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Division of Plastic Surgery

Leg Transplant Patient Guide

Why are leg transplantations being done?

You may have heard about a new surgical procedure called leg transplantation. Only a small number of these surgeries have been performed around the world thus far.

The procedure of leg transplantation is a promising new method to restore the limb(s) of lower extremity amputees. However, this procedure is new and not without significant risks. Therefore, leg transplantations have to be performed as part of a research study. The leg transplant team at Brigham and Women's Hospital (BWH) is conducting such a research study.

The purpose of the study is to find out more about the outcomes of leg transplantation. We are studying people who have suffered amputation of both legs. We hope to learn more in this research study about how to do a leg transplant in the best possible way and how to stop the body from rejecting the transplant.

In this study, our patients already have lost their legs. Some patients in our study have undergone attempts at traditional limb reconstruction that have resulted in suboptimal outcomes. Most patients in our study have tried different kinds of prostheses, with consistently unsatisfactory results.

The transplantation of one or both legs from one person (the donor) to another (the recipient) is a new research approach for patients with amputations. A lot is unknown about the outcomes of this procedure. As of July 2012, only two patients have undergone successful leg transplants, and not enough time has yet passed for us to know the long-term results of these procedures. Based on our experience with hand transplants, we know that most patients are likely to regain protective sensation in their transplanted limbs (e.g., the ability to tell if something is hot or sharp), as well as discriminatory sensation (e.g., the ability to tell if something is hot or sharp). Patients who have undergone leg transplants to date are still in the process of regaining the ability to walk without assistance, which is expected to result in significant improvement in their satisfaction and quality of life. However, we do not know how easy it will be to find tissue donors for this purpose. There are so many different colors and textures of skin, so it might be hard to find a perfect match.

Normally, the body's immune (protective) system treats any new organ or tissue as an invader, like a germ, and tries to destroy it. Transplant drugs, however, partially shut down the immune system so that the body can accept the new organ or tissue. Patients have to take strong drugs for the rest of their lives to prevent rejection of the transplant.

This is a pilot study. The purpose of a pilot study is to see what is possible and to learn more about how best to do it. We are doing a pilot study on a small group of patients to learn more about the leg transplant procedure.

Screening

The minimum age requirement for participation in the study is 18 years, and the maximum is 60 years. The time between the injury and the transplant must be more than six months, but less than 15 years. Patients must have a strong motivation to proceed with a transplant and accept dedicating at least two years toward extensive post-transplant rehabilitation. Patients must be willing to take immunosuppressants – drugs that help prevent rejection of the transplant – for the rest of their lives. Patients must report less than optimal outcomes with prostheses, as evaluated by an experienced physical therapist, during a minimal trial period of 6 months.

Furthermore, pregnant women cannot take part, as the transplant drugs may harm a fetus or embryo (a developing baby still inside the mother's body). Women who are pregnant must wait until at least six weeks after the completion of their pregnancy before a transplant can be considered.

Each patient that is considered for a leg transplant has to undergo a screening process that may require several visits. During this time, the patient will meet with the various specialists on the leg transplant team. The purpose of the screening is to find out whether a patient is a suitable candidate for leg transplantation. The leg injury, as well as the patient's overall physical and mental health, will be thoroughly evaluated. More specifically, the evaluation includes various blood tests, imaging tests, and appointments with physicians and nurses from many different medical disciplines.

The research study

Patients enrolled in the study will have several different examinations before and after the procedure. These examinations are important to plan and prepare for the procedure, monitor for complications, and evaluate the results. We also want to make sure that all patients accepted for the procedure have the necessary social/family support and overall capability to cope with the different psychological and practical aspects of this procedure.

There will be imaging procedures before and after the transplant surgery, some of which are invasive (e.g., require minor surgical procedures) and some of which are non-invasive. Prior to transplant, patients must undergo a formal angiogram of their amputated limb(s) in order to provide information regarding the arteries and veins in the injured area(s). This test is performed with the patient under sedation and involves the placement of a large temporary IV in the groin, as well as the administration of a special dye into the bloodstream. In addition, patients will need to undergo non-invasive imaging studies – including CT (CAT-scan) and magnetic resonance imaging (MRI) – that provide information concerning internal tissues, nerves, and blood vessels.

