

Allergic complications from orthopaedic joint implants: the role of delayed hypersensitivity to benzoyl peroxide in bone cement

Andreas Bircher¹, Niklaus F. Friederich², Walter Seelig³ and Kathrin Scherer¹

¹Allergy Unit, Department of Dermatology, University Hospital Basel, University of Basel, CH-4031 Basel, Switzerland, ²Department of Orthopaedic Surgery, Kantonsspital Bruderholz, Bottmingen, Switzerland, and ³Hirslanden Klinik Birshof, Münchenstein, Switzerland

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Summary

Background. Orthopaedic implants and osteosynthesis materials are increasingly being used. Complications include mainly physical–mechanical problems and infections. Uncommonly, an allergic reaction towards an alloy metal or a bone cement component has been implicated. Potential bone cement allergens include acrylates, benzoyl peroxide, *N,N*-dimethyl-*p*-toluidine, and gentamicin. Typical symptoms are pain, swelling, inflammatory skin reactions, implant loosening, and fistula formation.

Objectives. To report on 5 patients with complications from a knee or a shoulder joint implant in whom a relevant sensitization to benzoyl peroxide was shown.

Methods. Patch tests were performed with the European baseline series, an extended metal series, and a bone cement series. Patch tests with benzoyl peroxide were performed twice in all patients. A bone cement-free replacement was chosen in sensitized patients.

Results. In 4 patients sensitized to benzoyl peroxide, a bone cement-free replacement resulted in a considerable decrease or disappearance of pain and swelling, and complete clearing of cutaneous symptoms.

Conclusions. Components of bone cement, such as benzoyl peroxide, may rarely cause allergic complications. However, because of the irritant potential of these substances, careful performance, reading and interpretation of the patch tests is required.

Key words: benzoyl peroxide; bone cement; complication; contact allergy; dermatitis; loosening; orthopaedic implant; pain; patch tests; swelling.

In recent years, there has been a considerable increase in the number of reports and studies on hypersensitivity reactions to orthopaedic implant materials, and in some countries recommendations have been published (1–3). Apart from mechanical and infective complications, adverse effects of orthopaedic implants include a wide spectrum of disorders: cutaneous symptoms and signs (localized and generalized dermatitis, and inflammatory

skin infiltrates), fistulae, aseptic inflammation, persistent pain and swelling, fibrosis and aseptic loosening have been implicated. The pathomechanisms leading to such events are not well understood. Contact allergies to alloy metals and local inflammatory responses to metal ions have been implicated (4). However, knee prostheses, for example, cause complications considerably more often than hip prostheses, suggesting that not only material but also mechanical, physical and other factors may be relevant.

In addition to commonly used alloy metals, for example nickel, cobalt, chromium, and, rarely, others such as titanium (2, 3, 5), components of the bone cement have been implicated as relevant allergens. Bone cement typically contains acrylates such as monomeric methyl methacrylate, polymerization initiators, for example *N,N*-dimethyl-*p*-toluidine and benzoyl peroxide,

Correspondence: Andreas J. Bircher, Allergy Unit, Department of Dermatology, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland. Tel: +41 (0)61 265 4359; Fax: +41 (0)61 265 4885. E-mail: andreas.bircher@unibas.ch

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the stabilizer hydroquinone to prevent premature polymerization, in some gentamicin or other antibiotics as antimicrobial agents, green dye (chlorophyll) for macroscopic intraoperative visibility, and zirconium oxide or barium sulfate as radiocontrast agents (6, 7). Contact sensitization to some of these components is known from dental restorations (8), and rarely contact allergies to one or more of these ingredients have been implicated. Most of these have involved *N,N*-dimethyl-*p*-toluidine and monomeric methyl methacrylate (7, 9, 10).

We report 5 patients with complications after orthopaedic implants, in whom relevant contact allergy to benzoyl peroxide was identified. Removal or replacement with cement-free implants resulted in a considerable improvement of symptoms and signs and in a stable condition in 4 individuals.

