Adverse reactions and events related to musculoskeletal allografts: reviewed by the World Health Organisation Project NOTIFY

M. Hinsenkamp · L. Muylle · T. Eastlund · D. Fehily ·
L. Noël · D. M. Strong

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Abstract

Purpose The use of bone and connective tissue allografts has grown rapidly and surpassed the use of autografts in many countries. Being of human origin, bone and tendon allografts carry the risk of disease transmission and complications have been reported. As part of the Project NOTIFY led by the World Health Organisation, an effort to improve recognition, reporting, tracking and investigation of adverse outcomes of allografts was initiated, achieving a comprehensive review of associated disease transmission and failures. Those involving the use of musculoskeletal allografts are reported here. A major objective is to involve orthopaedic surgeons in the improvement of the safe use of the musculoskeletal allografts. **Methods** We reviewed the medical literature, requested reports from surgeons in selected professional organisations and informally surveyed tissue bank organisations and selected tissue bank professionals to discover reported and unreported cases of adverse outcomes. We analysed each case to decide the likelihood that the complication was truly allograft related.

Results The efficiency of the procedures involved in bone banking and bone and tendon allograft has improved significantly during the last three decades. The evolution of the incidence of reported adverse reactions and events reflects positively on the safety of transplanted tissues. Cases of bacterial and viral transmission by bone and tendon allografts occurred mainly with those that contained viable cells, were not processed to remove cells, or were not disinfected or sterilised. We documented cases of transmission of human immunodeficiency virus (HIV), hepatitis C virus (HCV), human T-lymphotropic virus (HTLV), unspecified hepatitis, tuberculosis and other bacteria. Reporting of these adverse outcomes has led to corrective actions and has significantly improved the safety of allograft use. However, it is probable that not all cases have been reported and investigated.

Conclusions Considering the high quality standards achieved in many countries, the best approach for further improvement in the safety of allografts is through a systematic reporting of all serious adverse reactions and events in the context of a global biovigilance programme.

M. Hinsenkamp (✉)
Department of Orthopaedic Surgery and Traumatology,
Hôpital Erasme, Brussels University,
808 route de Lennik,
1070 Brussels, Belgium
e-mail: mhinsenk@ulb.ac.be

L. Muylle
Antwerp University Hospital, Edegem and Antwerp University,
Antwerp, Belgium

L. Muylle
Federal Agency for Medicines and Health Products,
Brussels, Belgium

T. Eastlund
Division of Transfusion Medicine, Dept. of Pathology,
University of New Mexico, School of Medicine,
Albuquerque, NM, USA

D. Fehily
Italian National Transplant Centre, National Institute of Health,
Rome, Italy

L. Noël
Health System Governance and Service Delivery,
World Health Organization-HQ,
Geneva 27, Switzerland

D. M. Strong
Department of Orthopaedics and Sports Medicine,
University of Washington School of Medicine,
Seattle, WA, USA

Introduction

Bone and tendon allografts, including demineralised bone matrix, represent a useful and sometimes indispensable tool for the orthopaedic surgeon to repair bone defects and to improve function. Even if in the previous reported cases of viral transmission (the last one happened in 2000) non sensitive hepatitis C virus (HCV) or human immunodeficiency virus (HIV) tests were performed before the use of the graft, a major concern of their use remains the well-documented risk of transmitting infectious agents and malignant cells [10].

The reporting of allograft-associated complications by the orthopaedic surgeon triggers an investigation that is essential to correct errors and accidents and improve safety of allograft use and preventing bone donations from the same donor or same batch being transplanted into other recipients. Facing the globalisation of tissue transplantation this requires systematic and rigorous procedures of bio-vigilance. As requested by resolution 63.22 of the Sixty-third World Health Assembly in 2010, the World Health Organisation (WHO) in collaboration with the Italian National Transplant Centre (CNT) and the European Union (EU)-funded project Vigilance and Surveillance of Substances of Human Origin (SOHO V&S) launched Project NOTIFY with the aims of optimising global vigilance and surveillance for cell, tissue and organ transplantation. A key objective is to improve recognition, reporting, tracking and investigation of adverse outcomes associated with tissue and cell transplantation [57, 58].

