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Spacer polymethylmethacrylate bone cement

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(56) Related Art
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Abstract

Spacer Polymethylmethacrylate Bone Cement

This describes a polymethylmethacrylate bone cement that is characterized in that it contains a hydrolytically-degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter. The polymethylmethacrylate bone cement is used as temporary placeholder.

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Invention Title:	Spacer polymethylmethacrylate bone cement

The following statement is a full description of this invention, including the best method of performing it known to me/us:

Spacer Polymethylmethacrylate Bone Cement

The subject matter of the invention is a spacer polymethylmethacrylate bone cement that is suitable for the production of temporary placeholders for two-stage revision of articular endoprostheses.

Articular endoprostheses currently have a serviceable life of several years, e.g. 10-15 years on average in the case of cemented hip-joint prostheses. However, there are cases, in which the articular endoprostheses become loose undesirably prior to reaching the usual serviceable life. In this regard, a distinction is being made between septic and aseptic loosening. Microbial pathogens have not been detected yet in cases of aseptic loosening. Aseptic loosening may be due to a large variety of causes. Aseptic loosening is often caused by abrasion on the sliding surfaces of the articular endoprostheses. The loosening process in septic loosening is elicited by microbial pathogens. In this regard, a distinction is made between early and late infections depending on the time of manifestation. Septic loosening is a very serious disease for the patient and, in addition, associated with very high costs. It is common to perform a revision in cases of aseptic and septic loosening. In this regard, a distinction is made between the one-stage and the two-stage revision.

In general, a placeholder, a so-called spacer, is used in the two-stage revision. This spacer fills the space of the previously revised endoprosthesis for several weeks until the manifest infection has subsided. This placeholder function is very important in order to effectively prevent shrinking of the muscles during this period of time and attain stabilization of the resection situation. Moreover, articulating spacers maintain the mobility of the afflicted extremities. This allows mobilization of the patients at an early time.

Spacers are usually produced by the surgeon using conventional PMMA bone cements and suitable molds. In the process, one or more antibiotics are admixed to the PMMA bone cement powder prior to spacer production according to which microbial pathogens are detected in biopsies and after obtaining an antibiogram. The antibiotics are selected specifically for the microbial pathogens that are present. This procedure is very advantageous, in particular in the presence of multiply-resistant pathogens or in the case of mixed infections involving different pathogens.

The development of spacers can be traced back to the original work of Hovelius and Josefsson (Hovelius L, Josefsson G (1979). An alternative method for exchange operation of infected arthroplasty. Acta Orthop Scand 50: 93-96). Other early work on

spacers was performed by Younger (Younger AS, Duncan CP, Masri BA, McGraw RW (1997). The outcome of two-stage arthroplasty using a custom-made interval spacer to treat the infected hip. J Arthroplasty 12: 615-623), Jones (Jones WA. Wroblewski BM (1989) Salvage of failed total knee arthroplasty: the `beefburger` procedure. J Bone Joint Surg Br. 71: 856-857.), and Cohen (Cohen JC, Hozack WJ, Cuckler JM, Booth RE Jr (1988), Two-stage reimplantation of septic total knee arthroplasty. Report of three cases using an antibiotic-PMMA spacer block. J Arthroplasty 3: 369-377). McPherson contributed the concept to produce spacers from bone cement exclusively and to perform no reimplantation of original parts of the prosthesis (McPherson EJ, Lewonowski K, Dorr LD (1995), Techniques in arthroplasty. Use of an articulated PMMA spacer in the infected total knee arthroplasty. J. Arthroplasty 10: 87-89).

The spacers that have been used thus far are problematic in that they show a certain degree of abrasion because of the very hard X-ray opaquer particles, such as zirconium dioxide and barium sulfate, that are present in the underlying PMMA bone cement. Abrasion events are a very critical event, in particular at the gliding surfaces of articulating spacers. There is an ongoing discussion as to whether the abrasion that is produced during the use of spacers may possibly cause aseptic loosening of the revision endoprostheses in the two-stage revision.

Another problem of the spacers used thus far is that the antibiotic particles incorporated into the PMMA bone cement are dissolved therefrom only on the surface thereof by the action of body fluid. In order to have high initial release, it is therefore common to add very large quantities of antibiotics that are not common in normal PMMA bone cements for permanent fixation of total articular endoprostheses. A release of major quantities of antibiotics over a period of time of several days up to a few weeks is desired.

It has been disclosed in DE 2905878 that the release of antibiotics from PMMA bone cements can be increased by adding sodium chloride or other soluble alkali halogenides. As an alternative, it was proposed in US 4233287 to incorporate water-soluble amino acids in PMMA cements in order to improve the release of active ingredient. The essential disadvantage of both of these methods is that the use of major quantities of water-soluble alkali halogenides and/or amino acids in PMMA bone cements, exposed to the action of wound secretions and/or blood on the hard bone cement effecting dissolution of these additives, leads to the local production of hypertonic solutions which are non-physiological.

