron is safe, tolerated, and if it decreases the need for blood transfusions.

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

The experimental part of this study is giving EPO and iron to prevent blood transfusions. This medication has been shown in some patients to prevent blood transfusions in high

risk individuals. EPO injections are FDA approved for patients with cancer and chronic renal failure, but the use in this population has not been approved. This is a randomized controlled trial.

Your child will be assigned by chance to a study group (1 group will receive the study medication, and one will be observed). Your child has an equal chance of being assigned to Group 1 or 2.

Group 1 (treatment group):

- Patients in the treatment group will receive weekly EPO injections and iron supplementation for 6 weeks starting before 8 weeks of age, 1 week after their first procedure (surgery or heart catheterization). They will be followed for 14 weeks.

Group 2 (control group):

- Patients in the treatment group will not receive any extra intervention outside of standard of care. They will receive iron supplementation for 6 weeks starting before 8 weeks of age, 1 week after their first procedure (surgery or heart catheterization). They will be followed for 14 weeks.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We will be enrolling up to 60 subjects to be in this study with a minimum of 20 subjects in each group.

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Your child will be in the study for 14 weeks.

You can stop your child's participation at any time. However, if you decide to stop your child from participating in the study, we encourage you to talk to the research doctor.

WHAT IS INVOLVED IN THE STUDY?

This is what will happen if your child participates in this study:

Group 1 (treatment group):

- Patients in the treatment group will receive weekly EPO injections for 6 weeks starting before 8 weeks of age (at least one week after their surgery) at 500 units/kg/injection (SQ) and oral ferrous sulfate (iron) at 3 mg/kg/day of elemental iron, which is an accepted treatment for anemia and prevention of anemia.
- If oral iron cannot be tolerated and there is laboratory evidence of iron deficiency, intravenous iron will be used to replace iron stores
- All injections will be administered with a weekly visit in the cardiology clinic or in the hospital if the infant remains hospitalized by a member of the care team.
- Iron studies (Serum iron, ferritin, total iron binding capacity) will be obtained at

baseline and at week 14 with the final lab draw. If intravenous iron is used for replacement, iron studies will be repeated after replacement to ensure adequate iron stores.

- A complete blood count will be obtained prior to initiation of treatment, after the 1st dose and weekly during weeks 2 through 7 of the study (to confirm that there is no over-shoot, i.e. that the hemoglobin is increased to an abnormally elevated level), and week 14. They will be assessed at these time intervals. You will not be billed for clinic visits and laboratory tests performed as part of the research study.
- Any unused blood samples from the baseline through week 14 draw of the study will be banked for antibody testing if needed.

Group 2 (non-treatment group):

- Patients in the non-treatment group will not receive injections. They will be started on oral ferrous sulfate (iron) at 3 mg/kg/day of elemental iron.
- If oral iron cannot be tolerated and there is laboratory evidence of iron deficiency, intravenous iron will be used to replace iron stores
- Iron studies (Serum iron, ferritin, total iron binding capacity) will be obtained at baseline and at week 14 with the final lab draw. If intravenous iron is used for replacement, iron studies will be repeated after replacement to ensure adequate iron stores.
- They will be assessed at baseline for enrollment in the study, at week 7 and 14 after enrollment. A complete blood count (lab draw or heel stick) will be obtained at these intervals for comparison with the treatment group.
- Additional visits and labs will be done only as indicated by the clinician primarily taking care of the infant.
- Any unused blood samples from the baseline through week 14 draw of the study will be banked for antibody testing if needed.

If you consent to this study, there is a chance that your child may not become eligible for enrollment if his/her hematocrit never falls below the minimum threshold. In this case, your child will continue to receive the standard care during their hospitalization.

WHAT ARE THE RISKS OF THE STUDY?

The most common side effects seen with erythropoietin injections per the prescribing information are:

- ✓ Injection site reactions and pain
- ✓ GI upset symptoms (nausea, vomiting)
- ✓ Fever
- ✓ Swelling
- ✓ Itching

Over 2200 neonates have been a part of studies involving EPO. No significant adverse events have been reported in the literature with neonates receiving EPO.

