Use of Structural Allograft and Post-Surgical Infections

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ABSTRACT
Introduction: The use of allografts carries the risk of various complications. Among the most frequent is infection. An important risk factor for infection with the use of bone grafts is the transmission of germs through the graft itself. Our objectives are to determine if there is a relationship between possible contamination of the grafts from this bank and postoperative infections; demonstrate how the proper donor selection, procurement, and processing of the graft decrease the rate of contamination; and report other complications related to the quality of the graft. **Materials and Methods:** We selected patients who received structural bone grafts from our bank. All grafts were microbiologically studied. A review of the health records, anamnesis, physical examination, and radiographs was performed to evaluate infection and other complications. The ISOLS Osseointegration Scale was used to asses the consolidation of the grafts. **Results:** No graft contamination was detected. One case (7.7%) of infection by carbapenemase-producing Klebsiella pneumoniae (KPC) and 3 cases (23%) of nonunion were identified. Consolidation was good to excellent in 77% of cases, satisfactory in 8%, and poor in 15%. No other complications were found. **Conclusion:** There is a risk for infection transmission with structural allograft. Regulated donor selection criteria and control of bone bank procedures reduce the risk of infection due to graft contamination and other complications related to graft quality.
Key words: Structural allograft; bone bank; infection; complications.
Level of Evidence: IV

Uso de aloinjerto estructural e infecciones posquirúrgicas

RESUMEN
Introducción: El uso de aloinjertos conlleva el riesgo de complicaciones. Una de las más frecuentes es la infección. Un importante factor de riesgo de infección con el uso de injertos óseos es la transmisión de gérmenes a través del injerto. Nuestros objetivos fueron determinar si existe una relación entre la posible contaminación de los injertos de este Banco y las infecciones posquirúrgicas; demostrar cómo la selección del donante, la procuración y el procesado del injerto adecuados disminuyen la tasa de contaminación e informar otras complicaciones relacionadas con la calidad del injerto. **Materiales y Métodos:** Se seleccionaron pacientes que recibieron injerto óseo estructural de nuestro Banco. Todos los injertos fueron estudiados microbiológicamente. Se revisaron las historias clínicas, y los pacientes fueron sometidos a una anamnesis y un examen físico, y se les tomaron radiografías para detectar infección y otras complicaciones. Se utilizó la Escala de Osteointegración ISOLS. **Resultados:** En ninguno de los injertos, se detectó contaminación. Se identificó un caso (7,7%) de infección por *Klebsiella pneumoniae* productora de carbapenemasas y 3 casos (23%) de falta de integración. La integración fue entre buena y excelente en el 77% de los casos, satisfactoria en el 8% y pobre en el 15%. No hubo otras complicaciones. **Conclusiones:** Existe riesgo de transmisión de infecciones con el aloinjerto estructural. Los criterios reglados de selección de donantes y el control de los procedimientos dentro del banco de huesos disminuyen el riesgo de infección por contaminación del injerto y de otras complicaciones relacionadas con la calidad del injerto.
Palabras clave: Aloinjerto estructural; banco de huesos; infección; complicaciones.
Nivel de Evidencia: IV

INTRODUCTION

The use of bone grafting in trauma and orthopedic surgery is constantly growing.[1,2] There are many and varied conditions that require the contribution of this biological material, such as the treatment of tumors, pseudotumor lesions, consolidation defects, pseudarthrosis, congenital malformations, spinal arthrodesis, bone defects, and prosthesis revisions, among others.[1-4]

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The graft that meets the best conditions for the recipient patient is the autologous,[5] since it does not cause immune response disorders in the host against the donated graft and does not pose the risk of disease transmission. However, the bone graft requirements of certain surgeries, for example, when massive structural grafting is needed, make it impossible to obtain it from the same patient. In these cases, the use of the allograft is justified, that is, graft obtained from another individual of the same species and transplanted to the recipient.

