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Mechanical and elution properties of G3 Low Viscosity bone cement loaded up to three antibiotics

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ABSTRACT

Objective: Periprosthetic Joint Infection (PjI) is considered one of the most difficult complication to manage after total knee or hip arthroplasty, with a mean incidence of 1%. Antibiotic loaded bone cement is used as prophylaxis during primary arthroplasty and as local therapy during two-stage revision. The aim of this study is to evaluate the mechanical and elution properties of G3 Low Viscosity Bone Cement (G-21 San Possidonio, Modena, Italy) loaded with different doses of up to three antibiotics (12 specimens).

Methods: Compressive Strength, Bending Strength and Bending Modulus were evaluated. Cumulative Vancomycin elution by adding different doses of antibiotics was evaluated.

Results: The mean Compressive Strength was 81.55 MPa, the mean Bending Strength was 2161.7 MPa, and the mean Bending Modulus was 36.6 MPa. The highest cumulative Vancomycin elution was observed in specimen 12 (1906.9 mg at 2 weeks). This is the first study, at our knowledge, that analysed how cement mechanical properties, and antibiotic elution kinetics, are modified by adding up to three antibiotic.

Conclusion: The results obtained in this pilot study using G3 Low-Viscosity Bone Cement, demonstrated that mechanical properties not decrease significantly by adding large doses of antibiotics, while the Vancomycin elution increase until swelled to twice.

1. Introduction

Demand for joint arthroplasty are constantly increasing, epidemiological evidence suggests that in 2030 more then 500.000 total hip arthroplasty and more then 1,3 billion total knee arthroplasty will be performed each year,[1] while the revision burden is remaining constant at approximately 17.5%.[2] Periprosthetic Joint Infection (PjI) is considered one of the most difficult complication to manage after total knee or hip arthroplasty, with a mean incidence of 1%, range from 0.7 to 2%.[3–5] To reduce the risk of this devasting complication, many authors have suggested to utilized antibiotic laden bone cement during primary implant, using Polymethylmethacrylate (PMMA) as carrier to reach local adequate concentration of drug.[6] For this prophylaxis proposal a low dose (1 or 2 g maximum) of a broad-spectrum antibiotic is reccomended by recent guidelines.[7] Antibiotic loaded bone cement could also be used a therapeutic tool to eradicate PjI, adding a high dose of antibiotic (suggested 4g)[7] to craft a spacer during two-stage septic revision. Adding antibiotics to bone cement could affect its mechanical properties[8,9] potentially preventing fixation during primary arthroplasty or causing mechanical complications in the interim period.[7] Moreover, pharmacokinetics of antibiotics elution from bone cement it is still not clear. Usually, it presents a biphasic kinetics, with a maximum release within the first 72 hours and a lower and constant release for the successive two-six weeks.[7] Several factors could influence mechanical properties and elution characteristics of bone cement, from preparation of cement to the brand of cement and/or of the type of antibiotic.[10] Not every antibiotic could be blended with bone cement. Is suggested to use antibiotics in powder. Liquid antibiotics must be avoided due to very negative influence on the cement mechanical properties.[7] Furthermore, some antibiotics are deactivated during the exothermic reaction of PMMA polymerization. Currently the majority of the study regarding bone cement were conducted using Palacos or Simplex cements.[8–12] The aim of our study is to evaluate the mechanical properties while adding different doses of single or multiple antibiotics (Table 1) to G3 Low-Viscosity Bone Cement (G-21 Srl, San Possidonio, Modena, Italy).

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Table 1
Antibiotics Doses in the twelve Specimens.

