COMBAT Research Study

Questions & Answers

What is the title of this research study?

The Control Of Massive Bleeding After Trauma (COMBAT): A prospective, randomized comparison of early fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid.

Why is this research study being conducted?

The purpose of this study is to see if giving thawed plasma earlier to trauma patients will help stop bleeding. Usually we give trauma patients AB-FP24 plasma in the hospital, but we want to see if giving AB-FP24 plasma in the ambulance will help slow or stop their bleeding.

How is this study different from other research studies?

This study is different because it involves patients who may not be able to give consent and the treatment must be given immediately after injury. In order to do this study without initial consent, we must inform and consult with the public through community outreach before this study will be approved or started. Eligible subjects will be enrolled into the study without their consent unless they have opt out items that can be easily seen.

What is Exception from Informed Consent?

Regulations established by the Federal government, (21 Code of Federal Regulations §50.24) specify the conditions under which an exception from informed consent in emergency situations is allowed so that research can be carried out even when consent is not possible because of the nature and extent of the patient's injuries.

What is the process to opt out of the research study?

To "Opt Out" means you do not want to be enrolled in this research study. In order to OPT OUT of the study, you need to fill out a form stating that you understand what it means to opt out. Denver Health will provide free the two (2) methods to opt out: a bracelet and dog tag necklace that specifies "NO COMBAT STUDY". It is recommended these items be worn at all times to maximize the ability for the research team to understand your wishes. None of these methods are perfect since one of the methods may become lost in trauma. To opt out, visit www.denverhealth.org/COMBATstudy.

What is AB-FP24 Plasma?

AB-FP24 plasma is the type of plasma that will be used in this study. Plasma is the liquid portion of whole blood, which contains the essential proteins or factors required to stop bleeding. Type AB plasma is the universal donor type. This means that the plasma and the blood type of the patient getting the transfusion do not have to match.

What is the design of this research study?

Severely injured patients in "hemorrhagic shock" will be given either saline (salt water) or thawed AB-FP24 plasma as the first treatment fluid. A method of chance, like flipping a coin, is used to decide which treatment the patient will get. The patient is randomized to either the standard (saline (salt water) solution) or experimental (AB-FP24 plasma) group. There is an equal chance of being in either group.

If the patient is assigned to the standard group, he/she will receive saline (salt water) as the first fluid in the ambulance. He/she will then be treated as all trauma patients are treated at the hospital. The doctors who see the patient at the hospital may decide to treat with a red blood cell (RBC) transfusion or AB-FP24 plasma. If blood products are transfused, they are donated blood products. This is the standard of care for all patients who come into the hospital after a severe injury.

If the patient is assigned to the experimental group, he/she will get 2 units AB-FP24 plasma as the first fluid in the ambulance. After the AB-FP24 plasma, the doctors at the hospital may decide that he/she needs a RBC transfusion, saline (salt water) or more AB-FP24 plasma. If more RBC transfusions or AB-FP24 plasma are needed, donated blood products are used.

After the first fluid treatment, both groups are treated in the same way. Blood samples are collected at several times after injury

What is the current standard of care? How are trauma patients usually treated?

Based on the Advanced Trauma Life Support Guidelines from the American College of Surgeons, the current standard of care for trauma patients is to give sterile saline (salt water) through the veins either at the scene or in the ambulance. When the patients arrive at the hospital, they are evaluated and are given blood products including red blood cell and plasma transfusions, if they are bleeding.

How is the control and experimental group different?

Trauma patients in hemorrhagic shock are likely to receive AB-FP24 plasma regardless of the group assigned. The experimental group would receive the AB-FP24 plasma sooner (at the start of the resuscitation period) than the control group (who gets it after the initial evaluation).

Who can be in this research study?

- Patients who have lost more than 30% of their blood volume and are in shock
- Patients who are at least 18 years old
- Patients who have life threatening injuries

Who will not be in this research study?

