

# Benzoyl peroxide: is it a relevant bone cement allergen in patients with orthopaedic implants?

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Contact allergies to orthopaedic implant material are discussed to be relevant for postoperative complaints. We aimed at determining the prevalence of sensitizations to implant metals and to bone cements in patients with implants. We investigated 13 consecutive patients with suspicion of contact allergy to implant material. Epicutaneous patch testing was performed with metals and bone cement components including benzoyl peroxide (BPO). The chief complaints were skin disorders ( $n = 3$ ), loosening of implant ( $n = 2$ ), swelling ( $n = 6$ ), and pain ( $n = 2$ ). 6 patients had a sensitization to at least 1 allergen. 3 patients reacted to BPO, being of possible relevance in 1 of these patients suffering from dermatitis. Other sensitizations, such as those to nickel, fragrance, and balsam of Peru, were observed, with no clinical relevance ( $n = 1$ , respectively). BPO in bone cements may lead to type 4 sensitizations of which the relevance, however, remains questionable. Nevertheless we recommend this allergen to be tested in patients with complicated cemented orthopaedic implants.

**Key words:** allergy; benzoyl peroxide; bone cement; implant. © Blackwell Munksgaard, 2007.

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Allergies caused by implant materials are often thought to be a reason for postoperative complaints (1). Previous investigations focused on the role of metal components, particularly contact allergies to nickel, chromium, and cobalt, have been discussed to be of relevance for aseptic loosening of implants (2–6). Among patients with well-functioning or poorly functioning implants, the prevalence of metal sensitivity was reported to be twice as high as that of the general population. Interestingly, in patients with a failed implant metal, sensitivity was found to be to be 5 times as high as in the general population (4). Still, it remains unclear, if sensitization in those patients is a primary or a secondary problem: specifically, does the loosening lead to a release of allergens with subsequent sensitization or is the loosening the result of an already existing sensitization leading to an allergen-driven inflammatory response? (4) Moreover, cutaneous disorders such as eczema, urticaria, vasculitis, and other complaints like pain and swellings have been related to allergies to implant material (2).

While there has been intensive investigation of allergies to metals (1–6), less attention has been paid to a possible allergenic role of bone cement components. Examples of these bone cement components are as follows: (i) acrylates; (ii) additives to polymerize those acrylates such as activators (i.e. *N,N*-dimethyl-*p*-toluidine [DMT]), initiators (i.e. benzoyl peroxide [BPO]), and stabilizers (i.e. hydroquinone [benzene-1,4-diol]); (iii) radio contrast media (i.e. zirconium dioxide, barium sulfate); (iv) antibiotics (i.e. gentamycin); and (v) dyes (i.e. chlorophyll copper) (7). Even though allergic reactions to those bone cement components seem to be much rarer than those to metals, their allergenic potential might be underestimated because of inadequate testing.

## Methods

We investigated 13 consecutive patients presenting in our allergy department for suspicion of contact allergy to implant materials. After a clinical examination, a patch test was performed according to the guidelines of the Deutsche Kontaktallergiegruppe (8) with the standard series including potassium dichromate 0.5% petrolatum (pet.), nickel sulfate 5% pet., and cobalt chloride 1% pet.; with the bone cement components BPO 1%

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pet., gentamycin 20% pet., hydroquinone (benzene-1,4-diol) 1% pet., hydroxyethyl methacrylate 1% pet., and copper sulfate 1% aqueous solution (HERMAL, Reinbek, Germany); as well as with the metals manganese chloride 0.5% aqueous solution, molybdenum chloride 2% aqueous solution, titanium oxide 0.1% pet., and vanadium pentoxide 10% pet. (HAL-Allergie GmbH, Düsseldorf, Germany). Readings were done at days 2 and 3. Total IgE was investigated by CAP-FEIA system (Phadia, Freiburg, Germany).

## Results

Our patients had a median age of 61 years and had received their knee implants 6–36 months ago. Implants were composed of cobalt–chrome alloys,  $n = 11$ , or of titanium,  $n = 2$  (Table 1). About 2 of them (patients 3 and 10) also had a well-functioning hip implant. Complaints had started within 8–18 weeks after surgery and consisted of (i) skin changes, (ii) dysfunction (swelling and/or erythema or pain), (iii) pain only, or (iv) loosening of implant.

6 patients had a sensitization to at least 1 allergen. 3 of the 13 patients reacted to BPO; all of them had a crescendo reaction, favouring an allergic rather than an irritant origin. The sensitization was of possible relevance in a patient with dermatitis (patient 8, Fig. 1). In the others, the relevance of BPO sensitization was not clear: patient 4 had a pretibial plaque being clinically compatible with mucinosis (biopsy was denied) and patient 11 was complaining of persistent pain in his knee. None of them recalled a previous use of BPO, i.e. in acne therapeutics. However, patient 3 had also received a dental prostheses 2 years ago. 3 other



Fig. 1. Skin lesions in a patient with type 4 allergy to benzoyl peroxide.

patients were sensitized to nickel, fragrance, or balsam of Peru without any clinical relevance being evident. Total IgE was  $<100$  kU/l in 10 patients; in patients 1 and 6, total IgE was 115 and 175 kU/l without clinical signs for atopy, while patient 12 had an increased IgE of 616 kU/l and a known allergic rhinitis to birch pollen.

