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Arthroplasty Risk after Kidney or Liver Transplant

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Rezumat

Riscul artroplastiilor de șold sau genunchi la bolnavii transplantați hepatic sau renal

În ultimii ani rata transplantului renal sau hepatic a crescut considerabil, în același timp crescând și rata afecțiunilor osoase secundare medicației imunosupresoare. Astfel va crește și predispoziția acestor bolnavi către artroplastia de șold sau genunchi. Deși artroplastia reprezintă o intervenție sigură în cazurile obișnuite, siguranța sa în cazul pacienților transplantați este incertă. Scopul acestui studiu este evaluarea siguranței și a durabilității artroplastiei de șold sau genunchi la pacienții transplantați hepatic sau renal. În studiul nostru au fost incluse 5 atroplastii de șold sau genunchi practicate la transplantați hepatic și renal. Toți pacienții au urmat terapie imunosupresoare. Toate cazurile au urmat antibioterapie postoperator, iar pentru implanturile cimentate s-a utilizat ciment cu antibiotic. Nici un caz nu a prezentat sepsis postoperator sau la distanță, iar durabilitatea implantului nu a fost afectată din cauze direct legate de transplant. În concluzie artroplastia în cazul bolnavilor transplantați hepatic sau renal reprezintă o intervenție cu impact pozitiv asupra calității vieții acestora fiind sigură în condițiile unor minime măsuri de siguranță perioperatorii.

Cuvinte cheie: artroplastie șold/genunchi, transplant hepatic transplant renal, imunosupresie, infecție, revizie implant

Abstract

In recent years the rate of kidney or liver transplantation has increased considerably, with an increasing rate of immunosuppressant medication for secondary bone disorders. As the rate of organ transplantation increases, the greater predisposition of these patients to hip or knee arthroplasty is noticed. Although arthroplasty is safe in the general population, its safety in liver transplant recipients is unclear. The purpose of this study is to evaluate safety and durability of hip or knee arthroplasties in liver or kidney transplanted patients. Our study included 5 hip and knee arthroplasties performed in transplanted liver and kidney. All patients underwent immunosuppressive therapy. All cases were submitted to postoperative antibiotic therapy and in the case of cemented implants, antibiotic impregnated cement was used. There were no major short-term or long-term complications. We noticed no case of postoperative sepsis, and implant durability has not been affected by the directly transplant related causes. In conclusion arthroplasty for patients with kidney or liver transplant has a positive impact on their quality of life, being a safe and successful procedure with minimum perioperative safeguards.

Key words: hip/knee arthroplasty, liver transplant, kidney transplant, infection, implant revision

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Introduction

Development of surgical techniques and immunosuppressive therapy especially, led to marked increases in the incidence of liver or kidney transplantation for patients with severe chronic organ failure, transplant actually, being the main therapeutic option to these patients.

Currently, 12 000 kidney transplant surgery are practiced annually in the U.S. and 5000 liver (1). Although these interventions are life saving for the patient there are some side effects of immunosuppressive therapy to be taken into account in order not to diminish the quality of life post-transplant patient. Thus they are prone to infections, and malignancies of the bone: osteopenia, osteoporosis, aseptic osteonecrosis and chronic bone pain. As the rate of organ transplantation increases, the greater predisposition of these patients to the hip or knee arthroplasty is noticed.

For orthopedic surgeon, transplant patient group is a challenge, knowing their susceptibility to the infection, the risk of bleeding with thrombocytopenia and last but not least, the risk of degradation of the implant due to poor quality bone. Thus the question of exclusive use of cemented implants in these patients, but in literature there is no evidence of contraindication for uncemented implant.

Immunosuppressive medication

Calcineurin inhibitors

Calcineurin inhibitors - were discovered in 1970, opening a new era of immunosuppressive therapy. The main representatives of this class are Cyclosporine A and Tacrolimus.

Cyclosporin A (CyA) - CyA causes selective suppression of cell-mediated immunity via inhibition of T-cell activation. After forming a complex with its cytoplasmic receptor protein (cyclophilin), CyA binds to and inhibits the calcium and calmodulin-dependent phosphatase calcineurin, the latter playing a key role in activation of interleukin 2 (IL-2). CyA medication is used for induction of immunosuppression as well as maintenance medication.

Main side effects of CyA are represented by:

- Renal dysfunction secondary vasoconstriction (ischemia), or interstitial nephritis (long-term effect);
- Hyperkalemia;
- Hipomagnesiemie.