Methods

The patients were referred for evaluation of contact allergy to metals or bone cement to our clinic. For all patients, a detailed history was taken with regard to contact allergy to metals and to previous implantations of metal-containing materials, including dental implants and

fillings, osteosynthesis, orthopaedic arthroplasties, dental restorations, stents, and vascular clips, as well as non-occupational exposures, such as to jewellery and coloured tattoos, and previous or current occupational exposure to metals. Patients were also investigated for atopic disorders, and prick tests with common aeroallergens were performed. A complete dermatological examination with a particular focus on the implanted area and joint was performed. An extended European baseline patch test series (Almirall Hermal, Reinbek, Germany), an extended metal series (Chemotechnique Diagnostics, Vellinge, Sweden) and a bone cement series were tested in IQ chambers® (Chemotechnique Diagnostics). Benzoyl peroxide was tested in large Finn Chambers® (11 mm) on Scanpor® tape (Almirall Hermal) in exposed controls and patient 5 (Table 1). Contact allergens were applied on the upper back for 2 days; after removal, readings were performed according to the International Contact Dermatitis Research Group criteria on day 2, and again on day 3 or day 4.

The following patch test agents, vehicles and concentrations were used.

Table 1. Overview of patient characteristics

No.	Age (years)	Sex	Type of prosthesis	Symptoms and signs	Contact sensitization	Procedure	Follow-up
1	48	F	Total knee prosthesis	Chronic pain, generalized pruritus, local and disseminated eczematous lesions	Benzoyl peroxide (2 × positive at two time points, IQ chambers®), cobalt	Arthrodesis	Clearance of symptoms (exanthema, eczema, pruritus) 6 years
2	39	F	Total knee prosthesis, two exchanges	Chronic pain, joint swelling	Benzoyl peroxide (2 × positive at two time points, IQ chambers®), methylchloro-isothiazolinone/methylisothiazolinone, Palacos®, <i>p</i> -tert-phenol formaldehyde resin, cobalt (2 × positive at two time points)	Cement-free total knee prosthesis	Clearance of pain and swelling 5 years
3	76	M	Right knee: two knee prostheses Left knee: two knee prostheses	Chronic pain, swelling, recurrent loosening	Benzoyl peroxide (2 × positive at one time point, IQ chambers®), sodium metabisulfite, methylidibromo glutaronitrile	Right knee: arthrodesis Left knee: cement-free total knee prosthesis	Clearance of pain and swelling 3 years
4	70	F	Total shoulder prosthesis	Pain, swelling, cutaneous infiltrate	Benzoyl peroxide (2 × positive at one time point, IQ chambers®), rhodium chloride, sodium sulfatoaurate	Removal of cement New humerus head	Clearance of all symptoms 1 year
5	71	M	Total knee prosthesis	Loosening, pain, swelling	Benzoyl peroxide (1 × negative, 1 × positive in large aluminium Finn Chamber® at one time point)	ND	NA

F, female; M, male; NA, not applicable; ND, not done.

European baseline series and routine supplemental series

The European baseline series, omitting primin and sequiterpene lactone mix (11), and a routine supplemental series containing sodium metabisulfite (1% petrolatum), benzocaine (5% pet.), budesonide (0.1% pet.) and tixocortol pivalate (1% pet.) were tested in all patients.

Bone cement component series

Single ingredients of bone cement such as gentamicin sulfate (20% pet.), methyl methacrylate (2% pet.), benzoyl peroxide (1% pet.), hydroquinone (1% pet.), 2-(hydroxyethyl)methacrylate (1% pet.), *N,N*-dimethyl-*p*-toluidine (2% pet.), zirconium chloride (1% pet.), and barium sulfate (5% pet.) were tested. Also, Palacos® bone cement (tested 'as is'; contains methyl methacrylate, benzoyl peroxide, *N,N*-dimethyl-*p*-toluidine, chlorophyll, zirconium dioxide, and gentamicin) was freshly mixed, formed into a flat disk of approximately 1 cm in diameter, and left to dry before application.