Participants of the Project NOTIFY undertook a review of adverse outcomes of bone and tendon allograft transplantation, procedures followed by tissue banks to prevent disease transmission, issues surrounding the recognition, reporting and investigation of adverse outcomes, and measures taken to improve the safety of allografts. We provide here a preliminary report of the work of the musculoskeletal group Project NOTIFY.

Method

Project NOTIFY developed a database of adverse reactions and events related to the transplantation of musculoskeletal allografts collected from reported cases in the literature and from tissue bank specialists, orthopaedic surgeons and members of the International Society of Orthopaedic Surgery and Traumatology (SICOT). The members were consulted by e-mail and asked to return a standardised questionnaire. The details of each case were reviewed to determine whether transmission by a bone or tendon allograft was confirmed. The risk associated with tissue transplantation was reviewed based on the collected information.

The following definitions of allograft adverse outcomes adopted in the European Directives for Tissues and Cells were considered appropriate and useful for international application with a slight modification in order to include “human application” and “donors”:

1. Serious adverse event (SAE): any untoward occurrence associated with the procurement testing, processing, storage, distribution “and human application” of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients “or donors” or which might result in or prolong hospitalisation or morbidity.
2. Serious adverse reaction (SAR): any unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or prolongs hospitalisation or morbidity.

Results

HIV transmission

Nine cases of HIV infections reported were due to the use of frozen bone and/or tendon allografts. In a brief report that did not describe details, one possible case was associated with the use of lyophilised bone chips and in two possible cases, the nature of the bone was not known (Table 1). Except for one case involving an untested donor, in 1996, all other cases occurred between the years 1984 and 1986 suggesting a beneficial effect of more stringent donor selection procedures and improved efficacy of testing for HIV infection. Nine of the cases were due to the fact that HIV testing was not yet available at the time of the procurement of the allografts and, in one case, due to the failure to perform HIV testing of the donor. The diagnosis resulted from the finding of a positive test in seven asymptomatic patients and in five patients after the onset of general inflammatory symptoms. In eight cases the infection was confirmed in the donor, whereas in four cases the infection was not documented in the donor (two donors). Diagnosis was made three weeks to 1.5 years after transplantation. Two of the infected donors were multiorgan donors (one not tested for anti-HIV and one false-negative for anti-HIV).

From 1 of these donors, unprocessed cryopreserved bone was transplanted in 12 patients [44]. Four of these patients seroconverted, whereas seven did not. One patient died a natural death before testing could be performed. From the other multiorgan donor, allografts were transplanted in 48

Table 1 Cases of HIV transmission

<i>n</i>	Type of allograft	Date	Publication date	Proven	Author (reference)
1	Frozen femoral head ^a	1984	1988	+	CDC [35]
4	Cryopreserved bone ^a	1984	1996	+	Schratt et al. [44]
2	Frozen femoral head ^b	1985	1992	+	Simonds et al. [46]
3	Bone chip, lyophilised bone allografts (not specified) ^a	1985	1997	+/-	Karcher [26]
1	Frozen patella (including patellar ligament and tendon and a section of tibia) ^b	1986	1992	+	Simonds et al. [46]
1	Frozen femoral head ^a	1996	2001	+/-	Li et al. [32]

^aNo anti-HIV test performed on donor^bAnti-HIV-1 negative, NAT positive

identified patients and 41 of 48 patients were available for HIV testing [46]. All four organ transplant patients and all three recipients of unprocessed fresh-frozen bone or tendon seroconverted, whereas 34 recipients of other tissues (two corneas, three lyophilised soft tissues, 25 ethanol-treated bones, three gamma-irradiated dura mater and one fresh-frozen bone cleaned to remove bone marrow) did not seroconvert.

Today, the risk of HIV transmission to tissue recipients is greatly reduced by the use of HIV nucleic acid testing (NAT) of the donor.

With the frequent addition of screening for the p24 antigen followed by the use of HIV nucleic acid amplification tests (NAT), no new cases of HIV contamination have been reported during the last 15 years, although the performance of these tests is not a requirement in the EU.