	1	2	3	4	5	6	7	8	9	10	11	12
Vanco.	2g	4g	2g	2g	6g	4g	4g	2g	4g	3g	4g	4g
Tobra.	/	/	3g	2g	/	3g	4g	2g	5g	4g	3g	4g
Genta.	/	/	/	2g	/	/	/	4g	/	2g	2g	2g
Tot.	2g	4g	5g	6g	6g	7g	8g	8g	9g	9g	9g	11g

2. Materials and methods

2.1. Sample preparation

Specimens were prepared using G3 (G-21, San Possidonio, Modena, Italy), a Low Viscosity bone cement, in accordance with ISO 5833-2002 guidelines as reference documents.[13] Antibiotics and cements were stored at room temperature (23 ± 1 °C) for 1 week before mixing. The different doses of antibiotics (Table 1), were manually amalgamated with a single unit of 40 g of bone cement to guarantee homogenous distribution before the mixing process. Liquid monomer was added to the antibiotic-cement compound. Polymerization process took place in PicoMix Syringe (G-21, San Possidonio, Modena, Italy) at atmospheric pressure, to guarantee an adequate distribution and size of porous. Five Specimens per each antibiotic doses (Table 1) were crafted (Cylinders with 12 ± 0.1 mm high and 6 ± 0.1 mm diameter). Tests were performed immediately after specimens crafting (within 24 ± 2 hours).

2.2. Mechanical properties

The aim of the mechanical tests was to determinate how compressive strength, bending strength and bending modulus of the G3 Low-Viscosity bone cement laden with different antibiotics doses (Table 1, five cylinders per each antibiotics doses). Tests were performed following ISO 5833-2002 guidelines,[13] using Uniaxial Fatigue Testing Apparatus (ItalSigma, MEL2/5/UP-BS). To evaluate Compressive Strength, test machine was set to produce a curve of displacement against load, using a constant cross-head speed of 19.8 mm/min and stopped when the upper yield-point was reached. In particular, in the present study we want to evaluate if adding more than one antibiotics to the cement could influence the it's mechanical property. Three different groups of specimens were analysed: Group A, consist of specimens that contains 2g of Vancomycin (alone, or with other antibiotics). Group B, consist of specimens that contains 4g of Vancomycin (alone, or with other antibiotics). Group C, consist of specimens that contains different concentration of Vancomycin only (2g, 4g and 6g). One-way analysis of variance test (ANOVA) with comparative multivariable (Turkey test) were performed to evaluate the variance of mechanical properties.

2.3. Vancomycin elution

The aim of elution tests was to evaluate the cumulative elution by G3 Bone Cement adding different antibiotics doses (Table 1, five cylinders per each antibiotics doses).

Cylinders were submerged in 12 ml of Phosphate Buffer saline (PBS), simulating the in Vivo conditions, at 37° ± 1 °C and controlled at specific times (2 h, 4 h, 8 h, 24 h, 72 h and 2 weeks). PBS with the concentration of released antibiotic/s have been tested using liquid chromatography/mass spectrometry, for Tobramycin and Gentamycin, and High Performance Liquid Chromatography for Vancomycin. T-student test was used to asses statistically significant difference between Vancomycin elution by the different specimens, a p-value < 0.05 was considered statistically significant.

2.4. Data collection

All data were collected in a work sheet of Microsoft Excel for Mac (Version 15.19.1) and imported in a Statistic Software (Prisma 7, GraphPad, Version 7.0).