- Women who are obviously pregnant
- Patients who require CPR to maintain their heartbeat
- Patients who are known and have proof of objection to blood transfusions
- Patients who are wearing a bracelet or necklace stating “NO COMBAT STUDY”
- Patients who have a family member at the scene who object to enrollment to the paramedics

Is AB-FP24 Plasma safe?

The Food and Drug Administration (FDA) highly regulates AB-FP24 plasma through mandating strict protocols for collection, testing, processing, and storage. Although testing for infectious diseases has improved significantly over the years, there is still a very small risk of infection (see Potential risks of this study). However, all severely injured trauma patients are very likely to receive multiple transfusions, including RBC and AB-FP24 plasma since they are in shock. Plasma given early may decrease the need for multiple transfusions, and thereby, ultimately decrease the risks involved.

AB-FP24 plasma is tested for bacteria and viruses that can be transmitted in blood such as HIV and Hepatitis C.

What is the potential benefit of this research study that allows an exception of informed consent?

Being in this research study has the possibility of direct benefit to the enrolled patients because:

- Patients are in a life-threatening situation that requires intervention.
- Earlier transfusion of plasma may increase the likelihood of survival after traumatic injury. Previous studies showed patients who receive more plasma early with packed red blood cell transfusions were more likely to survive.
- A study showed that patients who received plasma while in the helicopter during transport were able to form clots better than patients who did not receive the plasma in the helicopter.
- Patients may get less blood products as seen in a review of patients who were transfused plasma earlier had a reduction in the overall amount of blood products needed, and an increase in survival.
- Patients may avoid the risks associated with multiple red blood cell (RBC) transfusions.
- Patients may avoid a reduction in the function of internal organs that sometimes follows blood transfusion.
- This study may help patients in the future.

What are the potential risks of participating in the research study?

- Fever or rash
- Allergic reaction
- Transfusion related acute lung injury: quick onset of difficulty breathing and changes on chest x-ray after a blood transfusion not caused by other conditions. Treatment often involves a machine called a ventilator to assist breathing.
- Other hemolytic reactions that results in RBC breakdown
- Transmission of Hepatitis B Virus (1 in 282,000 chance), Hepatitis C virus (1 in 1,149,000 chance), Human Immunodeficiency Virus (1 in 1,467,000 chance), or malaria (1 in 4,000,000 chance)
- Unnecessary transfusion of blood products
- Unintentional release of personal health information
- Chance that AB-FP24 plasma does not increase survival

What is the consent process?

Since this study focuses on severely injured people who may not be able to give consent because of the nature of their injuries, an eligible person will be enrolled in the research study without consent. Eligible means that the person is severely injured and does not have any of the opt out items visible. Once enrolled, the patient will be put into either the standard or the treatment group at random.

Once the patient arrives at the hospital, COMBAT researchers will work with hospital staff to locate family members. If the patient has a legally authorized representative (LAR), research will tell the LAR about the study and get consent for further data collection. If there is no LAR, then researchers and hospital staff will gather family members to identify a proxy decision maker. A proxy decision maker (PDM) makes medical decision for the patient until the patient is able to make his/her own decisions.

When the patient is awake and can consent, the researchers will obtain consent for use of data from the patient.

If the legally authorized representative, proxy decision maker, or the patient chooses not to allow further data collection, no additional blood draws or data will be collected. If a person chooses to withdraw from the research study, all data that was collected will be destroyed.

What if patients don't want to participate in the research study?

Patients may opt out by wearing a Denver Health-specific bracelet or dog tag necklace (which will be provided) that specifies "NO COMBAT STUDY". None of these methods are perfect since one of the methods may become lost in trauma. It is recommended that patients use both (2) methods to maximize the ability for the research team to understand the patient's wishes. Please see the website (www.denverhealth.org/COMBATstudy and click Opt Out on the right.)

Once the patient is enrolled and a legally authorized representative (LAR) or proxy decision maker (PDM) is contacted, an informed consent with information about the research study and permission to continue the study will need to be signed. Patients or their LAR/PDM can withdraw from this research study at any time by notifying the investigator listed on the informed consent.