HCV transmission

All of the ten cases of HCV transmissions resulted from the transplantation of frozen or cryopreserved allografts that were not heavily processed or sterilised (Table 2). The latest cases reported were caused by tissues recovered in 2000. No case has been reported since the implementation of HCV NAT for donors has become common, although this test is not required by authorities in many countries. The diagnosis

in the infected patients was made after the onset of acute clinical symptoms (one case) or after look back testing with new more sensitive tests of the implicated donors.

The paper by Tugwell et al. [54] illustrates the importance of both rapid notification of suspected cases of virus transmission (biovigilance) and full traceability from donor to patient and vice versa. A patient developed acute symptomatic hepatitis C six weeks after receiving a patellar tendon allograft. The treating physician reported the infection to public health officials. The look back showed that three recipients developed hepatitis C more than a year before, but these infections were not reported. If reported at that time, the use of 24 tissues from the same donor and at least three new transmissions of HCV could have been prevented. Furthermore, it was not possible to trace two of the recipients. Forty allografts had been distributed within a period of 22 months from the same donor initially negative for HCV antibodies tested by a second-generation immunoassay but subsequently tested positive by HCV NAT after the report of an infected recipient. Of the 40 recipients of tissues, three of three tendon-bone allograft recipients and one of three tendon allograft recipients seroconverted (plus three of three organ recipients and one of two vein recipients). In total eight recipients seroconverted and 30 did not. Regarding the remaining ten, five recipients were already infected with HCV before the implantation but for the five others, post-transplantation serum was not available.

Table 2 Reported cases of HCV transmission

<i>n</i>	Type of allograft	Date	Publication	Proven	Author (reference)
1	Frozen bone ^a	1986–1990	1993	?	Pereira et al. [39]
1	Frozen bone ^a	1990	1992	+	Eggen and Nordbø [12]
1	Frozen bone ^a	1991	1995	+	Conrad et al. [6]
3	Cryopreserved soft tissue (fascia, ligaments) ^a	1991	1995	+	Conrad et al. [6]
3	Frozen bone-tendon-bone ^b	2000	2005	+	Tugwell et al. [54]
1	Cryopreserved tendon ^b	2000	2005	+	Tugwell et al. [54]

^aNo anti-HCV test^bAnti-HCV negative, no HCV NAT

Table 3 Reported case of nonspecific hepatitis transmission

<i>n</i>	Type of allograft	Date	Publication	Proven	Author
1	Frozen bone	1952	1954	+/-	Shutkin [45]

Transmission of hepatitis, unspecified type

For musculoskeletal allografts one historical case of unspecified hepatitis following bone allograft use has been reported. This case involved a frozen allograft in 1954 (Table 3). The recipient developed jaundice ten weeks after allograft implantation.

HTLV-1 transmission

A reactive test in an asymptomatic recipient was reported after implantation of a frozen femoral head allograft from a patient who had previously been infected with human T-lymphotropic virus type 1 (HTLV-1) via a contaminated blood transfusion (Table 4).

EBV, CMV, WNV and CJD transmission

Transmission of Epstein-Barr virus (EBV), cytomegalovirus (CMV), West Nile virus (WNV) or prion disease such as Creutzfeldt-Jakob disease (CJD) has not been reported following bone or tendon transplantation. With vein, valve, skin or nerve allograft use, viral transmission occurred only with fresh, deep-frozen or cryopreserved allograft. Cases of CJD were only observed after transplantation of dura mater [15, 28, 29, 34, 57, 58] and corneal allografts [9, 19]. Although prion disease transmission by bovine bone xenografts has not been observed, the risk is unknown and avoiding use of bovine xenografts has been recommended. WHO recommends, exposure of allografts to 1 mol/l NaOH for one hour to prevent prion transmission, which is supported by most authors [8, 56].

Transmission of bacterial infection

Bacterial infections resulting from the implantation of musculoskeletal allografts have been reported since 1953 in relatively limited numbers [11]. From the reviewed literature cited in references, 49 possible transmissions were documented with only ten proven and 39 remaining possible [1, 5, 21–24, 27, 30, 31, 52, 53, 57, 58]. Symptoms of infection appeared between three days and 20 weeks after implantation. No specific trend can be

drawn from the identified bacteria, as they include species from all the major groups (Table 5).