3. Results

The mean Compressive Strength of the twelve specimen was 81.55 MPa (range 111.3 to 66.8 MPa), ten out twelve specimens reach the minimum level suggested by ISO 5833,[13] only specimen 10 (total 8g of antibiotics: 4g of Vancomycin and 4g Tobramycin) and specimen 12 (total 10g of antibiotics: 4g of Vancomycin, 4g of Tobramycin and 3 g of Gentamycin) doesn't reach the minimum treshold of 70 MPa (respectively, 69.1 MPa and 66.8 MPa). The compressive strength decrease with the increase of dose of antibiotics, confirming that large amount of antibiotics influence the mechanical properties of bone cement. The mean Bending Strength and Bending Modulus were respectively 2161.7 MPa (range, 1920.1 to 2438,7 MPa) and 36,6 MPa (range, 28.2–47.4 MPa). Bending Modulus seems not affected by the amount of antibiotics, while bending strength shows a similar pattern as bending strength (Table 2). For *Group A*, a statistically significant reduction of Compressive Strength was observed between specimens 1–3, 1–4 and 1–8; a statistically significant reduction of Bending Strength was observed between specimens 1–4 and 1–8; a statistically significant reduction of bending modulus was observed between specimens 4–8. For *Group B*, a statistically significant reduction of Compressive Strength was observed between specimens 2–6, 2–7, 2–9, 2–11 and 2–12; a statistically significant reduction of Bending Strength was observed between specimens 2–6, 2–7, 2–9, 2–11 and 2–12; no statistically significant reduction of Bending Modulus was observed. For *Group C* a statistically significant reduction of Compressive Strength was observed between specimens 1–5 and 2–5; a statistically significant reduction of Bending Strength was observed between specimens 1–5 and 2–5; a statistically significant reduction of bending modulus was observed between specimens 1–5 and 2–5. Compressive Strength of 2g or 4g Vancomycin-loaded cement decrease adding a second or a third antibiotic, while the reduction is least important (not statistically significant) if a third antibiotic is added. Bending Modulus is not influenced by the addition of antibiotic at the cement, and only in few cases it's value showed statistically significant variation.

Total Vancomycin cumulative elution from G3 cement from different specimens is showed in Table 3. For all the specimens the antibiotics release was rapid in the first 72 hours (mean ratio 72 h/2-weeks 65.6%, range 48.2–91.2%), showing a slightly reduction in the following days. For specimens containing 2g of Vancomycin, the highest elution was observed in specimen 8 (600,76 mg at 2 weeks), while for specimens containing 4g of Vancomycin the highest elution was observed for specimen 12 (1906.9 mg at 2 weeks). Adding one more ($p < 0.05$) or two ($p < 0.05$) antibiotics, showed a statically significant increase of Vancomycin elution.

4. Discussion

The objective of this study was to evaluate how different doses up to three antibiotics, influences mechanical and elution properties of G3 Low-Viscosity Bone Cement. Antibiotic-laden cement could be used as prophylaxis purpose (during primary hip or knee arthroplasty) requiring a low doses of antibiotic, or as therapeutic tool (during two-stage hip revision usually with 4g of antibiotic) to guarantee a local higher concentration of antibiotics to eradicate the infection.[1,2] Several studies have already demonstrated that mechanical properties are modified by high concentration of antibiotics, the majority of studies were performed with Palacos[8–10] or Simplex bone cement.[11,12] In the study of Lee and colleagues,[10] kinetics of four different bone cement brands was evaluated (Palacos R, DePuy-CMW, Simplex P and

Table 2
Results of Mechanical Test on Compressive Strength, Bending Strength and Bending Modulus divided into three groups (Based on Vancomycin Dose).

Group A	Tobramycin [gr]	Vancomycin [gr]	Gentamycin [gr]	Avg. Compressive Strengh (MPa) and SD	Avg. Bending Modulus (MPa) and SD	Avg. Bending Strength (MPa) and SD
1	–	2	–	111.3 ± 5.2	2198.9 ± 51.4	47.4 ± 1.5
3	3	2	–	80.0 ± 3.1	2191.8 ± 121.8	39.8 ± 4.2
4	2	2	2	84.0 ± 2.6	1895.4 ± 219.0	36.4 ± 0.3
8	2	2	4	80.5 ± 4.0	2432.4 ± 160.2	37.0 ± 3.7
Group B	**Tobramycin [gr]**	**Vancomycin [gr]**	**Gentamycin [gr]**	**Avg. Compressive Strengh (MPa) and SD**	**Avg. Bending Modulus (MPa) and SD**	**Avg. Bending Strength (MPa) and SD**
2	–	4	–	107.9 ± 3.9	2204.9 ± 40.3	44.1 ± 1.9
6	3	4	–	73.5 ± 3.2	2094.0 ± 138.9	36.9 ± 2.8
7	4	4	–	69.1 ± 2.3	2203.5 ± 155.7	34.3 ± 4.4
9	5	4	–	70.5 ± 4.6	2438.7 ± 354.2	34.2 ± 1.9
11	3	4	2	72.4 ± 3.7	2127.3 ± 471.9	28.2 ± 4.9
12	4	4	2	66.8 ± 8.7	2308.9 ± 172.7	35.2 ± 1.4
Group C	**Tobramycin [gr]**	**Vancomycin [gr]**	**Gentamycin [gr]**	**Avg. Compressive Strengh (MPa) and SD**	**Avg. Bending Modulus (MPa) and SD**	**Avg. Bending Strength (MPa) and SD**
1	–	2	–	111.3 ± 5.2	2198.9 ± 51.4	47.4 ± 1.5
2	–	4	–	107.9 ± 3.9	2204.9 ± 40.3	44.1 ± 1.9
5	–	6	–	91.4 ± 3.4	1920.1 ± 97.9	35.4 ± 2.7