As a result of this need, the Musculoskeletal System Tissue Banks were created, which are organizations responsible for the detection of the potential donor (whether living or cadaveric), its selection, the ablation or obtaining of grafts, their processing (decellularization, evaluation of type and quantity of germs, sterilization, packaging, etc.), their storage and subsequent distribution to the requesting doctors authorized so that they can be used in surgeries. All this is done through a series of orderly and traceable processes.[1,2]

The use of structural allografts, such as cortical tables and rings, diaphyseal segments, or osteoarticular allografts for complex reconstructions, carries the risk of various complications that can result in a high failure rate.[4] Among the most frequent are infection, lack of integration of the graft with the host bone, and other complications related to the alteration of the biomechanical properties of the graft. The frequency of these complications varies with each of the types of structural graft mentioned.[4]

Regarding infection, when structural allografts are used in surgeries, there are many factors related to this complication, regardless of the use of the graft. Some of these factors include extensive bone resections, loss of soft tissue coverage, and prolonged duration of surgery.[5] Other risk factors for infection have also been described in surgeries requiring allografts, such as surgical technique, age of the recipient (>60 years), diabetes, smoking, excessive alcohol consumption, or a history of other infections.[6]

However, one of the risk factors for infection with the use of bone grafts most mentioned in the literature consulted is the transmission of germs through the same graft.[2,7,8]

The primary objective of this study was to determine if there is a relationship between the possible contamination of the grafts of this Bank and the published post-surgical infectious complications. As a secondary objective, we tried to demonstrate whether the selection criteria properly applied to the donor, the standardization of procurement methods, and the correct processing of the procured parts reduced the rate of microbiological contamination of the structural graft. Finally, we reported on the results of other complications related to the quality of the graft.

MATERIALS AND METHODS

A retrospective and descriptive study of the experience of the Bone Bank of Hospital Alemán and an analysis of the literature on the subject were carried out.

We selected a population of patients treated in our hospital for various reasons with bone tissue from the aforementioned Bone Bank between January 1, 2012 and December 31, 2015. In all cases, the type of graft received was structural. The minimum accepted follow-up was 6 months.

To obtain these grafts, all donors were accepted according to the selection criteria established by the *Instituto Nacional Central Único Coordinador de Ablación e Implante* (INCUCAI) and by the Bone Bank of Hospital Alemán. All the grafts obtained were processed according to the processing protocols of our Quality Guide; in each of the stages, from the selection of the donor to its use, they were handled by personnel belonging to our Bone Bank. This Tissue Bank and its staff are authorized as established by INCUCAI Provisions No. 088/16 and 089/16.

Cultures were performed in all tissues for the control of microbiology at the time of ablation and processing in its different stages. The microbiological control was always carried out in the Microbiology Laboratory of Hospital Alemán, and included culture of bacteria, mycobacteria, and fungi. According to the quality policies of the Bone Bank Procedure Manual, tissues will be properly discarded if either of the two microbiology tests (ablation or processing) yields positive results.

With respect to the inclusion criteria, patients of both sexes were incorporated, without age restriction, with a diagnosis of any condition that required treatment with structural bone graft and who had received grafts exclusively from our Bone Bank for treatment. The exclusion criteria were: previous active infectious disease at the graft recipient site (infected pseudarthrosis, osteomyelitis, septic arthritis), concomitant immunosuppression, and prior use of grafts not belonging to this Bone Bank.

14 structural grafts were studied in 12 patients. One (1 graft) of these 12 patients was excluded because he had osteomyelitis as the initial disease of the graft recipient site. Finally, 13 grafts were analyzed in 11 patients (Table 1).