We also have included a test called functional MRI (fMRI). Functional MRI shows brain areas that are active when the patient moves, sees, hears, speaks, reads, or remembers. Since the muscles and tissues of the leg are involved in most of our daily activities, we are interested in how the brain adapts to leg injury and to the repair through transplantation. Using this test, we may be able to detect brain

changes resulting from the gradual return of sensation and motor activity to the patient's leg.

We also will perform two tests called electromyography, or EMG, and nerve conduction study, or NCS. These tests measure the electrical activity in the leg muscles and the function of the nerves. During EMG, small needles are inserted into the muscles and this may cause some discomfort. However, these needles are much finer than the needles used for shots, and there is no injection. Thus, the discomfort is much less than with receiving shots. The needles are disposable, so there is no risk for infection. During NCS, small electrodes are placed on the skin. There is a brief and mild shock, which may be a bit unpleasant. Most people find it only slightly uncomfortable. Muscle activity will be monitored through a speaker during the test, which may make a popping or soft roaring noise. There will be no restriction of patient activities following these procedures.

Finally, we will perform an ultrasound test in order to provide additional information about blood vessels in the amputated extremity. During this test, a special gel is applied to the skin in the arm(s) and a transducer is passed back and forth. There may be some pressure from the transducer, which may be uncomfortable. Ultrasound tests cause no pain.

Quality-of-life surveys will be used to assess perception of health and well-being. The surveys will be given at the time of listing on the transplant list, approximately every six months while the patient is on the list, and periodically after transplantation.

The leg transplant procedure

We are working with the New England Organ Bank (NEOB) team to find donors for leg transplantation. This search may take days or weeks, but, more commonly, months. If we have not located a suitable donor within one year, then we will talk with the patient and make sure they still want to take part in this study.

Once a donor is found, we will contact the patient with instructions about when to come to BWH for the operation. This timing is very important. It is imperative that the BWH staff can reach the patient at all times, and that the total travel time for the patient to reach our hospital does not exceed 12 hours.

Leg transplantation requires that the recipient be under general anesthesia (fully asleep) for a prolonged period of time. Prior leg transplantation procedures have taken anywhere from 12 to 24 hours to complete, depending on whether the procedure involves one or both legs. Once the recipient is asleep, the amputated limb(s) will be prepared to receive the donor leg(s). This portion of the procedure will be performed by one or two BWH surgical teams, depending on the number of limbs involved. Simultaneously, one or two additional surgical teams will begin harvesting the donor limb(s). Depending on where the donor patient is located, this may or may not be performed at BWH. At times, organ donor patients are located at a separate hospital; in such a circumstance, the donor limb(s) would be procured by one or two BWH surgical teams who would travel to the external site, obtain the limb(s), and transport them back to BWH while the recipient preparation procedure is taking place.

Once both the donor and recipient limbs are ready, the transplantation procedure is performed. Leg transplantation includes the transfer of soft tissues and bone from the donor to the recipient. The survival of the transferred tissues depends on the re-

establishment of blood circulation. This is accomplished by connecting blood vessels of the leg transplant to vessels on the recipient. Nerves also are connected to allow for the return of sensation and motility to the leg. Connection (anastomosis) of vessels and nerves is made by the use of a microscope.

The hospital stay

After the surgery, the patient will first go to the Intensive Care Unit (ICU) for close observation and then move to a private transplant room on a patient floor. All aspects of the patient's gradual recovery will be closely followed by the different specialists on the team. A physical therapist will start working with the patient shortly after surgery to rehabilitate the leg, and a psychiatrist will help with any psychological concerns. The hospital stay will last approximately 7 to 14 days.

Follow-up

After discharge from the hospital, patients will need to come to BWH for routine visits. Close observation and rigorous testing serves to monitor for any complications and to evaluate the results of the procedure. It also is very important that we give patients all the help and support needed to cope with the psychological and social aspects of this procedure.

Patients will need to come to BWH for physical therapy for several hours a day, every day, during the first several months. Physical therapy is very important for the rehabilitation of the transplanted legs; therefore, the rehabilitation program will be very demanding. Progress is usually slow. Highly trained and skilled therapists will help and support the patient throughout the rehabilitation process. Support from the patient's family, psychiatrist, and physical therapist will be important to maintain the patient's motivation.