## Discussion

We aimed at investigating the prevalence of contact allergies in our group of patients with complicated knee implants. The patient's complaints were mainly swelling and pain, 3 had skin lesions, and 2 had aseptic loosening. We could not show a contact allergy to any of the suspected metals cobalt, chromium, or titanium. In contrast, there was a surprisingly high prevalence of sensitization to BPO in 3 of 13 patients, raising the question if this bone cement component plays a role in post-operative complaints. No other sensitizations to known bone cement allergens were demonstrable, but DMT could not be tested in our patients because of lack of availability.

The most commonly described bone cement allergens are acrylates, and those sensitizations have been reported in patients with pain and aseptic loosening as well as in a patient with dermatitis (7, 9–11). Sensitizations to DMT (12, 13), to antibiotics (7), and to hydroquinone (benzene-1,4-diol) (11) have been reported occasionally (Table 2).

Table 1. Patch test results in patients with complicated knee implants

|    | Age, sex | Implant material | Chief complaint                | Patch test result |
|----|----------|------------------|--------------------------------|-------------------|
| 1  | 42, f    | Co–Cr–Mo         | Swelling/pain                  | Negative          |
| 2  | 58, f    | Ti               | Swelling                       | Negative          |
| 3  | 61, m    | Co–Cr–Mo         | Pain, dysidrotic palmar eczema | Nickel++          |
| 4  | 65, f    | Co–Cr–Mo         | Pretibial plaques              | BPO+              |
| 5  | 62, m    | Co–Cr–Mo         | Loosening                      | Negative          |
| 6  | 78, f    | Co–Cr–Mo         | Pain                           | Balsam of Peru+   |
| 7  | 94, f    | Co–Cr–Mo         | Pain                           | Negative          |
| 8  | 52, f    | Co–Cr–Mo         | Dermatitis                     | BPO++             |
| 9  | 61, m    | Co–Cr–Mo         | Loosening                      | Negative          |
| 10 | 54, f    | Co–Cr–Mo         | Swelling                       | Fragrance mix+    |
| 11 | 70, f    | Co–Cr–Mo         | Swelling/pain                  | BPO++             |
| 12 | 53, f    | Ti               | Swelling                       | Negative          |
| 13 | 66, m    | Co–Cr–Mo         | Swelling/pain                  | Negative          |

f, female; m, male; Co, cobalt; Cr, chromium; Mo, molybdenum; Ti, titanium; BPO, benzoyl peroxide.

Table 2. Previous reports upon type 4 allergies to bone cement components in patients with implants at various localizations

| Author                      | n  | Complaint               | Bone cement allergens tested                                       | Localization of implant |
|-----------------------------|----|-------------------------|--------------------------------------------------------------------|-------------------------|
| Jager and Balda et al. (15) | 1  | Aseptic loosening       | BPO positive                                                       | Hip                     |
| Gil-Albarova et al. (9)     | 26 | Aseptic loosening       | Polymethyl MA n = 13 positive; DMT and HQ negative; BPO not tested | Hip                     |
| Haddad et al. (13)          | 1  | Pain, aseptic loosening | DMT positive                                                       | Hip                     |
| Haddad et al. (14)          | 15 | Aseptic loosening       | DMT n = 7 positive; BPO, MA, HQ negative                           | Hip                     |
| Dejobert and Piete (16)     | 2  | Erythema, mucositis     | BPO positive                                                       | Dental                  |
| Richter-Hintz et al. (10)   | 1  | Dermatitis              | Methyl MA positive                                                 | Knee                    |
| Granchi et al. (11)         | 50 | Aseptic loosening       | MA n = 2 positive; HQ n = 2 positive; BPO negative                 | Hip                     |

BPO, benzoyl peroxide; DMT, *N,N*-dimethyl-*p*-toluidine; HQ, hydroquinone (benzene-1,4-diol); MA, methacrylate.

BPO was first recognized as a bone cement allergen in a patient with loosening of total hip prosthesis (14) and in 2 cases with stomatitis following dental implants (15). Only recently, 2 more patients with complicated orthopaedic implants and BPO allergy have been mentioned in a review paper (7).

Mostly, BPO is known as an effective topical treatment for acne vulgaris; it breaks down in contact with skin, producing benzoic acid and oxygen, neither of which is significantly toxic. Previous studies have documented BPO to be a strong irritant and a weak allergen (16). Contact allergies to BPO because of its use in acne therapy (16–18) or following leg ulcer therapy (19) have been reported. BPO can be found in hair dyes, in teeth whitening systems, and in adhesive tapes (18–20). It is also used in the preparation of flour and as an initiator and catalyst for polyester thermoset resins (7, 16, 17). In bone cements, BPO initiates the polymerization of methacrylates (7).

One may speculate that the sensitization in our patients was because of their contact to BPO in bone cements, but in patient 11, a possible route of sensitization may as well been the dental implant (15). The best demonstration of a clinical relevance of a BPO sensitization would have been the complete recovery of symptoms after removal of the implant, which has not been performed in any of our patients during follow-up. However, as BPO is rapidly metabolized, it is questionable if several weeks after implantation, the allergen is still present and may be a causal allergen for the complaints. Patients 4 and 8 were treated with topical corticosteroids, which led to improvement of symptoms. In all other patients, complaints could not be related to an allergy to implant material, and patients were referred to their orthopaedists.

In conclusion, our data suggest that BPO in bone cements may lead to type 4 sensitization to

this allergen. The relevance of this sensitization remains questionable. Nevertheless, we recommend that BPO should be patch tested in all patients with suspected allergies to implant materials. In case of proven allergy to any bone cement component, a cement-free implant should be favoured (21).

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