Tacrolimus (TAC) - is another immunosuppressant in the same class. TAC exerts its action by binding to FK binding protein (FKBP12). This complex then inhibits calcineurin, which is responsible for transcription of IL-2, IL-3, IL-4, IL-8, and various chemotactic factors.

It is used as maintenance medication as well as medication to "rescue" the phenomenon of acute graft rejection. Side effects are similar to CyA, in addition to being present neurological symptoms (confusion, tremor, headache).

If renal transplantation is needed, close supervision of calcineurin inhibitors doses is mandatory because of their nephrotoxicity, this being able to lead to chronic renal graft dysfunction.

Multicenter study showed that patients who are treated with TAC compared with CyA, showed a low rate of graft rejection in the first year and in those infected with hepatitis C virus (HCV), liver graft had a longer survival.

Corticosteroids - is the most commonly used class of non-calcineurin immunosuppressant, in organ transplantation.

Corticosteroids exert their most critical immunosuppressive effect by blocking T-cell – derived and antigen-presenting cell-derived cytokine expression. This includes IL-1, IL-2, IL-3, and IL-6.18 Corticosteroids are used both in acute graft rejection phenomenon as well as maintenance therapy.

Side effects are numerous, including:

- Osteoporosis;
- Aseptic osteonecrosis;
- Peptic ulcer.

Although it is a widely used medication, the percentage of patients undergoing corticosteroid therapy during hospitalization in the U.S. fell from 91% in 2002 to 82% in 2003 (1), maintaining its trend until today. This decrease can be attributed to the negative impact of corticosteroid therapy on HCV recurrence.

Antimetabolites

Azathioprine – was first antimetabolite used in kidney or liver transplantation.

The mechanism of action consists in blocking the synthesis of purine metabolism. The result is an inhibition in synthesis of DNA, RNA, and proteins. Currently using small-scale, 5% of U.S. transplant centers (1) due to its severe adverse effects: myelosuppression and hepatotoxicity.

Currently most used antimetabolites are Mycophenolate mofetil (MMF) (Cellcept) and Micophenolic acid (MPA) (Myfortic). Both molecules inhibit de novo synthesis of purine nucleotides leading to blockage of DNA replication in T and B lymphocytes.

Although side effects: confusion, diarrhea, neutropenia, anemia, thrombocytopenia requiring dose reduction in a high percentage (24% - 57%) (1), MMF and MPA antimetabolitii is widely used, 50% of transplant centers U.S. (1).

Other therapies

Biological therapy - induction of antibodies is used to delay initiation of therapy to facilitate maintenance or exclusion of an immunosuppressive agent. Are also used in acute graft rejection phenomenon.

Antithymocitare globulin (ATG) - Are represented by polyclonal antibodies. These antibodies cause depletion of T cells by apoptosis, antibody mediated cytolysis and internalization of the cell surface receptors. The main side effect is the "first dose effect" (cytokine release syndrome), manifested by fever with chills, tachycardia, fluctuations of blood pressure, bronchospasm. These symptoms are diminished by treatment with corticosteroids. Their use is increasing, doubling from 3% in 2002 to 6% in 2003 (1).

T cell monoclonal antibodies - Muromonab-CD3 (OKT3) acts by binding to CD3 surface Ag, this blocking T cell

activation, resulting in a severe reduction in the number of mature T lymphocytes. Side effects are similar to ATG. OKT3 is the main treatment for cortico-resistant rejection phenomena, having a high success rate.

CD25 monoclonal antibodies - Basiliximab (Simulect) and Daclizumab (Zenapax) Immunosuppression is achieved by competitive antagonism of IL-2-induced T-cell proliferation being used in induction therapy. These agents presents reduced adverse effects, in a minimal number of cases, Basiliximab hypersensitivity was reported.

Sirolimus - a macrolide antibiotic whose mechanism consists of FK-binding protein binding, resulting in a complex with inhibitory role on G1 phase of cell division up to S phase. Thus the proliferation of T lymphocytes is inhibited. It is used in maintenance therapy in chronic rejection phenomenon.

Side effects recorded are multiple:

- Leukopenia;
- Anemia;
- Healing of wounds late;
- Joint pain.

Methods of administration

Usually a triple therapy it is used, based on: a calcineurin inhibitor (CyA / TAC), an antimetabolite agent (MMF / MPA) and a corticosteroid (methylprednisolone) (14).

