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Antibiotics in frozen bone grafts can cause allergic reactions in recipient patients

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ABSTRACT

Antibiotic prophylaxis is a routine procedure during total hip arthroplasty (THA), and the vast majority of cadavers within the multitissue procurement receive one or more antibiotics. Upon harvesting, bone grafts are stored in the bone banks on the temperature as low as -80°C for up to 5 years. It is shown in the literature that the antibiotics remain active and viable in the bone grafts even after being exposed to extremely low temperatures in the prolonged periods. Possibility of remnant antibiotic concentrations in the bone grafts and the fact that these antibiotic remnants maintain active even after being exposed to extremely low temperatures create the environment in which the possibility for the allergic reaction in sensitive patient receiving bone graft exists. We hypothesize that harvested bone grafts containing active antibiotic substance have the potential for local and systemic allergic reaction in sensitive recipient patients thus increasing morbidity and the costs of the treatment. Allergic reactions can mimic surgical site infections as well with the consequent substantial pitfalls in the treatment. Following that, in the setting of an assumed but not confirmed surgical site infection, the immunological evaluation on antibiotics for recipients of bone grafts could be added to the standard diagnostic algorithms. In addition, bone banks should be obliged to provide information of all potential drugs that can be found in every specific bone graft to the end users.

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Introduction

One of the operative challenges of orthopaedic revision surgeries and limb saving tumour surgeries is the bone loss, which has to be compensated [1–6]. The gold standard for bone substitutes are autologous grafts [7]. However, harvesting of autologous bone graft is associated with donor site morbidity and limited availability [8]. Allografts are a quality and safe alternative and can be obtained from cadavers within multitissue procurement or from living donors when femoral heads are harvested during total hip arthroplasty (THA). Antibiotic prophylaxis is a routine procedure during THA, and the vast majority of cadavers within the multitissue procurement receive one or more antibiotics. Upon harvesting, bone grafts are stored in the bone banks on the temperature as low as -80°C for up to 5 years [9]. It is shown in the literature that the antibiotics

remain active and viable in the bone grafts even after being exposed to extremely low temperatures in the prolonged periods [10–12]. Antibiotic allergy, although relatively low in the general population with the reported incidences of up to 5% accounts for a small but significant proportion of adverse drug reactions [13–16]. These allergic reactions are immunologically mediated and can affect multiple organ systems with different extent of intensity and can mimic the surgical site infection (SSI) as well [14,15]. Possibility of remnant antibiotic concentrations in the bone grafts and the fact that these antibiotic remnants maintain active even after being exposed to extremely low temperatures create the environment in which the possibility for the allergic reaction in a sensitive patient receiving bone graft exists.

Hypothesis

Given that antibiotics are administered to most cadaveric donors and virtually all donors of femoral heads during THA, harvested bone grafts can contain active antibiotic substance that has the potential for local and systemic allergic reaction in sensitive recipient patients.

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Evaluation of hypothesis

Until used, bone graft specimens are stored in the bone banks at temperatures as low as -80°C before thawed and used in the operating room. Bone grafts can be stored in such conditions for up to 5 years [9]. Mathijssen et al. demonstrated that storage of bone chips impregnated with different antibiotics at temperatures of -80°C even after 12 months does not affect their activity [10]. Cefazolin, vancomycin, linezolid, oxacillin, clindamycin were all included in the study and comprise the majority of antibiotics encountered in the orthopaedic surgery. In addition Coraça-Huber et al. showed similar results with the bone chips impregnated with gentamicin and stored for 6 months [12]. What is the influence of periods longer than 12 months in conditions of -80°C to the activity of antibiotics, remains to be seen. Furthermore, Chang et al. showed that femoral heads harvested during THA contain effective antibiotics after storage at low temperatures in the bone bank [11]. Although potentially beneficial as a prophylaxis against infection, these remnant concentrations of antibiotics in bone allografts can cause allergic reaction in sensitive patients. In orthopaedic surgery the first choice antibiotics for prophylaxis are cephalosporins, especially cefazolin [17,18]. IgE-mediated hypersensitivity reactions have been reported with the use of cephalosporins, as a cross-reaction between different cephalosporins or as a cross-reaction to other β -lactam antibiotics, namely, penicillin [19–21]. Allergic reaction is as a form of hypersensitivity, formally known as Type 1 hypersensitivity, and although distinctive, results in inflammation. Most common manifestations are skin eruptions, fever and life threatening anaphylaxis which is linked with the penicillins and cephalosporins in the majority of cases [14,15]. However, clinical signs of pain, swelling and redness found in the allergic reactions all herald surgical site infection as well, and even the elevated CRP and ESR can be misleading. Because of the possible poor outcome any suspected surgical site infection (SSI), and especially periprosthetic joint infection (PJI), necessitates quick confirmation and aggressive therapy. We believe that some of those diagnosed SSI could be in fact allergic reactions to remnant antibiotics found in bone grafts used. These adverse reactions account for substantial morbidity, mortality, extra costs and lead to decreased outcome of the treatment [22,23]. Although rare, allergy to cephalosporins in general population can be as high as 3% [15,16]. In an in-patient population allergy to penicillin was found to be 5% [13]. While conducting ordinary surgery, with the check lists implemented, the chance of administering an antibiotic for prophylaxis to a sensitive patient is decreased to a minimum. The problem can arise when the surgery mandates the use of allograft that can contain remnant antibiotic concentrations. Current protocols in the bone banks and protocols during transplantation of bone grafts do not contain information of the antibiotics used during the procurement of the bone grafts thus creating conditions for the potential adverse reaction in the recipient patient [9].

Consequences of the hypothesis

Active antibiotic remnants can be found in the bone grafts even after being exposed to the temperatures of 80°C below freezing in the prolonged periods. These antibiotics can induce adverse reactions in the recipient patients. Most concerning are allergic reactions that lead to increased morbidity and even mortality in the setting of anaphylaxis. Allergic reactions can mimic surgical site infections as well with the consequent substantial pitfalls in the treatment. In the setting of an assumed but not confirmed surgical site infection we propose the immunological evaluation on antibiotics for recipients of bone grafts in addition to the stan-

dard diagnostic algorithms. Skin testing, in vitro IgE antibody test or even provocation test can be a part of such evaluation. In addition, bone banks should be obliged to provide information of all potential drugs that can be found in every specific bone graft to the end users. These critical information could decrease adverse reactions to a lowest possible rate. It will ultimately have positive implications on bone banking and bone graft managing and lead to decreased morbidity, mortality and the overall cost of treatment for the patients.

Conflict of interest

The authors declare no conflicts of interest.

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