Sencan *et al.* investigated the adherence of bacteria to PMMA bone cement containing teicoplanin and calcium sulfate (I. Sencan, I. Sahn, T. Tuzuner, D. Özdemir, M. Yildirim, H. Leblebicioglu: In vitro bacterial adherence to teicoplanin and calcium sulfate-soaked bone cement. J. Chemother. 17 (2005) 174-178.). He detected a release of major quantities of teicoplanin in the aqueous medium in the first three days followed by the release of lesser quantities of teicoplanin for up to 33 days.

The invention is based on the object to develop a polymethylmethacrylate bone cement for the production of temporary placeholders that can, on the one hand, not release major quantities of hard abrasion particles and, on the other hand, exhibits high antibiotic/antibiotics release when exposed to the action of aqueous media, such as wound secretion or blood. The polymethylmethacrylate bone cement to be developed should be designed such that antibiotics in lower-lying areas of the bone cement can also be dissolved from the cement by exposure to the action of aqueous body fluids.

According to a first aspect of the present invention, there is provided a polymethylmethacrylate bone cement, wherein it contains a hydrolytically-degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter, wherein it contains zirconium dioxide, barium sulfate or tantalum in addition to the hydrolytically-degradable X-ray opaquer.

According to a second aspect of the present invention, there is provided use of a polymethylmethacrylate bone cement as temporary placeholder, wherein the polymethylmethacrylate bone cement contains a hydrolytically degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter.

According to a third aspect of the present invention, there is provided use of a polymethylmethacrylate bone cement for permanent fixation of articular endoprotheses, wherein the polymethylmethacrylate bone cement contains a hydrolytically degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter.

There is disclosed herein a polymethylmethacrylate bone cement that is characterized in that it contains a hydrolytically-degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter.

Preferably, the hydrolytically-degradable X-ray opaquer is micro-porous and may contain a pharmaceutical excipient.

It can also contain zirconium dioxide, barium sulfate or tantalum in addition to the hydrolytically-degradable X-ray opaquer.

Preferably, the total quantity of X-ray opaquer is 5 - 25 wt.%.

Preferably, the quantity of the hydrolytically-degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter is 3 to 12 wt.%.

Calcium carbonate, magnesium carbonate, calcium sulfate dihydrate and calcium sulfate hemihydrate are preferable as hydrolytically-degradable X-ray opaquer. Calcium carbonate (calcite) has a Mohs hardness of 3 and therefore is a very soft X-ray opaquer. It is particularly advantageous that calcium carbonate usually contains no crystal water which may possibly undergo a side reaction involving the formation of ethylene glycol during ethylene oxide sterilization, which is common for PMMA bone cements. Calcium carbonate dissolves in the presence of carbon dioxide-saturated aqueous solutions such as are present in the human body, e.g. in blood, by the action of bicarbonate. Calcium sulfate dihydrate has a Mohs hardness of 2 and therefore is a very soft X-ray opaquer.

Calcium sulfate dihydrate dissolves slowly in water and is physiologically non-objectionable.

Calcium sulfate can also have a water content that is between that of calcium sulfate dihydrate and anhydrous calcium sulfate. In addition, calcium sulfate may contain small quantities of magnesium sulfate and strontium sulfate. Calcium carbonate can contain small quantities of physiologically non-objectionable strontium salts and magnesium salts such as strontium sulfate, strontium carbonate, and magnesium carbonate.

The invention also relates to the use of the PMMA bone cement described herein as temporary placeholder.

The PMMA bone cement described can also be used for permanent fixation of articular endoprostheses. In principle, the bone cement is suitable for the implantation of common hip, knee, and shoulder joints. In addition, it is feasible to produce from the bone cement according to the invention 2-dimensional implants that can be used in reconstructing bone defects of the cerebral and facial cranium. In addition, it is also feasible, in principle, to use the bone cement for vertebroplasty and kyphoplasty.

The invention is illustrated in more detail by the following examples without limiting the scope of the invention.

Examples

Firstly, 9 cement powders are produced by comminution. The composition is shown in the following table. Examples 1-3 serve as a reference in this context.