Extended metal series (in pet. if not otherwise stated)

This comprised aluminium 100%, aluminium chloride 2%, amalgam 5%, amalgam alloy metals 20%, ammonium hexachloroiridate 0.1% (aqua), ammonium molybdate tetrahydrate 1% (aqua), ammonium tetrachloroplatinate 0.25% (aqua), beryllium sulfate 1%, cadmium chloride 0.5%, calcium titanate 10%, chromic chloride 1%, cobalt[II] chloride 1%, copper oxide 5%, copper[II] sulfate 1% (aqua), indium[III]chloride 10% (aqua), indium sulfate 10% (aqua), iridium[III] chloride 1% (aqua), iron chloride 2%, lead acetate trihydrate 0.5% (aqua), magnesium chloride 5%, manganese chloride 2%, mercury 0.5%, mercuric[II] amidochloride 1%, mercuric chloride 0.1%, molybdenum 5%, nickel[II] sulfate 5%, niobium chloride 1%, palladium chloride 1%, potassium dichromate 0.5%, potassium dicyanoaurate 0.002% (aqua), rhodium chloride 3%, ruthenium oxide 2%, silver nitrate 1% (aqua), sodium tetrachloropalladate 2%, sodium thiosulfatoaurate 0.5%, thimerosal 0.1%, tin 50%, tin[III] chloride 0.5%, titanium 10%, titanium nitride 5%, titanium[IV] oxalate 1%, titanium tetrachloride 0.2% (alcohol), tungsten 5%, vanadium 5%, vanadium[III] chloride 1%, and zinc 2.5%.

Osteosynthesis alloy disk series (approximate weight percentage in parentheses) (12). This comprised titanium alloy disk 1 TiAlVd [(titanium [balance), aluminium (5%), and vanadium (4%)], titanium alloy disk 2 TiAlNb [titanium (balance), aluminium (6%), and niobium (7%)], titanium

disk [titanium (>99%)], and a Vitallium® disk [cobalt (60%), chromium (25%), and molybdenum (6%)]. These were obtained from the manufacturers of the respective implants.

Case reports and results

In all 5 patients (Table 1), no relevant previous skin disorders, including severe acne, or relevant contact allergy to jewellery or other metals or atopic dermatitis were present. Patients 1 and 3 had a past history of seasonal allergic rhinitis.

Patient 1

In October 2003, a 48-year-old woman received a total knee prosthesis (unknown composition) for osteoarthritis. She then continuously suffered from chronic pain. Four weeks after surgery, severe pruritus developed, initially localized to the operated knee but with subsequent spread. In May 2005, she was patch tested with the European baseline series elsewhere; a positive reaction to cobalt (+/+) was found. The prosthesis was removed because of suspected infection, and no replacement was implanted. A relevant infection could not be shown. The patient was referred to our clinic. Eczematous lesions were present on her right leg and both arms. She was again tested with the European baseline series, metal series, and acrylate series, as well as with metal alloy disks. A positive reaction to benzoyl peroxide (++/+++) was present, which was reproduced (+/+) 1 month later. All metals, including cobalt, were negative. For technical reasons, she had an arthrodesis of the knee, and after this the pruritus and eczematous lesions completely cleared.

Patient 2

A 39-year-old woman had recurrent problems for over 10 years with her right knee joint, owing to previous trauma. In total, she has had over 40 surgical interventions, including a total knee arthroplasty (P.F.C. Sigma®; DePuy Switzerland, Johnson & Johnson, Medical DePuy Division, Spreitenbach, Switzerland) in 1996, at the age of 29 years. She then developed chronic recurrent swellings, knee joint effusion, and chronic pain; skin changes were not observed. Arthroscopy and open synovectomy were performed 2 years later. Loosening and infection were extensively and repeatedly excluded. In 2002, 4 years later, revision arthroplasty (P.F.C. Sigma®; DePuy Switzerland, c/o Johnson & Johnson, Medical DePuy Division, Spreitenbach, Switzerland) was performed to definitely exclude infection. All of the

bacteriological specimens and cultures were negative, and there was no clinical sign of an infection. The chronic pain, the recurrent swelling and knee joint effusion did not improve. At presentation in our unit, the patient had several non-irritated scars, and no signs of eczematous lesions. The patient was then tested with the European baseline series, extended metal series, and acrylate series, as well as with metal alloy disks and components of Palacos® bone cement.