Table 1. Patient overview

Patient	Date of surgery	Follow-up	Age	Sex	Illness	Treatment		Postoperative complications
						Surgery	Type of Graft	
1	10/ OCT/2012	34 months	12	M	Ollier disease, femur enchondroma with deformity and misalignment.	Resection + corrective osteotomy + intercalary graft	Distal femur + diaphysis 23 cm	No
2	28/ SEPT/2012	10 months	8	M	Proximal femur Ewing sarcoma	Resection + intercalary graft	Proximal tibia with extensor apparatus + 15 cm diaphysis	No
3	9/ SEPT/2013	16 months	69	F	Nonunion of periprosthetic hip fracture	Osteosynthesis revision + graft	13 cm table	Yes
4	26/ NOV/2013	30 months	18	M	Relapsed chondroblastoma of proximal humerus	Resection + alloprosthesis	Proximal humerus with cuff + 15 cm diaphysis	No
5	12/ JUN/2014	23 months	40	M	Pelvic chondrosarcoma	Resection + intercalary graft	Proximal tibia + 10 cm diaphysis	Yes
6	19/ AUG/2014	21 months	74	F	Periprosthetic shoulder fracture	Revision of total prosthesis to shoulder hemiarthroplasty + osteosynthesis + graft	10 cm table	Yes
7	12/ DEC/2014	18 months	29	F	Uninfected nonunion of the femur	Osteosynthesis revision + graft	20 cm table	No
8	7/ JAN/2015	17 months	40	F	Osteosarcoma of the femur	Resection + intercalary graft	Femoral diaphysis 15 cm	No
9	8/ JAN/2015	17 months	72	F	Histiocytic sarcoma of the humerus	Resection + intercalary graft	Humeral diaphysis 20 cm	No
10	22/ JAN/2015	16 months	71	F	Nonunion/refracture of periprosthetic hip fracture	Revision of hip prostheses + graft	15 cm table	No
11	27/ OCT/2015	7 months	75	F	Revision of shoulder arthroplasty	Revision of hemiarthroplasty to inverted total shoulder prosthesis + revision of osteosynthesis + graft	Distal tibia 10 cm	No
12	15/ NOV/2015	7 months	41	M	Uninfected nonunion of the femur	Osteosynthesis revision + graft	15 cm table	No
13	15/ DEC/2015	6 months	53	M	Uninfected nonunion of the femur	Osteosynthesis revision + graft	20 cm table	No

Patient 3 is the same as patient 10 and patient 6 is the same as patient 11. They were included twice in the list because they were treated with structural grafting twice.

In addition to the review of the medical history, all the patients included were called and subjected to anamnesis and physical examination by the same examiner to objectively evaluate the presence of infectious complications or any other complication (lack of integration, fracture of the graft, etc.) related to the structural bone graft. Likewise, a radiographic study was carried out to evaluate the condition of the graft at the time of the study. The Osseointegration Scale of the International Symposium on Limb Salvage (ISOLS) was used to evaluate graft integration. (Table 2).

Table 2. ISOLS Osseointegration Scale

Radiological osseointegration	Outcome
100%	Excellent
>75%	Fair
25-75%	Acceptable
<25%	Poor

RESULTS

All microbiological studies were carried out in the Microbiology Laboratory of *Hospital Alemán.* The analyses and cultures were carried out twice: on a first sample taken during ablation and on a second sample taken during the processing or preparation of the graft, before the final packaging. The results of all samples were negative.

During the clinical evaluation, no patients had signs or symptoms of active infection, or sequelae or complications due to the use of structural grafting.

According to radiographic studies, none had signs of graft or surgical site infection or loosening of osteosynthesis material (Tables 3 and 4, Figures 1 and 2).