Immunosuppressive therapy is done in three phases:

Induction therapy

First two weeks after surgery. Aims at blocking the immune system rapidly, reducing the risk of early graft rejection.

Agents used: Cyclosporine A may be used in liver transplantation. In case of renal transplantation it is better to use polyclonal antibodies antithymocitari (ATG), T cell monoclonal antibodies - Muromonab-CD3 (OKT3), anti CD25 monoclonal antibodies. These agents are used in renal transplantation to protect the graft in the first period post-translant by nephrotoxic effects of calcineurin inhibitors.

Initial therapy

Between 2 weeks and 3 months postoperatively. Usually consists of a triple therapy: calcineurin inhibitor + steroid + antimetabolites. Occasionally dual therapy can be used: calcineurin inhibitor + steroid.

Maintenance therapy

Long-term therapy, virtually the entire life of the graft. Usually it is based by the same agents as initial therapy, but in low doses, because the graft is more stable in terms of immunology. In this phase, the three classes mentioned, may be associated with Sirolimus, in parallel or replacing calcineurin inhibitors, especially in renal transplantation.

In addition to these standardized three stages the therapy for acute rejection phenomenon can be added (15). For this situation, maintenance therapy may be stopped temporarily or permanently as a result of one or more episodes of graft rejection. If the acute episode does not resolves with corticosteroid therapy, the so-called "corticorezistent rejection phenomenon" polyclonal antibody therapy with ATG, monoclonal OKT3, ALG or with increased doses of tacrolimus will be established.

Study premises

As already mentioned, transplant patients are prone to orthopedic surgery, particularly hip and knee arthroplasty due to bone disease, commonly present. They can be induced by immunosuppressive medications, but may be due to metabolic disorders, secondary to chronic organ dysfunction.

In the case of liver failure, vitamin D metabolism is severely affected, malnutrition and hyperbilirubinemia leading to diminished bone formation. Similarly, in renal failure, phosphate depletion will occur concurrently with hyper-calcemia and hyperparathyroidism deceiving so-called renal osteodystrophy, manifested bybone mineralization deficiency.

Postoperatively, massive doses of corticosteroids lead to osteoporosis and high risk of fracture. Also increases and the incidence of aseptic bone necrosis, which is noticed in about 3-41% of kidney transplant patients (15) and approximately 9% of the transplanted liver. (16,17).

As mentioned for hip or knee arthroplasty for transplanted patients, orthopedic surgeon's attention should be focused on detecting immediate complications - periprostetic infections, postoperative severe anemia as well as on remote complications - implant degradation.

Although the number of transplant patients increased in parallel with osteoarticular disease incidence, all studies of literature presents small batches, 8-10 patients, this indicates a reluctance to surgery.

The most common indication for arthroplasty among these patients is represented by aseptic osteonecrosis of femoral head, femoral condyles or tibial plateau, as mentioned by Maguire or Bradford (18,19). Also hip arthroplasty can be performed in case of femoral neck fracture in osteoporotic bone (Papagelopoulos 21)

Because of theoretical risk of infection, perioperative prophylactic antibiotic therapy is essential. Generally, second or third generation cephalosporins are used as mentioned by the most authors (18,19,20,21). In parallel with these, antifungals medication can be administered in order to combat fungal infections. Although perioperative stopping of the immunosuppressive therapy it is a frequent question, there is no evidence reported to support this hypothesis. For all of these reasons, surgery is not indicated during induction and the initial therapy (up to 3 months after surgery), even if osteoarticular phenomena are acute.

For the vast majority of cited authors in international literature (8 of 9), there are no reports of severe immediate complications, especially infections, in case of hip or knee arthroplasty, in patients with liver and kidney transplant.

However, Tanenbaum (22), in a study on a group of 24 arthroplasties (hip / knee) post kidney transplant and 3 post-liver transplant, has reported a high rate of postoperative

infections - 19%. Periprostetic infections have developed in a period of 3.4 years, being involved 2 patients with liver transplantation and 3 with renal graft. Increased rate of infection in liver graft group may be attributed to high doses of immunosuppressive medication compared with renal transplantation.

Cemented implants have been used in all cases, but without antibiotic mixed cement.