There were positive patch test reactions to methylchloroisothiazolinone/methylisothiazolinone (+/+), Palacos® cement (contains methylmethacrylate, benzoyl peroxide, *N,N*-dimethyl-*p*-toluidine, chlorophyll, zirconium dioxide, and gentamicin) (+/+), *p*-tert-butyl phenol formaldehyde resin (+/+), benzoyl peroxide (+/+) and cobalt (-/+) at 48 and 72 hr, respectively.

After the repeated demonstration of contact sensitization to benzoyl peroxide and the Palacos® bone cement, it was decided that there was an indication for revision surgery for another total knee prosthesis. In 2006, the cemented knee was removed, and a cement-free revision arthroplasty was performed with a CoCrMo and titanium alloy (Natural-Knee® II System – Revision Knee, Durasul®; Zimmer, Münsingen, Switzerland), despite the weak positive reaction to cobalt. After an uneventful postoperative period, the swelling and the effusion disappeared, and pain was considerably reduced.

Patient 3

A 78-year-old male patient suffered a trauma to the right knee in 1996. After meniscectomy and necrosis of the femoral condyle, in 1998, a unicondylar sled prosthesis (Link, Hamburg, Germany) was implanted. Owing to ongoing pain and swelling, repeated cultures were taken, always with negative results. Later in 1998, a total knee prosthesis (LCS®; DePuy, Leeds, UK) was implanted. At the end of 1998, an infection with *Staphylococcus* was suspected. After treatment and no further infections (several negative arthroscopic punctures and lavages), no loosening could be shown. However, recurrent swelling and pain continued, and in early 2000 the knee prosthesis was replaced with a long-stem LCS® prosthesis (DePuy). However, pain and swelling of the knee joint persisted. An initial allergy workup was performed in 2004, including the European baseline series, acrylate series, and metal series. All tests gave negative results. In 2005, the prosthesis was removed and arthrodesis of the right knee was performed. In 2008, a cemented sled prosthesis (Link) was implanted in the left knee, which again caused chronic pain and swelling. Because of suspicion of loosening resulting from a hypersensitivity reaction, the patient was sent for a second allergy workup. Apart

from the knee swelling, no skin changes were present. In 2009, patch tests were performed again with the European baseline series, acrylate series, and extended metal series.

There were positive patch test reactions to benzoyl peroxide (-/+), sodium metabisulfite (-/++) and methylidibromo glutaronitrile (-/+) on day 2 and day 3, respectively. The patient received a non-cemented total knee prosthesis (Natural-Knee® II System – Revision Knee; Zimmer). The chronic pain faded, and no further swellings were observed during a follow-up of 3 years.

Patient 4

A 70-year-old woman suffered from trauma with rupture of the rotator cuff at the right shoulder in 2006. Rotator cuff reconstruction was performed 1 year later. Rupture of the rotator cuff was demonstrated by magnetic resonance imaging 5 months after reconstruction. Owing to secondary osteoarthritis of the right shoulder joint and ongoing pain, an inverse total shoulder prosthesis (Anatomica Invers®, Zimmer, Ti6VdAl4, CrCoMo, Ti6Al7Nb, Sulene Polyethylene UHMW) was implanted in 2008. The shaft was fixed without cement; the glenoid component was cemented with Palacos® bone cement. Shortly thereafter, the patient developed chronic pain in the right shoulder area, and loosening of the glenoid component was diagnosed. Infection of the prosthesis was excluded. Revision arthroplasty was performed in early 2009 (SMR Invers Revision, Lima®, WG Healthcare Ltd., Letchworth, UK; Ti6Al4Vd, CoCrMo, Palacos®). The glenoid component was again cemented. Two weeks later, the patient developed an erythematous infiltrated plaque on the right upper arm, which gradually descended towards the elbow (Fig. 1). Histology revealed a lymphocytic infiltrate. In addition, chronic pain was still present. In January 2010, an allergy workup was performed.