Example no.	Composition of the cement powder				
	Dibenzoyl peroxide	Polymethyl-methacrylate-co-methylacrylate	ZrO_2	$CaSO_4 \times 2H_2O$	Gentamicin sulfate (AK600)
1	0.4 g	33.7 g	5.9 g	-	1.66 g (equivalent to 1.0 g gentamicin base)
2	0.4 g	33.7 g	5.9 g	-	3.33 g (equivalent to 2.0 g gentamicin base)
3	0.4 g	33.7 g	5.9 g	-	6.66 g (equivalent to 4.0 g gentamicin base)
4	0.4 g	33.7 g	4.0 g	1.9 g	1.66 g (equivalent to 1.0 g gentamicin base)

5	0.4 g	33.7 g	4.0 g	1.9 g	3.33 g (equivalent to 2.0 g gentamicin base)
6	0.4 g	33.7 g	4.0 g	1.9 g	6.66 g (equivalent to 4.0 g gentamicin base)
7	0.4 g	33.7 g	2.0 g	3.9 g	1.66 g (equivalent to 1.0 g gentamicin base)
8	0.4 g	33.7 g	2.0 g	3.9 g	3.33 g (equivalent to 2.0 g gentamicin base)
9	0.4 g	33.7 g	2.0 g	3.9 g	6.66 g (equivalent to 4.0 g gentamicin base)

Example No.	Composition of the cement powder				
	Dibenzoyl peroxide	Polymethylmeth-acrylate-co-methylacrylate	ZrO_2	Opaquer	Gentamicin sulfate (AK600)
10	0.4 g	33.6 g	4.0 g	2.0 g $CaCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
11	0.4 g	33.6 g	4.0 g	2.0 g $MgCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
12	0.4 g	33.6 g	4.0 g	1.0 g $CaSO_4x$ $2H_2O$ + 1.0 g $CaCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
13	0.4 g	33.6 g	4.0 g	1.0 g $CaSO_4x$ $2H_2O$ + 1.0 g $MgCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
14	0.4 g	33.6 g	2.0 g	4.0 g $CaCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
15	0.4 g	33.7 g	2.0 g	4.0 g $MgCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)
16	0.4 g	33.7 g	2.0 g	2.0 g $CaSO_4x$ $2H_2O$ + 2.0 g $CaCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)

17	0.4 g	33.7 g	2.0 g	2.0 g $CaSO_4x$ $2H_2O$ + 2.0 g $MgCO_3$	3.33 g (equivalent to 2.0 g gentamicin base)

Subsequently, 40 g cement powder each are mixed with 20 ml methylmethacrylate, in which 1.0 mass-% dimethyl-p-toluidine is dissolved. A paste is thus formed that is then spread into hollow molds where it cures after a few minutes. T he cylinder-shaped test bodies thus generated have a height of 1 cm and a diameter of 2.5 cm. Five test bodies are produced for each cement variant. The test bodies are stored separately in 20 ml distilled water each at 37°C. Each day, all of the release medium is removed and the quantity of gentamicin released into the medium is determined. The test bodies are then stored again in 20 ml of fresh distilled water each at 37°C. The gentamicin content of the eluate is determined using a TDX analyzer made by Abott. The mass of gentamicin base released in each case is listed by test body in the following table as a function of the time of storage of the test bodies in the release medium.

Sample no.	Gentamicin release per form body [µg/form body]		
	1 d	3 d	5d
1	1,806	74	45
2	4,568	191	141
3	14,386	1,507	888
4	1,979	99	122
5	4,672	370	293
6	18,887	2,545	1,529
7	2,476	134	75
8	6,073	497	286
9	22,602	2,565	1,659
10	4818	367	325
11	5169	420	460
12	5294	391	353
13	6665	515	598
14	6344	836	593
15	6877	693	478
16	5202	415	442
17	6166	391	323

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In addition, the cements of examples 1-9 are used to produce plates and strips are then cut from the plates. The 4-point flexural strength and the modulus of elasticity are then determined on these strips. The results are shown in the following table. Common PMMA bone cements used for fixation of articular endoprostheses should have a flexural strength in the 4-point bending test of ≥ 50 MPA and a modulus of elasticity of ≥ 1800 MPA. The results show that the minimum requirements with regard to flexural strength and modulus of elasticity were met by all cements with the exception of the cement of sample number 9. The cement of example 9 is an exception in that its flexural strength is approximately 5 MPA lower. Even this finding is quite acceptable for a spacer PMMA bone cement, since the spacer PMMA bone cement is implanted only temporarily and does not have to possess permanent strength.

Sample no.	4-point bending	
	Flexural strength [MPa]	Modulus of elasticity [MPa]
1	60.9	2516
2	60.8	2651
3	55.4	2657
4	61.3	2,722
5	53.9	2,654
6	51.2	2,826
7	52.1	2,768
8	54.9	2,728
9	45.3	2,671
10	61.5	2686
11	58.9	2859
12	61.2	2867
13	56.7	2773
14	60.7	2859
15	55.6	2917
16	59.7	2923
17	53.8	2863

In addition, three segments without antibiotic were produced and their flexural strength and bending modulus were determined.