Evaluation of remote functionality of the operated member as well as the degree of wear of the implant will be achieved by using the clinical scores as American Knee Society Score for knee arthroplasty and Harris Score in case of hip arthroplasty, and at the same time, radiological evaluation of the implant.

The mean follow-up recorded in specialized studies is approximately 5-6 years, during this period no revision was reported (21,24), while reading marked improvement of the clinical scores: Harris 34 to 82, AKSS 49/25 to 100/100 (21).

Cases reported

Between 07.2010 - 07.2011 five arthroplasties were performed in our clinic in 3 patients with kidney and liver transplant. The distribution of the interventions is shown in the Table 1.

All patients were males with mean age of 51 years (44-55). The mean period of time between transplantation and arthroplasty was 12 months (8-18).

Case 1

P.O. - M / 55 years. (Fig. 1, 2) Arthroplasty: right hip - total cemented prosthesis (PTC); - Acrylic cement containing antibiotics (gentamicin). Liver Transplant 7 months ago. Diagnosis: right femoral head aseptic necrosis (NACF). Past medical history: not relevant. Immunosuppressive treatment: - Cyclosporin A; - Ursofalk. Preoperative tests: - Full blood cell count; - Coagulation; - Urea and electrolytes; Liver function tests; - Urine culture / pharyngeal exudate.

Prophylactic antibiotics - Vancomycin (12 days postoperatively) - Tienam; - Diflucan. Prophylactic antithrombotic treatment - Clexane f 0.4 ml, 35 days after surgery. Aspirated amount of blood / blood transfusion: 350 ml / 3 u erythrocytes concentrate (MER) + 2 u of Plasma.

Complications: Postoperative anemia.

Table 1.

	Liver transplant	Renal transplant
Hip	Total cemented prosthesis	Total uncemente prosthesis
	Total uncemented prosthesis (revision of a previous implant)	Total uncemented prosthesis
Knee	Total cemented prosthesis	

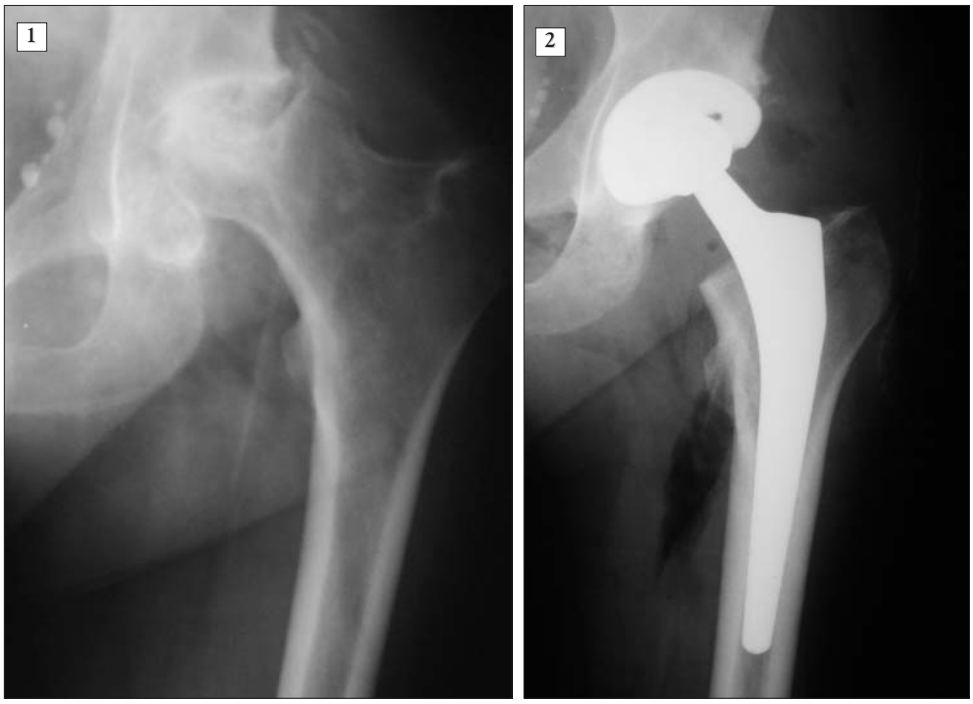
Case 2

P.P. - M / 44 years. Arthroplasty: Right hip - total uncemented prosthesis (PTNC). Left hip - total uncemented prosthesis (PTNC). Renal transplant 8 / 14 months ago. Diagnosis: Bilateral NACF. Past medical history: not relevant.