Considering the case histories, a proven causative link between the allograft and the infections is difficult to establish formally [23]. Often, allografts are used to repair bone defects or damaged tendons in patients who have had multiple operations, have altered vascularisation at the operative site and are at increased risk of local infection. To be proven, the contamination needs to be confirmed by the identification of the same pathological agent in the donor or in the graft and in the recipient, sometimes requiring DNA sequencing or special bacterial typing. Replacing unreliable surface swabbing associated with false-positive or false-negative results by a sample of the tissue used for the microbiological test would increase reliability of the results.

In most of the confirmed cases the same contaminant was identified in the donor or in other allografts derived from the same donor and in the recipient. This occurred mostly with frozen tissues. Less frequent were recipient infections originating from contamination of the graft during processing. Usually, in these cases, the contaminant was an uncommon pathogen which was subsequently detected in the bank facilities or selected by antibiotic cocktails used in the procedure [5]. Transmitted fungal infection was not observed in musculoskeletal allograft but has been documented for heart valves and arterial grafts.

The risk of transmitting malignancy from the donor

To our knowledge, no cases of transmission of malignancies by musculoskeletal allografts have been reported. Exclusion of potential donors with a history of most types of malignancy is required by many guidelines and regulations although there are differences between the rules in the EU and the USA. In a study on the histopathological examination of 1,146 femoral heads recovered from living osteoarthritic patients undergoing hip arthroplasties, Palmer et al. identified two well-differentiated lymphocytic lymphomas and one low-grade chondrosarcoma in the donated femoral head [37]. In another study, six of 504 donated femoral heads that fulfilled the criteria for bone transplantation were highly suspicious for low-grade B-cell lympho-

Table 4 Reported case of HTLV-1

<i>n</i>	Type of allograft	Date	Publication	Proven	Author
1	Frozen femoral head	1991	1997	+	Sanzén and Carlsson [43]

Table 5 Bacterial agents responsible for the contamination

Genus	Species	Genus	Species
<i>Citrobacter</i>	<i>workmanii</i>	<i>Hafnia</i>	<i>alvei</i>
	<i>youngae</i>	<i>Klebsiella</i>	<i>oxytoca</i>
<i>Clostridium</i>	<i>bifermentans</i>	<i>Mycobacterium</i>	<i>tuberculosis</i>
	<i>septicum</i>	<i>Pseudomonas</i>	<i>aeruginosa</i>
	<i>sordellii</i>	<i>Serratia</i>	<i>marcescens</i>
<i>Elizabethkingia</i>	<i>meningoseptica</i>	<i>Staphylococcus</i>	<i>aureus</i>
<i>Enterobacter</i>	<i>cloacae</i>		<i>epidermidis</i>
<i>Enterococcus</i>	<i>faecalis</i>	<i>Streptococcus</i>	<i>agalactiae</i>
			<i>pyogenes</i>

ma [60]. Two of the six mentioned patients who donated femoral head allografts subsequently developed systemic malignant disease. These conditions were not known at the time of joint replacement and bone donation. It shows that the presence of a malignant tumour in the allograft cannot be excluded. The tumours would also not have been detected by screening the donor's medical history and a histopathological examination is not routinely part of the quality check for recovered bones. It is not known if the processing or freezing of the allografts can destroy the malignant cells. However, to date, transmission of malignancy through bone allograft transplantation has not been reported.

Other adverse reactions

Adverse reactions presumably caused by chemical products used for the processing or sterilisation of the allograft have been reported. Ethylene oxide used for terminal sterilisation was reported to produce intra-articular reactions with persistent synovial effusion after bone-tendon allograft implantation [21]. If bone allografts are cryopreserved with dimethyl sulphoxide (DMSO), hypersensitivity of the recipient should be considered as a possibility and reported.

Regarding immunological responses, sensitisation to HLA class I and II antigens was observed after frozen massive osseous or osteochondral allograft transplantation [13, 14, 48].