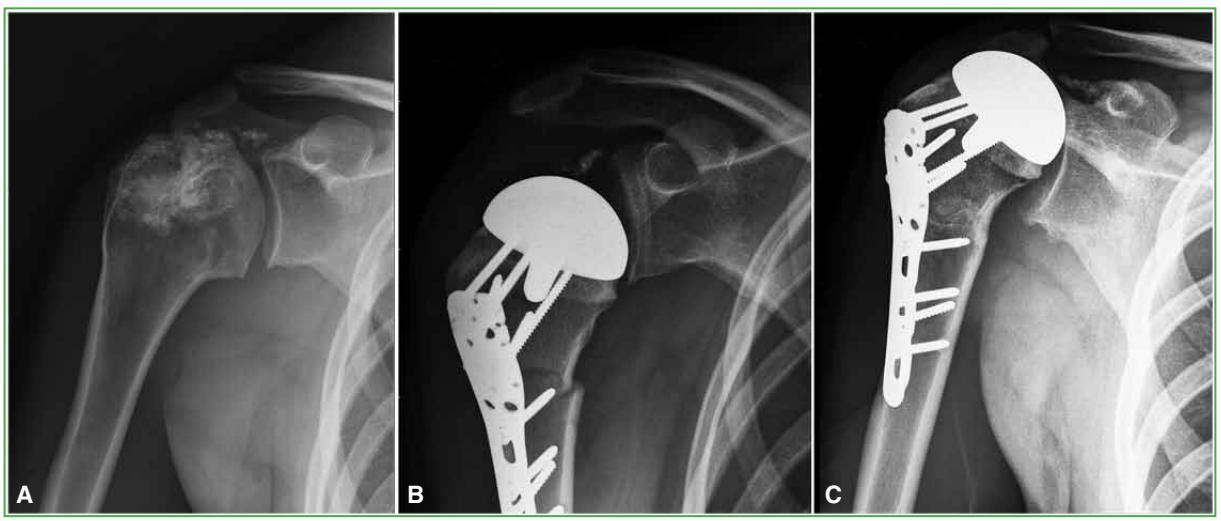

Figure 1. Case 4. Proximal humerus chondroblastoma. The progressive integration of the graft is observed. **A.** Preoperative right proximal humerus radiograph. **B.** Radiograph of the right proximal humerus in the immediate postoperative period. **C.** Radiograph of the right proximal humerus 6 months after surgery.

Table 3. Patient treatment details

Patient	Treatment				
	Surgery	Type of graft	Type of fixation	Preoperative chemotherapy	Postoperative chemotherapy
1	Resection + corrective osteotomy + intercalary graft	Distal femur + diaphysis 23 cm	Plate with screws	No	No
2	Resection + intercalary graft	Proximal tibia with extensor apparatus + 15 cm diaphysis	Plate with screws	Yes	Yes
3	Osteosynthesis revision + graft	13 cm table	Plate with screws	No	No
4	Resection + alloprosthesis	Proximal humerus with cuff + 15 cm diaphysis	Plate with screws	No	No
5	Resection + intercalary graft	Proximal tibia + 10 cm diaphysis	Rods and screws	No	No
6	Revision of total prosthesis to shoulder hemiarthroplasty + osteosynthesis + graft	10 cm table	Plate with screws + wire cerclage	No	No
7	Osteosynthesis revision + graft	20 cm table	Plate with screws	No	No
8	Resection + intercalary graft	Femoral diaphysis 15 cm	Plates with screws	Yes	Yes
9	Resection + intercalary graft	Humeral diaphysis 20 cm	Plate with screws	Yes	Yes
10	Revision of hip prostheses + graft	15 cm table	Wire cerclage	No	No
11	Revision of hemiarthroplasty to inverted total shoulder prosthesis + revision of osteosynthesis + graft	Distal tibia 10 cm	Plate with screws + wire cerclage	No	No
12	Revision of osteosynthesis + Graft	15 cm table	Plate with screws	No	No
13	Revision of osteosynthesis + Graft	20 cm table	Plate with screws	No	No

Table 4. Complications and their treatment

Patient	Complications					Treatment of the complication
	Infection	No integration	Reabsorption	Fracture	Other	
1	No	No	No	No	No	___
2	No	No	No	No	No	___
3	No	Yes	No	No	No	Revision of osteosynthesis + new graft
4	No	No	No	No	No	___
5	Yes*	Yes	Yes	No	No	Debridement, chemotherapy + antibiotic
6	No	Yes	Yes	No	No	Arthroplasty revision + new graft
7	No	No	No	No	No	___
8	No	No	No	No	No	___
9	No	No	No	No	No	___
10	No	No	No	No	No	___
11	No	No	No	No	No	___
12	No	No	No	No	No	___
13	No	No	No	No	No	___

*Patient 5: Infection 12 days after surgery (admitted to the Intensive Care Unit). Germ: Carbapenemase-producing *Klebsiella pneumoniae.* Antibiotics: intravenous fosfomycin/gentamicin and then doxycycline.