Some possible adverse effects for neonates include:

- ✓ Iron deficiency (which can be prevented by ensuring adequate supplementation).
- ✓ Low white blood cell counts (self-correcting after stopping treatment) may occasionally occur.
- ✓ Low platelet counts
- ✓ High platelet counts
- ✓ High blood pressure
- ✓ Early use has been associated with more severe eye disease (retinopathy of prematurity) if given in extreme premature neonates.

Side effects seen less often (in adults) are:

- ✓ "Over-shoot" of target red blood cell levels (Abnormally elevated number of red blood cells)
- ✓ Decreases or increases in the production of other blood cell types
- ✓ High blood pressure
- ✓ Cough
- ✓ Soreness of mouth
- ✓ Headache
- ✓ Dizziness
- ✓ Low potassium levels
- ✓ Weight loss
- ✓ Transmission of viral disease
- ✓ Joint, muscle, or bone pain
- ✓ Seizures
- ✓ High blood sugar
- ✓ Insomnia
- ✓ Depression
- ✓ Trouble swallowing
- ✓ Heart attacks
- ✓ Strokes
- ✓ Congestive heart failure: Failure of the heart to pump with normal efficiency
- ✓ Thrombosis of vascular access: Clotting of lines placed in blood vessels
- ✓ Other blood clotting events (i.e. DVT, Pulmonary embolism)
- ✓ Tumor progression or recurrence
- ✓ Serious Allergic reactions: vomiting, low blood pressure, swelling of the tongue and face, difficulty breathing, skin rash, hives
- ✓ Pure red cell aplasia: Failure of the body to make any red blood cells
- ✓ Antibodies to EPO

If your child has any illness or discomfort as a result of using the study drug call your study doctor immediately. If necessary, the study drug may be stopped and other therapy may

be started.

Your child will be assigned to a study group at random (by chance). Your child's assignment is based on chance rather than a medical decision made by the researchers. The study group to which your child is assigned to might not be the group you would prefer your child to be in. It might also prove to be less effective or have more side effects than the other study group(s), or other treatments available for your child's condition.

Possible side effects from blood drawing or heel stick include:

- Faintness
- Irritation of the vein, such as redness or swelling
- Pain
- Bruising or bleeding at the blood draw site.
- There is also a slight possibility of infection.
- Need for blood transfusions because of more frequent lab monitoring

If your child uses the numbing cream for blood draws there may be skin irritation, the skin may temporarily turn red, white or develop a rash.

Other risks in this study include the following:

- ✓ Your child's condition may not improve; it may stay the same; or it may worsen while participating in this study.
- ✓ There may be side effects or discomforts associated with this study, which are not yet known.
- ✓ The researchers in this study have determined to target a red blood cell level (hematocrit) that is higher than the recommended amount of 33% as listed in the prescribing label for EPO. The EPO prescribing information is based on and includes data of various adult populations which suggest that targeting a hematocrit level above 33% is associated with increased severe adverse events. Specifically, when higher targets of hematocrit levels of 42% were used in clinical trials, the risk of death, blood clotting events, and other adverse events were seen in the higher target groups, in adult patients with chronic kidney disease as well as cancer. This has not been replicated in pediatric studies especially neonates. There are some studies in pediatric patients showing that a higher hematocrit level may not be necessary to ensure adequate oxygen delivery to the body, however given what we know about "blue" (cyanotic) heart conditions, these patients require a hematocrit level of 40-45% to ensure adequate delivery of oxygen to the body. A blood transfusion is often considered when the hematocrit level is below 40% in this population in our practice. EPO has been used safely in premature infants, however safe hematocrit target levels in pediatric patients has not been well studied or well established. We will be targeting a hematocrit level between 40-45%.
- ✓ Possible risk of loss of confidentiality associated with participant study data. The study doctor and the study staff will take care to de-identify any information about your child, including using a subject number rather than your child's name, as one

of the ways that his/her personal information will be protected.