Adverse events

Mechanical properties of bone allografts can be modified by certain processing steps. The surgeon should select the proper allograft taking into account the likely modification of the mechanical resistance produced by the different processing techniques and the mechanical requirements of the particular clinical application. For instance, a deep-frozen allograft may have better mechanical resistance than the original bone ($\pm 110\%$) [3, 38, 40] while freeze-drying processing will decrease its resistance (30–40%) [25, 36,

40, 47, 51]. The effect of sterilisation by gamma irradiation on the mechanical properties of the bone is a function of the dose. The level of 25 kGy, generally accepted for bacterial inactivation, can affect the mechanical properties of soft tissues but not significantly of bone [2, 38, 49, 55, 59]. However, virucidal doses over 30 kGy decrease the mechanical strength of bone [2, 7, 18, 38, 40, 42]. Also depending on the size of the bone graft, the revascularisation and progressive integration decrease the mechanical resistance over several months [4, 40]. Good communication with the tissue bank staff will help the surgeon to select the adequate type and size of the allograft for its specific purpose including the osteoinductive properties expected from demineralised bone matrix allograft [16, 20].

Errors and accidents can occur in the donor selection, and during allograft processing including the packaging and the delivery of the tissues, for example, mislabelling of the graft package. Usually, they do not cause harm to the recipient. However, these events may have serious consequences for the recipient and therefore when discovered they should be reported so that measures can be taken to define and implement corrective actions and the lessons can be shared with others in the field.

Discussion

Although the risk of disease transmission from allografts cannot be excluded, their improved safety reflects more precision in donor screening and testing procedures and progress in processing, disinfection and sterilisation. Several factors have contributed to improved allograft safety: the better performance of serological assays for infectious disease testing [41], the screening and selection of the donors, the processing protocol used by the bone bank, guidelines and recommendations of scientific associations, national and international regulation and the importance of programmes of biovigilance.

The selection and screening of donors is now subjected, in most of the countries, to a strict regulation prohibiting recovery from at risk donors. With regard to viral contamination, one of the main factors was the evolution of the serological assay from the basic antibody immunoassays to the testing by NAT, which decreases the diagnostic window period [17]. For more than at least 11 years depending on the virus, contamination has not been reported for musculoskeletal tissues thanks, in part, to the reliability of testing.

The positive influence of processing protocols developed within the bone bank appears also in the review. Historically, with one possible exception, all of the viral contamination cases involved fresh-frozen or cryopreserved allografts. No transmitted infections and very few adverse

events came from processed freeze-dried bone allograft. Tissue bank quality processes include the validation of tissue bank procedures for viral and microbiological decontamination.

National and international regulation, such as the EU Directives, require the official authorisation of the bone bank with periodical regulatory audits. A very important new step for improving allograft safety is the additional requirement for an effective biovigilance programme, relying on the recognition and reporting of adverse outcomes by surgeons. A recent US Food and Drug Administration (FDA) publication demonstrates increasing reporting of adverse incidents associated with tissue transplantation since this became mandatory in the USA [33]. Reliable reporting of adverse reactions and events will be the best way to continue to improve the safety and the quality of musculoskeletal allografts. In this evolution, the surgeon must play an important role in the reporting of those incidents. The reporting and investigation of one incident will prevent many others. After investigating whether the pathogen could have arisen from environmental contamination in the operating theatre, or was of patient origin, the infection should be reported to the tissue bank with an indication of the imputability of the transplanted allograft and an indication of the severity of the reaction and consequences in the long term. The imputability is an evaluation of the probability that the adverse outcome in the recipient has been caused by the transplanted allograft and it should be assessed, based on available information, as either: proven, probable, possible, unlikely or excluded.

Providing a precise diagnosis, the type of pathogen and exclusion of environmental and hospital causes will be very important to ensure that the tissue bank can focus on their own investigation. For example if the suspected allograft contamination is viral with symptoms developing weeks or months after the surgery, the tissue bank will focus more on investigating donor eligibility, screening and testing and less on failures of tissue processing.

