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Vascularized knee joint transplantation in man: a report on the first cases

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Abstract Four transplantations of an allogeneic vascularized human knee joint were performed at the Trauma Center Murnau between April 1996 and July 1997. The indication for the procedure was the total loss of the knee joint including the extensor apparatus due to severe trauma. These were the first transplants of this type. Management of patients started with closure of soft-tissue defects. After successful completion, stabilization was achieved with femoral and tibial nails plus a temporary arthroplasty. AB0 compatibility and a negative cross-match were the main criteria for selecting patients for transplantation. Interlocking compression nails were used for osteosynthesis. Vascular anastomoses between graft and recipient vessels were established by the end-to-side technique. Immunosuppression was started as a quadruple induction therapy for 3 days, then reduced to a two-drug maintenance therapy with cyclosporine and azathioprine. Six months posttransplantation the osteotomies were bridged by callus and the patients became completely mobile. Radiographic and histological examinations revealed vital graft tissue.

Key words Knee joint · Vascularized graft · Bone · Transplantation

Introduction

Severe trauma may cause the loss of the knee joint in a young patient, thereby drastically reducing the quality of life of an otherwise healthy person. The patient faces the following treatment options: (1) primary arthrodesis with subsequent bone lengthening, (2) arthroplasty, (3) above knee joint amputation, or (4) allogeneic transplantation. Primary arthrodesis may lead to successful management of the wound, finally resulting in the closure of bone and soft tissue defects. Subsequent bone lengthening in accordance with Ilizarov's technique is necessary to regain the original length in most cases. However, this procedure is time consuming, has many possible complications, and the loss of mobility is irreversible. Although arthroplasty of the joint provides a stable leg with restored length as well as a mobile joint, its disadvantages are well known to traumatologists: the arthroplasty's life expectancy is generally limited, and functional failure may occur at an early postoperative stage due to loosening or endoprosthetic infection. Loss of the extensor apparatus has to represent a contraindication for obvious reasons. Therefore, arthroplasty is the procedure of first choice in older patients and in those with tumors. Above knee joint amputation might be considered "the last line of defense." Undoubtedly there is no quicker way to rehabilitate a young patient than using an orthesis. Nevertheless, everyone would agree that the surgically caused loss of a limb has to be considered the most unsatisfactory solution. A new option, the allogeneic vascularized knee transplant, is introduced in this paper. We report our experiences and the first preliminary results.

Patients and methods

To date, four allogeneic vascularized transplantations of human knee joints have been performed by our group (recipients: male 17 years, male 30 years, female 34 years, male 34 years). The strategy of treatment consists of the four main steps which are briefly described as follows.

Restoration of bone and soft tissue

As all of the patients suffered from severe deep infection of the knee joint, a radical debridement had to be performed initially. An extensive resection to eliminate all necrotic parts of bone and soft tissue resulted in a defect zone of up to 30 cm, which was stabilized by external fixation. A regularly performed lavage program was maintained until three consecutive microbiological swabs proved to be free of microorganisms. Only then was soft-tissue coverage performed using local and free pedicle flaps.

Preparation for transplantation

The patients were then provided with two interlocking compression nails (IC-N). Insertion was performed anterogradely in the femur and retrogradely in the tibia. Within the same operative setting, a simple arthroplasty made of polyethylene was attached on top of the nails in the former knee joint area. In that way, temporary passive mobility was achieved (CPM motor device), preventing contraction of the soft tissue. To exclude any latent contamination, the patient was put on transient immunosuppression with cyclosporine A for 2 weeks. The final preparatory examinations were angiography and phlebography of the femoral vessels and the evaluation of the serological status. He or she was then placed on a transplant waiting list.

Transplantation

Donor requirements

Only fundamental criteria of postmortem organ donation were applied: brain death, informed consent, exclusion of risk groups, and negative serology regarding hepatitis B/C and HIV. Since the knee is a heavily used joint it is subject to degenerative changes. Therefore an age limit for donors was set at 45 years. Special attention was paid to blood group compatibility, negative cross-match, and geometric similarity. Prior to the transplantations HLA typing was performed, but was not used as a criteria for transplantation. Most of the multiorgan donors were not acceptable because of geometric incompatibility. Subsequently the pool of donors for a knee joint transplant was too small to make it practical to wait for an optimal HLA match.

Harvesting

Each graft was harvested from a multiorgan donor (male 25 years, female 21 years, male 16 years, male 43 years). For preservation, 4 l of University of Wisconsin solution (UW) were applied through a catheter placed in the external iliac artery. The graft was procured with a long vascular pedicle of the femoral artery and vein. The joint capsule remained intact and closed.