Will patients still receive treatment if they do not want to participate in the research study?

Patients will still receive the standard of care if they choose to opt out of this research study.

How much will it cost patients to participate?

There is no charge to the patient to participate in this study. The study sponsor will pay for the costs of laboratory tests and procedures that are not standard of care, but necessary for the study.

Will patients get paid to participate?

No, patients will not be paid to participate in this research study.

Who is sponsoring the research study?

The United States Department of Defense's Telemedicine & Advanced Technology Research Center (TATRC) is sponsoring the research study. For more information, or to submit questions or comments, please contact the Study Coordinator, COMBATstudy@dhha.org, 303-602-3795 or go to www.denverhealth.org/COMBATstudy.

What if I am hurt in this research study?

If you are hurt by this study, the study coordinator will arrange all medical care. You or your insurance company is responsible for costs associated with your medical care.

I am trying to become pregnant or I am pregnant. What should I do?

The risks of AB-FP24 plasma to an embryo or fetus are unknown. For this reason, we are not including pregnant patients in this research study. However, it is difficult to know which trauma patients are pregnant unless the pregnancy is obviously visible. In the trauma setting, there is not enough time to do a pregnancy test. As a result, we are recommending that all women who are pregnant or trying to get pregnant opt out of the research study. (Please see the question "What is the process to opt out?")

If I am unconscious, can my family or LAR make a decision about enrolling me in the research study?

After a major traumatic event, the paramedics at the scene try to stabilize you quickly for transport. Based on our experience, the time from the scene to the emergency room is about 8 minutes. Once in the emergency room, the staff works quickly to stop bleeding-, and treat your injuries. There often is not enough time to contact family or an LAR to fully explain the study and you or family member at the scene is not suitable to make rational care decisions. For this reason, Denver Health is working with the FDA to obtain a waiver of consent for emergency research.

If a family member is present at the scene and not severely injured, easily accessible to paramedics, and the patient is not in immediate danger of death, the paramedics will ask the family member if there is any objection to enrollment. The paramedics will not be able to look for family members among a crowd of bystanders because of the importance of transporting the patient to the hospital as quickly as possible.

When does the research study end?

After the initial treatment with either saline (salt water) or AB-FP24 plasma, we will continue to monitor your ability to clot and other clinical measures with laboratory studies, which will require blood samples up to 7 days after injury. We will continue to follow your outcomes and clinical results up to 28 days after injury. If you are discharged before 28 days after injury, we will contact you 28 days after your injury to see how you are doing.

What are the demographics of patients within the City and County of Denver who had trauma this severe?

From 1/2009 to 9/2011, 123 patients had severe trauma and were transported by Denver Health paramedics and may have been eligible for this type of study. 78% were males, and the ethnic breakdown was 50% White, 26% Hispanic, 13% Black, 2% American Indian, and 8% Other. The average age was 38 years but age ranged from 18-80 years old.

Why is the study being done at Denver Health Medical Center?

Denver Health Medical Center (DHMC) has a long history of caring for trauma patients and uses the most up-to-date research to guide clinical decisions. DHMC also has a longstanding relationship with the Denver Health paramedics who are an essential part of the research team since they are the primary healthcare providers on the scene.

General Questions about Emergency Research

Why is there a need for improvement in the way trauma patients are treated now?

Trauma is the leading cause of death among Americans under the age of 45. In spite of major advances in science and medicine over the past 40 years, there have been few, if any major changes, in the early treatment of hemorrhagic shock.

What is COMIRB?

COMIRB or Colorado Multiple Institutional Review Board is the local Institutional Review Board. The Institutional Review Board (IRB) is a group of people, including medical, scientific, and non-scientific members, who are not involved with the study and whose duty is to ensure the protection of the rights, safety, and well-being of patients enrolled in clinical trials. It is federally regulated and is designed to protect people in a research study. Colorado Multiple Institutional Review Board (COMIRB) will review this study. For more information, their website is http://www.ucdenver.edu/academics/research/AboutUs/comirb/Pages/comirb-home.aspx.