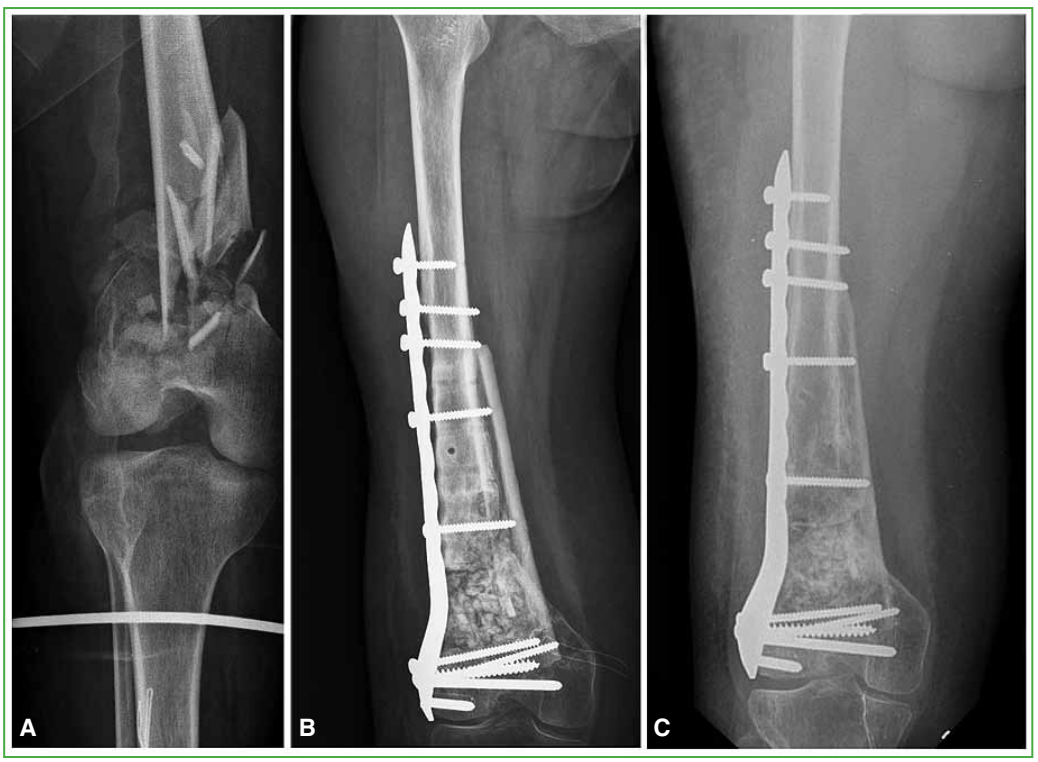

Figure 2. Case 7. Distal femur fracture. The progressive integration of the graft is observed. **A.** Preoperative right distal femur radiograph. **B.** Radiograph of the right distal femur one month after surgery. **C.** Radiograph of the right distal femur 9 months after surgery.

The correct alignment of the graft was corroborated in all cases. Likewise, according to the ISOLS Osseointegration scale, integration was excellent in 54% of patients (7 cases), good in 23% (3 patients), acceptable in 8% (1 case), and poor in 15% (2 cases). Table 5 details the results of each patient for graft integration according to the scale mentioned.