Patch tests (European baseline series, acrylate series, metal series, and bone cement series) were performed to exclude contact hypersensitivity to the shoulder prosthesis or the bone cement. There were positive reactions to benzoyl peroxide (+/+), rhodium chloride (+/+), and sodium sulfatoaurate (-/+). Relevant contact sensitization to benzoyl peroxide was diagnosed. In 2010, the cemented socket was explanted, and a socket-free solution with a CTA-head (Lima®; CoCrMo) was chosen. Histology revealed perivascular infiltrates of lymphocytes with rare eosinophil granulocytes. After 4 months, the pain had considerably decreased and the erythematous infiltrate had completely cleared (Fig. 3). The patient has now remained free of symptoms for 1 year.



Fig. 1. Patient 4: erythematous, pruritic infiltrate extending from the shoulder to the elbow. Histology revealed a lymphocytic infiltrate with some eosinophils.



Fig. 3. Patient 4: complete clearing of infiltrate in benzoyl peroxide-allergic patient 4 months after bone cement-free implant.

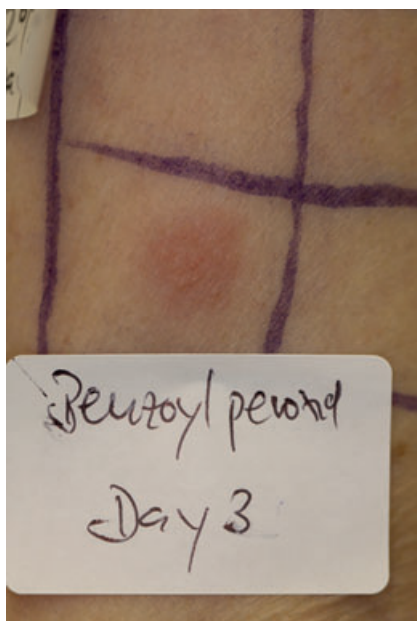


Fig. 2. Patient 4: positive patch test reaction to benzoyl peroxide 1% pet. at day 3.

Patient 5

Owing to meniscus trauma and arthrosis, a 71-year-old male patient received a cemented total knee prosthesis.

Eight months, later aseptic loosening of the cemented tibia plateau was detected, and replacement of the knee prosthesis was therefore necessary. Again, a cemented prosthesis was chosen. The patient suffered from ongoing pain and swelling of the knee; however, no eczematous skin lesions were present. There was a positive patch test reaction to benzoyl peroxide (++/+++), with a clear crescendo reaction. So far, the knee prosthesis has not been replaced. In case of the need for a replacement, a non-cemented solution has been strongly recommended.

Discussion

Contact dermatitis caused by benzoyl peroxide and other agents used in dental prostheses has been previously observed (8). For some of these substances, an allergic and irritant potential has been suspected (6). Rare cases where bone cement components were suspected to have caused swelling, pain, loosening or dermatitis in orthopaedic implants have been reported (7, 8, 10, 13, 14). Most often, sensitization to acrylates, *N,N*-dimethyl-*p*-toluidine and gentamicin was found; more rarely, sensitization to benzoyl peroxide was found (2, 7). In a series of 113 patients with cemented prostheses, sensitization to bone cement components was found in 24.8% (gentamicin in 16.8%, benzoyl peroxide in 8%, hydroquinone in 2.7%, and acrylates in 2.7%) (2). In 39 patients with a cemented knee prosthesis, sensitization was found

to benzoyl peroxide in 18%, to gentamicin in 18%, to hydroquinone in 2%, and to acrylates in 2% (10). Also, benzoyl peroxide, *N,N*-dimethyl-*p*-toluidine and gentamicin (15) and methyl acrylate (16) have been implicated in dermatitis, pain, and aseptic loosening of joint prostheses (17). However, a replacement with a bone cement-free implant resulting in clearing of symptoms has been performed in only a few patients (12). Recently, in one patient, development of disseminated vitiligo with partially pruritic infiltrates was observed, beginning 1 week after implantation of a cemented knee prosthesis. Later, because of infection with *Staphylococcus epidermidis*, a cement spacer was inserted. Vitiligo progressed, and contact allergy to benzoyl peroxide was suggested as an explanation. After implantation of a cement-free arthrodesis, the skin symptoms did not progress further (18). The variable prevalence of positive test reactions to the different cement components remains to be explained. In our experience, positive test reactions to other cement components, such as gentamicin, acrylates, and *N,N*-dimethyl-*p*-toluidine, are rare and not relevant. The dried complete bone cement (as is) was rarely positive.