For more information about these risks and side effects, ask your child's study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be any direct benefit to your child by participating in the study. However knowledge can be obtained to help infants in the future as well as provide a platform for more research in this area.

WHAT OTHER OPTIONS ARE THERE?

The alternative to study participation is to not be included in the study. Your child will continue to have standard of care treatment without erythropoietin which may include blood transfusions, but will not be included in the study data. Your child's care will not be compromised.

WHAT ABOUT CONFIDENTIALITY?

Your child will be given a study identification (ID) number. All study records and questionnaires will be labeled with this number and not your child's name or other personal data. This information will be kept on a password-protected computer, will be kept separately from the study data, and will not be shared with researchers outside the study center.

While your child is in this study all related records may be made available to:

- The UCSD Institutional Review Board (for the protection of human subjects in research)
- Other regulatory agencies responsible for overseeing research, such as the federal Office for Human Research Protections
- The Food and Drug Administration (FDA)

A copy of this permission form, and the HIPAA authorization form that you will sign, will be placed in your child's medical record. Your child's records and information will not be released without your permission unless required by law.

Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

If the study results are published or presented, your child will not be identified.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as

required by U.S. Law. This Website will not include information that can identify your child. At most the Website will include a summary of the results. You can search this Website at anytime.

WHAT ARE THE COSTS?

Labs (CBC) during an inpatient hospitalization are a part of acceptable standard of care and you or your health plan/insurance company will have to pay for these. Outpatient clinic visits and labs (i.e. CBC) that are not considered part of acceptable standard of care and pertain to this research will be covered by the research study funds. You will not be billed for clinic visits and laboratory tests performed as part of the research study. The study drug erythropoietin will be supplied at no cost while your child takes part in this study

You and/or your health plan/insurance company will need to pay for all of the other costs of your child's condition not specifically related to the research.

WHAT IF YOUR CHILD IS INJURED IN THE STUDY?

If your child is injured as a direct result of participation in this research, Rady Children's Hospital – San Diego or the University of California will provide any medical care needed to treat those injuries. Neither Rady Children's Hospital – San Diego nor the University will provide any other form of compensation to you if your child is injured. You may call the Human Research Protections Program Office at (858) 246-4777 for more information about this, to inquire about your child's rights as a research subject or to report research-related problems.

WILL YOU OR YOUR CHILD BE COMPENSATED?

There is no compensation for participation and completion of this study.

WHO DO YOU CALL IF YOU OR YOUR CHILD HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury during business hours, contact the research study doctor:

Dr. David Werho at 858-966-5855

For questions after normal business hours or on weekends, please call **(858) 576-1700** and ask for the cardiology physician on call.

WHAT ARE YOUR CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to let your child take part or you or your child may choose to leave the study at any time. Your decision will not result in any

penalty or loss of benefits to which your child is entitled. If you have questions about your child's rights you may call:

University of California, San Diego
Human Research Protections Program
(858) 246-4777

You will be told about any new information that may affect your child's health, welfare, or willingness to stay in this study.

SIGNATURE AND CONSENT TO BE IN THE STUDY:

Your signature below means that you have read the above information about the study and have had a chance to ask questions to help you understand what your child will do in this study and how your child's information will be used.

You or your child can change your minds later if you want to. You will be given a copy of this consent form and a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

You agree to allow your child to participate in this research study.

_____ _____
NAME OF PARTICIPANT AGE

_____
PRINTED NAME OF PARENT OR GUARDIAN

_____ _____
SIGNATURE OF PARENT OR GUARDIAN DATE

_____
PRINTED NAME OF WITNESS (person explaining this form)

_____ _____
SIGNATURE OF WITNESS (person explaining this form) DATE

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to the following:

1. Be informed of the nature and purpose of the research.

2. Be given an explanation of all procedures to be followed and of any drug or device to be used.

3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.

4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.

5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.

9. Be given a copy of the signed and dated written consent form.

10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your child's rights as a research subject, please contact your research doctor or the UCSD Human Research Protections Program at (858) 246-4777.