Why would such an exception be granted in connection with this research study?

An exception from consent may be granted for the study because patients are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions.

Participating in the research study must have the prospect of direct benefit to the enrolled patients because:

- Patients are in a life-threatening situation that necessitates intervention.
- Previous studies suggest trauma patients who experience serious and life-threatening bleeding and who received more plasma early with packed red blood cell transfusions were more likely to survive.
- Risks associated with the use of the experimental treatment are reasonable in relation to what is known about the patients' medical condition, the risks and benefits of standard therapy, if any, and the risks and benefits of the proposed intervention.

In life-threatening emergencies, it is expected that patients often are unable to give informed consent because of the extent of their injuries and the fact that they are in shock.

There often is not time to find and ask for consent from the patients' legally authorized representatives (LAR) before beginning treatment.

What needs to be done to allow an exception?

The Principal Investigator must present this study to representatives in the community and get feedback and publicly disclose information about the study. Then the study is complete, the results must also be publicly disclosed.

Who grants such exceptions?

The U.S. Food and Drug Administration (FDA) under regulations called 21 Code of Federal Regulations §50.24) specifies the condition under which an exception from informed consent may be obtained. The Institutional Review Board (IRB) associated with each institution approves its use locally.

What is the consent for?

The consent is to inform you, your LAR or family members about the study and to obtain permission to continue data collection for the study. You, your LAR, or your family can withdraw from the study at anytime.

What qualifies as Emergency Research?

All of the following conditions must be present (from 21 CFR 50.24 regulations):

- The human subjects are in a life-threatening situation that requires urgent action;
- Available treatments are unproven or unsatisfactory;
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention;
- Obtaining informed consent is not possible because the subjects cannot give their informed consent because of their medical condition;
- The intervention must be given before consent can be obtained from the subject's legally authorized representative;
- It is not possible to identify ahead of time individuals who may become eligible for the study;
- Participation in the research holds out the possibility of direct benefit to the subjects; and
- The clinical investigation could not practicably be carried out without the waiver.
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24

Definitions

What is hemorrhagic shock?

Hemorrhagic means the patient has experienced massive blood loss.Shock is a life-threatening condition that includes:

- A dangerously low blood pressure and/or a high heart rate
- Internal organs not receiving enough oxygen and not functioning properly
- High likelihood of death if not treated

What is coagulopathy?

Coagulopathy is a bleeding disorder, where someone cannot form clots to stop bleeding. In trauma, coagulopathy is usually treated with plasma since it has the proteins and factors necessary to clot.

What is the difference between Fresh Frozen Plasma(FFP) and AB-FP24 Plasma?

Plasma is currently used as the standard treatment of trauma patients, who are actively bleeding. In contrast, red blood cell transfusion is the part of whole blood that has the red blood cells that help carry oxygen. FFP is taken from donors and frozen within 8 hours. Type AB is the universal donor. Since it must be frozen within a short time, there is a limited amount of AB-FFP and limited time to know if the plasma is AB. To have more type AB plasma that can be given to trauma patients, we use plasma that is frozen within 24 hours called AB-FP24 plasma. AB-FP24 plasma is almost the same as AB-FFP. There are smaller amounts of a few specific proteins that help your body clot. This matters for patients who need those specific proteins, but AB-FP24 plasma still works for trauma patients who need clotting proteins after severe injury. AB-FP24 plasma used in this study is collected from pre-screened blood donors at blood banks (i.e. Bonfils Blood Center).

What is the resuscitation or treatment period?

The resuscitation or treatment period is the early treatment period after the injury when paramedics, doctors, and nurses do everything possible to help you survive. It includes the time at the scene of the injury and transportation to the Emergency Room, Operating Room or, Intensive Care Unit.

What is ATLS?

ATLS stands for Advanced Trauma Life Support. The American College of Surgeons has put together guidelines on how to initially care for the trauma patients. These guidelines come from the evidence that is available. This includes the type of resuscitation fluid and how much to give.

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