The increased recognition of issues related to traceability has resulted in various professional associations strengthening their standards and governments taking actions by adding to existing regulations. A globally unique identification system is required, and this should extend across all biological materials—blood, cells, tissues and organs. International cell therapy associations have agreed to the adoption of standard terminology and the International Society of Blood Transfusion (ISBT) 128 system (www.iccbba.org) and implementation is underway. A joint initiative by the international eye banking associations to develop agreed terminology using ISBT 128 is also at an advanced stage. The tissue banking and organ transplant communities are also in the process of determining how this system might be accepted and implemented [50]. Standardising nomenclature and coding systems internationally will provide institutions the ability to trace allografts from a common donor who may have donated multiple organs and tissues and cause adverse reactions in many patients.

The tissue bank considers several elements when investigating a reported infection: the type of allograft processing (fresh, frozen, cryopreserved, freeze-dried), the

Table 6 Standard requisites to deliver safe and reliable musculoskeletal allografts

Tissue establishments	Authorisation of tissue establishments and their activities by the competent authority(ies)
Tissue donors: selection, testing	Voluntary donation and informed consent
	Medical and social history: evaluation using strict selection criteria to exclude those with infection and malignancy
	Physical examination
	Testing for transmissible infectious agents by serological and NAT methods carried out by licenced testing laboratories
Processing of bone and connective tissue allografts	Review of postmortem autopsy, if performed
	Most have cells, fat, marrow, blood removed through mechanical and chemical means
	Many have been disinfected—many have been sterilised by gamma irradiation or other methods
	Processed aseptically in high-quality clean rooms
Tissue: quality and safety	Quality system put in place and updated—use of validated procedures
	Quality control (including microbiological testing)
	Pathogen inactivation
Traceability, biovigilance	Tissue identification and labelling
	Traceability of tissues from donor to patient and vice versa, and products and materials coming into contact with the tissues
	Biovigilance: reporting and investigation of adverse reactions, adverse events

origin and the nature (bone, tendon, skin, vascular) of the graft, review of the donor evaluation including blood tests, possible retest of stored donor blood samples and retained co-processed tissues and environmental monitoring results.

An investigation by the tissue bank will determine the cause of the contamination and whether standard operating practices were followed, whether there could have been failures in tissue processing, donor selection or testing and corrective and preventive measures can follow. The tissue bank is responsible for reporting this to the competent authority. Thus, the initial evaluation, investigation and reporting by the surgeon are important for improving future medical care.

Normally, an orthopaedic surgeon carries out a follow-up of the patient after surgery. Often, there is a long-term follow-up by the surgeon annually (as it is the standard for orthopaedic implants, e.g. hip arthroplasty). Sometimes due to distance or other factors, follow-up care is provided by the general practitioners and other health care providers in charge of the patient. Those who provide postoperative follow-up should report to surgeons any significant disease that arose after surgery. This is an important aspect of a vigilance biosurveillance system. Otherwise, the connection of an infection and an allograft may be missed and a tissue bank not notified. Project NOTIFY is developing a digital database for adverse events and reactions and developing educational materials for surgeons and other physicians providing medical care to transplant recipients to aid in recognition of transmitted diseases and other adverse outcomes.

Conclusion

The quality and safety standards for donation, procurement, testing, processing, preservation, storage and distribution of musculoskeletal allografts have improved significantly over the last three decades. At present, these allografts provide orthopaedic surgeons with a useful and safe tool to repair bone defects. In addition, depending on their processing and nature, they provide osteoconductive, osteoinductive and mechanical properties. When all the quality and safety requirements (Table 6) are fulfilled, adverse events and reactions should be extremely rare. However, adverse events still arise due to human error, accidents, equipment failure, unexpected tissue defects or unexpected new circumstances such as emerging diseases. It is only after the speedy reporting of those exceptional events and reactions that an investigation can start to analyse the cause and that corrective measures—when possible—can be defined and implemented in order to prevent recurrence of the events. Of course, an important prerequisite is ensuring the full traceability of the allograft applied. To maintain and

improve their safe use, WHO launched Project NOTIFY in 2010 encouraging all surgeons to report to their bone bank and national biovigilance institution the serious events and reactions related to the use of allografts. For orthopaedic surgeons working in countries with no national agency to receive their case reports, they can download from the SICOT website (www.sicot.org) a standard report form which can be returned to SICOT. This programme is especially important at a time when globalisation opens the exchange of medical products across national boundaries and when effective biovigilance is needed to preserve the safety of tissue transplantation.

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