Table 5. Results according to the ISOLS Osseointegration Scale

Patient	Percentage of radiologic osseointegration	ISOLS Score
1	100%	Excellent
2	100%	Excellent
3	25-75%	Acceptable
4	100%	Excellent
5	0-25%	Poor
6	0%	Poor
7	100%	Excellent
8	100%	Excellent
9	75-100%	Fair
10	100%	Excellent
11	100%	Excellent
12	75-100%	Fair
13	75-100%	Fair

The percentage of radiologic osseointegration achieved and its corresponding classification according to the ISOLS score for each patient is observed.

During the review of the health records, one case (7.7%) of surgical site infection was identified. This was a patient with a grade 3 chondrosarcoma in the left hemipelvis (Case 5), who had undergone an internal hemipelvectomy (type 1 resection) and a reconstruction with structural graft and osteosynthesis. After 12 days, while hospitalized in the Intensive Care Unit, he was diagnosed with surgical site infection. The germ detected was *Klebsiella pneumoniae*, a gram-negative carbapenemase-producing bacterium. Carbapenemases are enzymes that inactivate beta-lactam antibiotics, such as penicillin and cephalosporins. He underwent surgical debridement at the site and, after an interconsultation with the Department of Infectious Diseases, he was administered fosfomycin/gentamicin intravenously and then doxycycline orally, for 6 months. The infection progressed favorably (Figure 3).

During the review of the medical records, three cases (23%) of lack of integration were also identified, two of them (15.4%) due to graft resorption. One of the cases of lack of integration and resorption of the graft was that of the patient who evolved with infection of the surgical site (Case 5). The other (Case 6) corresponded to a patient with a periprosthetic shoulder fracture, undergoing a revision of total prosthesis to hemiarthroplasty with osteosynthesis and structural graft (cortical table), which finally resulted in pseudarthrosis of the fracture with resorption and lack of integration of the graft. The last case of lack of integration (Case 3) was a patient with an initial diagnosis of pseudarthrosis of periprosthetic hip fracture. A revision osteosynthesis was performed with a structural graft (cortical table) as a treatment. The evolution continued with the pseudarthrosis of the fracture and the lack of integration of the graft.