Osteobond). From their analysis Palacos showed the higher elution ability, while mechanical properties showed no statistically significant differences. The results obtained with G3 bone cement underlined that there is a difference, in terms of reduction of compressive and bending properties, of bone cement with a low (2g only) concentration of antibiotic if compared with greater concentration of antibiotics. But adding a third antibiotics, or increase the doses of the already presents antibiotics causes a poor reduction of mechanical properties that not reach a statistically significant level. Considering that usually a doses of 4g is generally suggested for preparation of antibiotic spacers,[10,14] and considering the synergic effect of antibiotic elution, G3 cement could be added with a higher doses of antibiotics not modifying its mechanical properties and allow a greater antibiotics release. Furthermore, in this study 11 out 12 specimens (only with specimen 12, loaded with 10 g of

Table 3
Cumulative Elution in mg of Vancomycin, Tobramycin and Gentamycin from the twelve different specimens.

	Antibiotics	2 h	4 h	8 h	1g	3g	2w	TOT	72/Tot
Specimen 1	Vancomicine 2	77,08	30,12	19,9	19,26	20,32	34,57	201,25	0,82
	Tobramicine 0								
	Gentamicine 0								
Specimen 2	Vancomicine 4	112,46	32,55	22,13	30,53	56,25	95,45	349,37	0,72
	Tobramicine 0								
	Gentamicine 0								
Specimen 3	Vancomicine 2	70,29	22,38	18,13	25,58	39,72	110,7	286,8	0,61
	Tobramicine 3	31,9	1	1	15,2	32	87,3	168,4	0,48
	Gentamicine 0								
Specimen 4	Vancomicine 2	112,54	38,68	25,36	38,42	108,81	162,44	486,25	0,66
	Tobramicine 2	84,1	25,9	17,6	33,5	46,2	87,2	294,5	0,70
	Gentamicine 2	15,54	11,55	9,97	12,63	16,74	39,95	106,38	0,62
Specimen 5	Vancomicine 6	131,54	53,48	40,71	67,7	119,45	334,55	747,43	0,55
	Tobramicine 0								
	Gentamicine 0								
Specimen 6	Vancomicine 4	136,5	60,78	38,2	65,1	102,77	296,8	700,15	0,57
	Tobramicine 3	82,9	12,1	5	22,6	46,4	135,6	304,6	0,55
	Gentamicine 0								
Specimen 7	Vancomicine 4	172,3	57,6	44,6	75,7	159,5	436,3		
	Tobramicine 4	204,1	33,1	26,1	70,7	108,8	328,7		
	Gentamicine 0								
Specimen 8	Vancomicine 2	112,54	45,84	33,78	56,9	100,8	250,9	600,76	0,58
	Tobramicine 2	92,5	28,1	19	49,3	84,9	145,1	418,9	0,65
	Gentamicine 4	176,2	45,96	21,78	76,4	149,4	288,75	758,49	0,61
Specimen 9	Vancomicine 4	275	76,9	52,6	93,6	170,7	552,7	1221,5	0,54
	Tobramicine 5	537,1	123,1	91,5	208,4	381,1	870	2211,2	0,60
Specimen 10	Vancomicine 3	225,3	95,8	83,96	150,14	171,5	394,3	1121	0,64
	Tobramicine 4	373,6	109,5	96,7	206,6	235,7	450	1472,1	0,69
	Gentamicine 2	248,6	73,3	50,48	120,3	130,6	318,4	941,68	0,66
Specimen 11	Vancomicine 4	250,6	91,6	88,3	138,8	204,5	483	1256,8	0,61
	Tobramicine 3	280,6	78	50,6	96,2	170,5	362,9	1038,8	0,65
	Gentamicine 2	105,22	33	29,5	44,62	97,89	249,57	559,8	0,55
Specimen 12	Vancomicine 4	542,8	253,2	210,2	286,3	243,2	371,2	1906,9	0,80
	Tobramicine 4	809	229,4	172,4	307	223	164,8	1905,6	0,91
	Gentamicine 2	377,9	116,5	87,2	147,3	132,6	147,1	1008,6	0,85