Immunosuppressive treatment: - Medrol; - Tacrolimus; - Myfortis. Immunosuppressive therapy was discontinued perioperative (24 h).

Preoperative tests: as above. Prophylactic antibiotic treatment - Ceftriaxone (12 days postoperatively); - Ciprofloxacin.

Prophylactic antithrombotic treatment - Clexane f 0.4 ml,



Figures 1, 2. *preoperative **(1)** postoperative **(2)***

35 days after surgery. Aspirated amount of blood / blood transfusion: - 250 ml / 1 u MER; - 850 ml / 3 u MER.

Complications: Postoperative anemia.

Case 3

S.A. - M / 51 years. Arthroplasty: left hip - total uncemented prosthesis, distal pented (Revision of a previous implant). Right knee - Cemented total knee prosthesis (PTG); - Acrylic cement containing antibiotics (gentamicin). Renal transplantation in 12 and 18 months ago. Diagnosis: Bilateral NACF operated PTNC bilateral implant degradation off. External femoral condyle osteochondritis off. Gonarthrosis left. Osteoporosis - Past medical history: Gaucher disease in treatment with imiglucerase. Splenectomy.

Immunosuppressive treatment: - Cyclosporin A; - Mycophenolate mofetil (Cellsept); - Lamivudine.

Preoperative tests: as above. Prophylactic antibiotics - Vancomycin (12 days postoperatively); - Meronem; - Diflucan.

Prophylactic treatment antitrobotic - f 0.4 ml Clexane, 35 days after surgery. Aspirated amount of blood / blood transfusion: - 500 ml / 4 u MER (PTNC); - 850 ml / 4 u MER (PTG).

Complications - Postoperative anemia

There was a case of degradation of uncemented implant consisting in a stuffed and sprain hip prosthesis. Revision with a cemented implant was required and perioperative preparation was identical to previous interventions. We had used acrylic cement with antibiotic (gentamicin). Hemoragic aspirate was 400 mL requiring three units MER for post-operative anemia correction. No other complications were recorded.

The patients were evaluated clinically and radiologically through periodic checks at 6 weeks, 3 months and one year postoperatively. Clinical evaluation was performed using the Harris hip score, for arthroplasty of the hip and AKSS in case of knee arthroplasty. The biological constants were also assessed (hemoglobin, fibrinogen, ESR, liver / kidney samples), blood loss, postoperative anemia being corrected. In the case of hip arthroplasty the average volume of blood aspirate was 550 ml for renal transplant and 425 ml for the liver transplant - while in the transplanted liver with knee arthroplasty 850 ml of blood were aspirated.

Results

Clinical scores were improved both for hip and knee arthroplasty. Chart 1 AKSS; Chart 2 Harris score.

No signs of periprosthetic infection were found in any case. Radiological assessment revealed no early loosening in any case. The patient with Gaucher disease and liver transplantation, mechanical complications occurred as clogging and dislocation of the femoral component of the prosthesis. As a consequence, revision was performed to cemented femoral component implant.

Postoperative anemia was detected in all cases, all patients having blood loss, and requiring blood transfusions at least 3 u MER.

Conclusions

Liver / kidney transplanted patients are generally young patients without a history of osteo-articular diseases.

The main postransplant osteoarticular disease was aseptic osteonecrosis. This has a rapidly evolution and severe clinical manifestations, arthroplasty representing the best way to restore joint function.

Although, in theory, the infection is a major risk, we have not registered any case in our group. Pre- and post-operative antibiotics are mandatory, but not liver or nephrotoxic antibiotics should not be used. These were adapted according to the transplanted organ.

We have not seen a benefit in the perioperative (24 h) suppression of immunosuppressive therapy.

Another common condition in transplanted patients is osteoporosis. In theory this requires the use of cemented implants. Uncemented implants used, however have not proved lower, when the indication is correct. So we have not noticed remote complications as loosening. Revision was practiced in only patient with Gaucher disease, this disease itself inducing severe changes in bone quality (osteonecrosis, osteoporosis, deformation). Thus, this latter case of implant degradation is not conclusive, as the patient was already prone to chronic organ failure affected bone.

In case of cemented implants the use of acrylic cement impregnated with antibiotic is mandatory.

In conclusion, the arthroplasty for patients with kidney or liver transplant has a positive impact on their quality of life, being a safe and successfully procedure with minimum perioperative safeguards.

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