Other follow-up visits will include checking transplant drug levels through regular blood draws; taking small tissue samples from the transplanted leg to look for any signs of rejection; monitoring the transplanted leg for the return of sensation and mobility; imaging tests; and quality-of-life surveys. In order to make the intense follow-up feasible, we highly recommend that our patients reside in the Boston area for at least three months after the procedure. When the leg transplant has fully stabilized, patients will continue to make regular visits to BWH for progress checks. After that, the planned visits will be less frequent and some check-ups could be done through video conferences with collaborating medical centers closer to the patient's home. As with any organ transplantation, leg transplant patients will need to reside near a major medical center for the rest of their lives.

Medications

Leg transplant patients need to take several different medications on a daily basis. The most important ones are the different types of medications that suppress the immune system. The blood level of these transplant drugs will be monitored by regular blood draws. Any signs of side effects will be closely checked. It is imperative that all transplant patients, for any organ or tissue, closely follow the prescriptions of these medications and keep their follow-up appointments. Drug doses that are too high may cause serious side effects, and drug doses that are too low may cause rejection of the transplant. The risks and side effects of these medications are described below.

If the leg transplant is completely rejected by the patient's immune system, the transplanted tissues will, unfortunately, have to be removed. If this happens,

different treatment options will have to be discussed with our surgical team. Options include conventional reconstructive leg surgery according to an already prepared plan or another leg transplant at a later time.

Publicity and privacy

Because this type of transplant is so new, it is likely that the news media will be very interested in both the donors and the people who receive the transplants. We will make every effort to protect the privacy of our patients. Despite this, the press may find out the names of both the donor and recipient. This may cause problems, including the stress and anxiety that come with such a loss of privacy.

Risks and discomforts

There are psychological risks and discomforts associated with participation in this study, as well as the physical risks of the experimental leg transplant procedure itself.

General transplant risks

All transplant patients have the following challenges:

Difficulty following the strict medication dosing required after the operation.

Understanding the complicated side effects and risks of taking drugs that stop your immune system from working normally.

Swings in emotions following transplant surgery.

Stress related to study procedures, and other new feelings and thoughts.

Leg transplant risks

We will provide psychiatric support to all patients before and after leg transplantation. This support will help the patients to cope with this event and learn to live with the changes, both positive and negative, that it brings.

Risks of taking transplant drugs for a lifetime

The medications suppressing the immune response, and thus preventing rejection of the transplanted tissue, have multiple side effects:

1) Infections:

It is important that patients receive certain vaccinations prior to transplant (pneumococcal vaccine, flu vaccine, etc.).

Medications that prevent the occurrence of infections will be given at the time of the procedure and for some time afterwards.

2) Diabetes:

Some of the transplant drugs may give rise to diabetes. The blood sugar levels will therefore be monitored and, if needed, anti-diabetes medication will be given.

3) Cancer:

Certain cancers are more common in people who have undergone transplantation. This is probably because the immune system after the transplant is not as effective at eliminating very early cancer cells. It is important to note that most transplant patients *do not* develop serious cancers. Some cancers that are more common after transplant are those of the:

- Skin (especially in white people)
- Lymph glands
- Cervix (of the uterus) in women

To minimize the chances of having cancer before a transplant, we ensure that all patients are screened before transplantation as follows:

- Patients over 50 years have a colonoscopy (screening test for bowel cancer)
- All men over 50 years have a PSA (screening test for prostate cancer). Because prostate cancer is more common in African-Americans, they should have a PSA if aged over 40 years.
- All women over 40 years have a mammogram.
- All women have a Pap smear.

4) Kidney failure:

Immunosuppressive medications have a negative impact on kidney function. A small number of transplant patients end up requiring dialysis because of kidney failure caused by these medications. It is, therefore, very important to test kidney function during the regular visits and change medications as needed to prevent kidney failure from happening. The lifetime risk of losing kidney function is unknown, but we believe that it should not exceed 10 percent.

The benefits of leg transplantation

We do not know if leg transplants will have more long-term success than the use of prostheses. We are optimistic, but there is no guarantee. Although the experience with the existing leg transplant patients in the world has been good, there are still few cases, and their success does not guarantee any other transplant patient's success.

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