Procedure for transplantation

The graft was prepared by back-table technique with special respect to its vascular anatomy. Subsequently the process of transplantation, consisting of five main steps, was started:

1. Preparation of the recipient's vessels. A sigmoidal approach of about 40 cm in length is used, beginning at the adductorial site of the thigh, crossing the lateral level of the former knee joint and running to the ankle, following the fibular site. Having exposed the superficial artery and vein, the popliteal vessels, and the peroneal and tibial nerves, they are marked with vessel loops.

2. Preparation of the transplant site. Removal of the above-described spacer is followed by one further debridement in order to provide an extended cavity for the graft.

3. Osteosynthesis. Intramedullary fixation is performed by using two IC-Ns (see above).

4. Vascular anastomoses of the graft. They are established in common end-to-side technique between the recipient's superficial femoral vessels and the graft's vascular pedicle.

5. Suture of muscles and ligaments. A most important step is the reinsertion of the donor's quadriceps tendon into the quadriceps muscle of the recipient. Further attention is paid to the *pes anserinus* and the biceps muscles.

Cold ischemia time was approximately 20 h. Continuous machine perfusion using an appropriate, cooled UW solution was employed from the beginning of back-table preparation until the anastomoses were performed, in order to avoid warm ischemic periods. For this reason, a catheter was placed in the graft's femoral artery. Immediately after reperfusion of the graft, the recipient received immunosuppressive treatment consisting of a quadruple induction therapy of cyclosporine A [CyA; 1 mg/kg body weight (BW) i.v.], azathioprine (AZA; 1 mg/kg BW, i.v.), anti-T lymphocyte globulin (4 mg/kg BW, i.v.), and methylprednisolone (250 mg/day, i.v.) for 3 days. Oral maintenance treatment was managed with CyA and AZA.

Follow up

Digital substraction angiography and duplex sonography were used to observe the graft's circulation from a macroscopic point of view. ^{99}Tc-DPD scintigraphy including single photon emission computed tomography was performed regularly since it can be used to assess the microcirculation and cellular metabolism of the transplant. Callus formation and osseous consolidation of the osteotomies were examined using conventional X-rays. Arthroscopy was only performed when clinically necessary. This direct visual examination is extremely useful in knee joint transplantation since it shows viability or evidence of an ongoing rejection via biopsies. Microarthroendoscopy was used to examine the capillary flow in the synovial membrane. After discharge from the hospital, a weekly outpatient follow up is performed by an experienced physician for a minimum of 4 weeks. Depending on the patient's condition, the follow-up intervals were increased to up to 6 weeks.

Results

Four successful transplantations of an allogeneic vascularized knee joint were performed. Three patients were discharged from the hospital 6–8 weeks posttransplantation, each of them already mobilized with two crutches and partially weight bearing (40 kg) on the operated leg. At present no complications of fracture healing have occurred. Early callus formation and the beginning

Fig. 1 View of a vascularized allogeneic human knee joint graft. Arthroscopy demonstrates an intact medial meniscus and regular cartilage of femur and tibia (by kind permission of Springer, Paris, France)

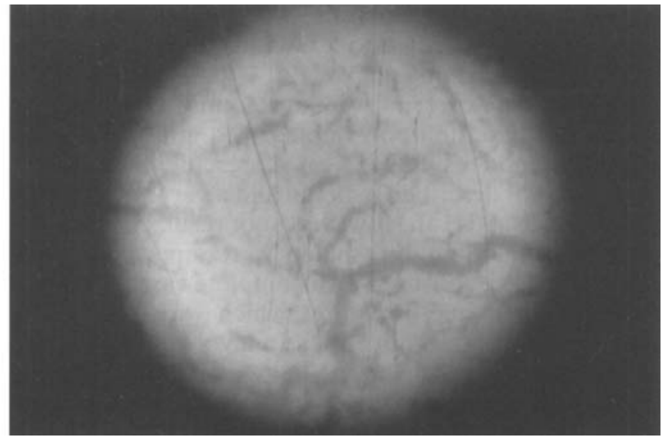

Fig. 3 Microarthroscopic evaluation of capillary flow in the synovial membrane of a transplanted knee joint (by kind permission of Springer, Paris, France)

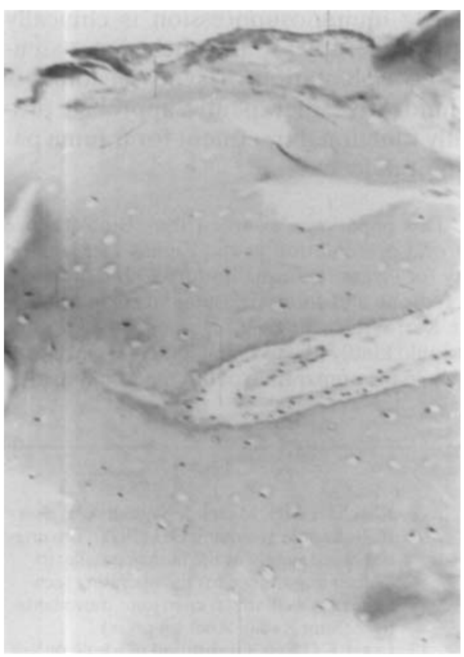

Fig. 2 Section of a bone biopsy taken during arthroscopy 6 weeks posttransplantation. The specimen reveals viable osteocytes in the grafted knee joint