antibiotics on 40 g of bone cement) reached the recommended level of resistance at compressive strength of 70 MPa[13] (level that is not reached "several times" in other studies,[10] with lower antibiotics concentration).

Two-stage revision is considered the gold standard treatment for culture positive (CP) and culture negative (CN) PjI. While the treatment of CP is well documented and reproducible,[14] the course of treatment in case of CN PjI is not well described. In a recent review,[15] the incidence of CN PjI reported was ranging from 7 to 42%[16–18] and the most frequent surgical intervention is two-stage revision using a spacer loaded with Vancomycin and Gentamycin.[15] The results obtained in the present paper revealed that both Gentamycin and Tobramycin cause a synergic effect on Vancomycin elution. The addition of a third antibiotic (In this case Gentamycin), increase elution of both Vancomycin and Tobramycin causing a not significant difference decrease of mechanical properties of bone cement. Specimen 1 (2g Vancomycin only) showed a cumulative elution at 2-weeks of 201.25 mg, in specimen 3 (2g Vancomycin + 3g Vancomycin), vancomycin elution was 29.9% greater, while in specimen 4 (2g of Vancomycin, Tobramycin and Gentamycin), Vancomycin elution showed a cumulative elution of 600.76 mg, respectively 198% greater than specimen 1 and 109% greater then specimen 3. In each of the reported cases the difference in vancomycin elution was statistically significant (p-value < 0.05). A similar pattern of elution was observed in specimens containing 4g of Vancomycin. For specimen 2 (4g Vancomycin only), the cumulative elution at 2-weeks was of 349,4 mg, in specimens 6 (4g Vancomycin and 3g of Tobramycin) was 700.2 mg (100,4% greater), while in specimen 11 (4g Vancomycin, 3g Tobramycin and 2g of Gentamycin) and 12 (4g Vancomycin, 4g Tobramycin, 2g Gentamycin), Vancomycin elution was respectively 259,8% and 445,9% greater than specimen 2. In each of the reported cases the difference in Vancomycin elution was statistically significant (p-value < 0.05).

In the next decades Orthopaedic Surgeons and infectious disease specialist will need to face up against an increase of PjI, and in particular with the increasing number of multi-drug resistant bacteria PjI.[19] The majority of the already published studies, either in vivo or in vitro,[8–12,16–18] have analysed the effects of adding one or at least two antibiotics to bone cement. This is the first study, at our knowledge, that analysed how cement mechanical properties, and antibiotic elution kinetics, are modified by adding up to three antibiotic. The results obtained in this pilot study using G3 Low-Viscosity Bone Cement, demonstrated that mechanical properties not decrease significantly by adding large doses of antibiotics, while the Vancomycin elution increase until swelled to twice.

Conflicts of interest

Giorgio Cacciola and Federico De Meo have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affi liations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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