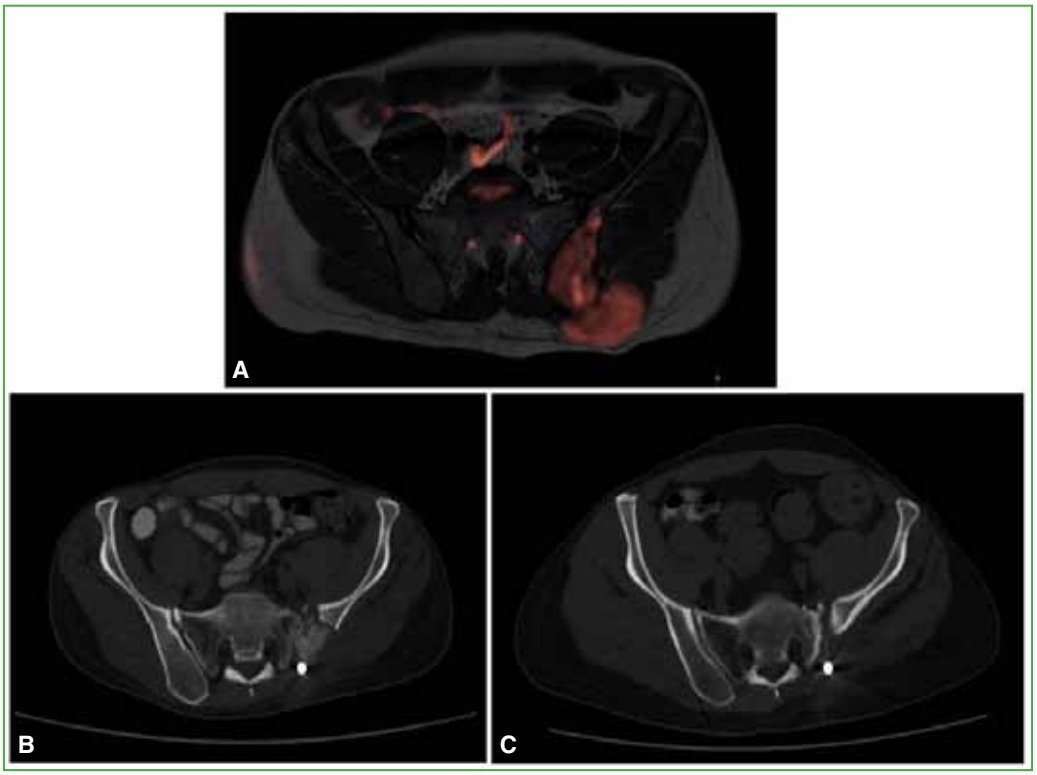

Figure 3. Case 5. Chondrosarcoma of the pelvis. Progressive reabsorption of the graft is observed. **A.** Preoperative pelvic MRI. **B.** CT scan of the pelvis 6 months after surgery. **C.** CT scan of the pelvis 2 years after surgery.

DISCUSSION

Infection associated with the use of an allograft is one of the most worrisome complications for the surgeon. One of the most mentioned risk factors for infection in the literature is the transmission of germs through the graft.[2,7,8]

According to most authors, contamination of bone pieces occurs at the time of ablation.[2,7,8] However, bacteria were sometimes detected in the donor's blood as a result of contamination at the time of death (trauma) or, in the case of multi-organ cadaveric donors, as a result of the previous removal of organs and other tissues.[9,10] Veen et al.[10] considered the number of ablation doctors (more than four) as a factor of contamination. In another similar study, Barrios et al.[11] showed that contamination also depends on the number of people handling the material and the prolonged duration of the ablation.

According to the analysis of the contaminated samples, the bacteria found usually correspond to low-pathogenicity genera of the skin microbiota.[2,8,9] Different studies, including that of James et al.,[12] identified coagulase-negative *Staphylococcus sp.* as the most frequent isolated microorganism in an allograft. Other germs, such as *Staphylococcus epidermidis, Propionibacterium* sp. and bacteria of the genus *Clostridium* sp., are also commonly detected, all of them gram-positive.[12]

On the other hand, there is a risk of viral transmission with the use of bank grafting.[2,13] Blood and bone marrow are primarily responsible for viral transmission, but there is evidence that cartilage, ligaments, tendons, and menisci would also have this property.[13]

In the United States, cases of human immunodeficiency virus transmission through allografts of donor musculoskeletal tissue were reported. In one of them, the Tissue Bank that distributed them found that three of the four unprocessed frozen musculoskeletal allograft receptors (2 femoral heads, and an anterior tibial patella-tendon-tubercle complex) were infected with the human immunodeficiency virus; however, other grafts from the same

donor, which were processed and frozen (fascia lata, other tendons and ligaments), did not transmit the disease.[14] This case exemplifies that the method of preservation by freezing without proper processing of the piece does not destroy the human immunodeficiency virus. The processing of the implanted material removes the core contents where the virus is found.

On the basis of previous internationally recognized studies,[2,8,9] this Bank has adopted decellularization by repeated washing with suitable solutions as a form of processing and freezing at -80 °C for the conservation and storage of structural bone pieces.

A rigorous control must be performed in the selection of the donor, in compliance with the protocols for tissue ablation. Likewise, an adequate processing of the obtained parts and a strict subsequent microbiological control must also be carried out. Disregarding these procedures can lead to post-surgical infection by a contaminated graft.[2,9]

In this study, there were no grafts removed due to microbiological contamination. On the other hand, as mentioned by Aponte-Tinao et al.,[4] several factors can produce a risk of infection during surgery, in addition to the use of allograft. Some risk factors for infection include extensive bone resection with soft tissue loss, the duration of the procedure, and adjuvant treatments, such as chemotherapy and radiation therapy in cases of bone tumors.

The frequency of infection of massive allografts in most published series is 5% to 30%.[15,16] For example, Aponte-Tinao et al.[15] reported a 9% incidence rate of infection in 673 patients. It should be noted that a complication such as infection usually leads to removal of the allograft, so it is related to a high surgical failure rate.