Benzoyl peroxide is difficult to test, because it may elicit irritant patch test reactions (19). In a large study on nearly 30 000 patients, benzoyl peroxide 1% pet. was tested; weak positive reactions were seen in 6.5% of the patients, and strong positive reactions in 1.3% (20). Young age and female sex were significant risk factors for weak and strong positive reactions to benzoyl peroxide. The high prevalence of young females could be attributable to the more common use of topical acne products containing benzoyl peroxide in concentrations of up to 10%. However, contact allergy to benzoyl peroxide in acne preparations and in occupational settings has uncommonly been reported (19). In a comparison between patch tests with benzoyl peroxide 1% and 0.5% pet. in 1643 patients, 194 patients (11.8%) reacted to the 1% concentration, 100 patients (6.1%) reacted to the 0.5% concentration, and 73 patients reacted to both concentrations. It was concluded that the 1% concentration may elicit questionable or irritant test reactions, which are difficult to discriminate from true allergic reactions (11).

In our 5 patients, relevant contact allergies to alloy metals were excluded, although some had positive test reactions to metals. In all patients, benzoyl peroxide 1% pet. was positive; this was routinely tested in IQ chambers®, and, in one, also in a large Finn Chamber®. Most often, the tests gave positive results at the first and second readings; in patient 5, only the large chamber test gave a positive result. In several patients, the tests were repeated, and showed similar results (Table 1). In our

series of over 120 patients with complications from dental and orthopaedic implant materials, benzoyl peroxide 1% was also tested, with negative or, rarely, irritant results. In >20 of these patients, benzoyl peroxide in large Finn Chambers® also gave negative results. Interestingly, the freshly mixed and dried bone cement was only rarely positive (Table 1). It was not possible to identify previous therapeutic or occupational exposure to benzoyl peroxide. The late onset of symptoms within weeks or months and previous cemented orthopaedic implants suggest a sensitization through bone cement components.

In the first patient, the implant was removed and arthrodesis was performed. Upon careful analysis of the situation, implantation of a cement-free arthroplasty was proposed in 3 patients. The follow-up of 1–6 years with a stable result and a considerable decrease in pain, effusion and swelling in patients 2 and 3, as well as the complete disappearance of pain and the pruritic exanthemas in patients 1 and 4 (Fig. 2), suggest that benzoyl peroxide has played a relevant role. Similar clinical findings have been reported in 4 patients with CoCrMo knee prostheses and sensitization to nickel, which is present at a concentration of approximately 1% (21). After replacement with titanium prostheses, alleviation of symptoms was observed. Because 3 of our patients had several implants with similar complications, it is unlikely that a mechanical problem was relevant, and that the change of the implant alone or the selection of another alloy was the cause of the alleviation of their symptoms.

It has been postulated that, upon complete polymerization of bone cement, no traces of benzoyl peroxide should be present. However, in an analysis of dental resins used for dentures, elution of ingredients such as monomeric methyl methacrylate, hydroquinone and benzoyl peroxide over a long time period has been shown (22–24).

Therefore, in rare cases, benzoyl peroxide or other cement components may be relevant contact allergens from bone cement, leading to pain, swelling, and, more rarely, to cutaneous infiltrates and loosening of the implants or the formation of fistulas. A cement-free solution may be helpful in such situations, as shown in 4 of our 5 patients. In our experience, cement-free implants have a similar life span to cemented prostheses. We propose that performance and interpretation of such tests, as well as establishment of the relevance, should be carried out by physicians experienced in the management of contact allergy and the reading and interpretation of patch tests, because benzoyl peroxide and other test agents may elicit irritant test reactions. We also suggest repeating patch tests if results are suspected to be irritant or questionable, and to use another type and size of test chamber. A dilution series

of benzoyl peroxide and histology to identify irritant reactions may be useful. The far-reaching consequences of replacement of an orthopaedic joint implant should

always be carefully considered, and other causes, such as physical–mechanical problems or infections, must be ruled out.

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