Sample no.	Dibenzoyl-peroxide	Polymethylmeth-acrylate-co-methylacrylate	Opaquer
18	0.4 g	33.6 g	6.0 g $CaCO_3$
19	0.4 g	33.6 g	6.0 g $MgCO_3$
20	0.4 g	33.6 g	6.0 g $CaSO_4x\ 2H_2O$

Example no.	4-point bending	
	Flexural strength [MPa]	Modulus of elasticity [MPa]
18	58.5	2820
19	58.9	2702
20	60.0	2619

Subsequently, spacer PMMA bone cements containing barium sulfate and containing tantalum as additional X-ray opaquer were also produced. Powdered barium sulfate and tantalum dust were used in the process. The cements of examples 21 and 24 were mixed without any problems and exhibited a release of active ingredient that was comparable to the test bodies of example 7.

Example no.	Composition of the cement powder				
	Dibenzoyl-peroxide	Polymethyl-methacrylate-co-methylacrylate	Opaquer	Degrad-able opaquer	Gentamicin sulfate (AK600)
21	0.4 g	33.7 g	2.0 g barium sulfate	3.9 g $CaSO_4x\ 2H_2O$	1.66 g (equivalent to 1.0 g gentamicin base)
22	0.4 g	33.7 g	2.0 g tantalum powder	3.9 g $CaSO_4x\ 2H_2O$	1.66 g (equivalent to 1.0 g gentamicin base)

23	0.4 g	33.7 g	2.0 g barium sulfate	3.9 g $CaCO_3$	1.66 g (equivalent to 1.0 g gentamicin base)
24	0.4 g	33.7 g	2.0 g tantalum powder	3.9 g $MgCO_3$	1.66 g (equivalent to 1.0 g gentamicin base)

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The claims defining the invention are as follows:

1. Polymethylmethacrylate bone cement, wherein it contains a hydrolytically-degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter, wherein it contains zirconium dioxide, barium sulfate or tantalum in addition to the hydrolytically-degradable X-ray opaquer.

2. Polymethylmethacrylate bone cement according to claim 1, wherein the hydrolytically-degradable X-ray opaquer is micro-porous and may contain a pharmaceutical excipient.

3. Polymethylmethacrylate bone cement according to claim 1 or 2, wherein it contains calcium carbonate, magnesium carbonate, calcium sulfate dihydrate, and calcium sulfate hemihydrate or mixtures thereof as hydrolytically-degradable X-ray opaquer.

4. Polymethylmethacrylate bone cement according to any one of the preceding claims, wherein the total quantity of X-ray opaquer is 5 - 25 wt.%.

5. Polymethylmethacrylate bone cement as claimed in claim 1, substantially as hereinbefore described with reference to any one of the examples.

6. Use of a polymethylmethacrylate bone cement as temporary placeholder, wherein the polymethylmethacrylate bone cement contains a hydrolytically degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter.

7. Use according to claim 6, wherein the hydrolytically-degradable X-ray opaquer is micro-porous and may contain a pharmaceutical excipient.

8. Use according to claim 6 or 7, wherein the cement contains zirconium dioxide, barium sulfate or tantalum in addition to the hydrolytically-degradable X-ray opaquer.

9. Use according to claim 6, 7 or 8, wherein the cement contains calcium carbonate, magnesium carbonate, calcium sulfate dihydrate, calcium sulfate hemihydrate or mixtures thereof as hydrolytically-degradable X-ray opaquer.

10. Use according to any one of claims 6 to 9, wherein the total quantity of X-ray opaquer is 5 - 25 wt.%.

11. Use according to claim 6, substantially as hereinbefore described with reference to any one of the examples.

12. Use of a polymethylmethacrylate bone cement for permanent fixation of articular endoprotheses, wherein the polymethylmethacrylate bone cement contains a

hydrolytically degradable X-ray opaquer with a Mohs hardness equal to or less than 3 and a water solubility at room temperature of less than 4 g per liter.

13. Use according to claim 12, wherein the hydrolytically-degradable X-ray opaquer is micro-porous and may contain a pharmaceutical excipient.

14. Use according to claim 12 or 13, wherein the cement contains zirconium dioxide, barium sulfate or tantalum in addition to the hydrolytically-degradable X-ray opaquer.

15. Use according to claim 12, 13 or 14, wherein the cement contains calcium carbonate, magnesium carbonate, calcium sulfate dihydrate, calcium sulfate hemihydrate or mixtures thereof as hydrolytically-degradable X-ray opaquer.

16. Use according to any one of claims 12 to 15, wherein the total quantity of X-ray opaquer is 5 - 25 wt.%.

17. Use according to claim 12, substantially as hereinbefore described with reference to any one of the examples.

Dated 19 May, 2010
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