In this study, there was only one case (7.7%) of surgical site infection and the isolated germ was carbapenemase-producing *Klebsiella pneumoniae.* The detection was early, during the stay in the Intensive Care Unit, and was treated with surgical debridement on postoperative day 12 and antibiotic treatment for 6 months.

Although the infection rate coincides with that of the literature studied, the isolated germ did not correspond to the germs normally detected in cases of graft contamination. Carbapenemase-producing *Klebsiella pneumoniae* is a germ related to hospital-acquired infections in closed units. Although structural allograft was used, due to the nature of the surgery (internal hemipelvectomy plus reconstruction), the large bone resection, and the surgical duration, we can conclude that the infection was not directly related to the graft, but to other concomitant factors.

Other non-infectious complications

Integration in the allograft-host junction takes a longer time than autograft-host integrations.[17-19] Dion and Sim[17] stated that a graft is considered not to have been integrated with the host bone when integration is not observed after one year and that the rate varies between 11% and 17%. Enneking and Mindel[18] demonstrated that integration between the graft and the host's bone occurs slowly by the formation of new bone on the surface of the graft through an external callus that comes from the host's cortical bone, and more rapidly inside the graft by resorption and formation of an internal callus from the host's trabecular bone.

Several factors are determinants for allograft integration, including the type of graft fixation and concomitant treatment with chemotherapy in patients with bone tumors.[20]

With regard to the method of osteosynthesis used, Aponte-Tinao et al.[21] observed that plates with screws have a lower incidence of lack of integration than intramedullary nails (15% versus 28%) for they provide more stable fixation.

Chemotherapy would have an inhibitory effect on the integration between the graft and the host. Enneking and Campanacci[22] demonstrated an association between delayed allograft-host integration and preoperative chemotherapy. Hazan et al.[23] reported a lack of integration in 32% of cases requiring chemotherapy and in 12% of those who did not require chemotherapy. On the other hand, Delloye et al. found no differences.[20]

In this study, 77% of the patients had an integration classified between good and excellent according to the ISOLS scale, which corresponded to a radiological osseointegration >75%. 8% of the cases had a satisfactory integration (25-75% of radiological osseointegration) and 15%, a poor one (<25% of radiological osseointegration). There were three cases (23%) of lack of integration.

There were no cases of lack of graft integration or other related complications in patients who had received preoperative chemotherapy.

These rates do not fully coincide with what is mentioned in the literature, although the small number of cases could justify this discrepancy.

Several authors, including Davy,[24] showed that the biomechanical properties of grafting, such as flexural, compressive, or torsional resistance, are not lost at storage temperatures between -70°C and -80°C, since at these temperatures the enzymatic degradation of tissues stops. In the Bone Bank of Hospital Alemán, bone allografts are kept in low-temperature freezers that, according to periodically surveyed records, oscillate in that range.

In this study, we used long cortical bones frozen and preserved at these temperatures, as recommended in the literature, and, in the patients analyzed, no complications related to the alteration of graft biomechanics were observed.

Finally, the weaknesses of this study were that the selected population was too scarce to obtain reliable results, that the follow-up time had not been extensive enough in all cases, that very diverse pathologies and age groups were analyzed, and that it was a retrospective study.

CONCLUSIONS

The use of structural allografts poses a potential risk of transmission of infectious diseases. However, the application of our standards and working protocols proved to be effective in preventing post-surgical infections due to graft contamination. To avoid contamination of the grafts, it is imperative to comply with standardized donor selection criteria, standardize procurement methods, perform a correct processing of the pieces obtained, and carry out an exhaustive control of other procedures that take place within a bone bank. In this way, the risk of postoperative infection due to contamination of the graft and also the eventual appearance of other complications related to the quality of the structural allograft is significantly reduced.

Conflict of interests: The authors declare they do not have any conflict of interests.

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