of osseous consolidation of the osteotomies monitored by X-rays took place regularly. No pathological processes were revealed arthroscopically, either during direct assessment (Fig. 1) or in the biopsies taken (Fig. 2). Hemoperfusion was demonstrated to be completely intact in all grafts (Fig. 3). One case of reinfection was observed posttransplantation. Subsequently, immunosuppressive treatment was discontinued followed by an immediate loss of perfusion and vitality as signs of rejection. After removal of the graft, the patient decided to enter the transplant waiting list again. Eight weeks following the operation the other three patients were fully weight bearing on the transplanted knee. Complete mobilization without any aid was allowed 4 months after transplantation. As varus and valgus stress needs to be avoided, the patients are required to wear a custom-made knee brace which allows only full-range extension and flexion. In our patients, complete extension and 100° flexion have been observed.

Discussion

In 1908 the first two pioneering whole-joint transplantations were attempted. Judet [9] reported an experimental approach and the clinical realization using human knee joints was described by Lexer [13, 14]. In both cases grafting was performed without a vascular pedicle or subsequent immunosuppression. The principles of transplant immunology, infection treatment through antibiotics, and organ preservation were not yet established at that time. Osteosyntheses were performed using simple techniques since intramedullary nailing was not invented until 1940 (Küntscher).

For osteosyntheses in these operating procedures, nailing with interlocking devices represents the ideal technique since the periostal blood supply is not affected by external plates. The periostal blood supply in knee joint transplantation is of the utmost importance because, in this region, no intraosseous blood supply exists via the nutrient arteries of the femur and tibia [11]. This anatomical knowledge has been considered in the current operating technique using intramedullary devices. Consequently postoperative scintigrams showed hyperemia in the early postoperative state and a normal perfusion at later time points [12].

The clinical experiences in knee joint transplantation to date are based on non-vascularized grafts. Unfortunately, the good results in 23 cases presented by Lexer in 1925 were not described in detail and a very short follow up was published [14]. However, poor results in non-vascularized whole-joint transplants were reported by Volkov in 1970 [17]. He observed incomplete vascularization with subsequent microfractures, which were followed by disintegration of the graft and the unavoidable total graft failure. Similar results were demonstrated in experiments by Bensusan et al. in 1992 when vascularized grafts proved to be significantly stronger when compared with non-vascularized grafts [1]. The high incidence of complications in non-vascularized bone allografting suggests that blood supply is one of the main factors in maintaining mechanical integrity. The conclusion to be drawn seemed to be that successful revascularization is of the utmost importance for satisfactory clinical results. Most of the experimental results underline this statement. The first experimental design for performing a vascularized total knee joint transplantation was introduced in 1968 by Reeves [15]. Azathioprine and goat anti-dog lymphocyte serum were administered to avoid rejection episodes. A remarkable further experimental model, especially because of its excellent documentation, was published by Goldberg et al. in 1973 and 1980 [3, 4]. Again vascularized knee joints were grafted in dogs. Immunosuppression consisted of anti lymphocyte globulin, AZA, and cortisone. At that time CyA was not available. Since the vascular anastomoses failed, severe cartilage destruction occurred due to a slow chronic rejection of the grafts.

Postoperative immunosuppression of bone graft recipients was proven experimentally in the early 1980s [16]. Immunological consequences of bone transplantation in man have been the subject of recent clinical investigations and have revealed a defined cellular and humoral response by recipients toward the graft [7]. Allogeneic grafted human bone with its immunogenical potential leads to an activation of the recipient's immune system in a very specific way. The relevant reactions are directed against class I and class II antigens of the donors HLA antigens [7]. The impact of the different antigens of whole knee joint transplants, such as bone, cartilage, synovial membrane, and vascular endothelium, is still unknown. However, it seems as if joints are more immunogenic than other organs such as heart, liver, and pancreas. Immunosuppressive treatment, therefore, proved to be mandatory for maintaining the circulation in the graft. From our experience, today's advanced immunosuppression is highly efficient in suppressing the immunological response to allogeneic vascular bone grafts [5, 6, 8, 10]. Because of the synergistic effect, a double-drug immunosuppression is clinically superior to CyA monotherapy [2]. In conclusion, vascularized allogeneic transplantation of synovial joints is suggested as an innovative therapeutic approach providing a biologically functional treatment for trauma patients with large joint defects.

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