International Orthopaedics (SICOT) (2009) 33:815–819
DOI 10.1007/s00264-008-0521-3

ORIGINAL PAPER

The effect of vancomycin addition to the compression strength of antibiotic-loaded bone cements

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Received: 30 October 2007 / Revised: 21 December 2007 / Accepted: 3 January 2008 / Published online: 19 February 2008

Abstract The purpose of this study was to record the effect of the addition of vancomycin on the compression strength of antibiotic-loaded bone cement and to compare the results with the international standards (ISO 5833–2). The formulations tested were: Palamed G and Copal. Vancomycin concentrations of 2.5%, 5% and 10% per powder weight were added. Samples of Palamed G with 5% vancomycin and non-standardised mixing procedures were also tested. The ISO requirements for the testing procedures were followed. None of the combinations tested fall short of the ISO standards for compression strength. Copal with 10% and Palamed G with 5% vancomycin and non-standardised mixing procedures, however, did not significantly exceed them. The addition of up to 5% vancomycin per powder weight to the Palamed G and Copal bone cements can be considered safe. Care should be given to the mixing procedure of the cement, as it significantly affects its compression strength.

Résumé Le but de cette étude est d'évaluer l'effet de l'addition de vancomycine sur les forces, en compression d'un ciment osseux aux antibiotiques et de comparer ces résultats avec les standards internationaux (ISO 5833–2). Matériel et méthodes: les formules testées ont été: Palamed G et Copal. Les concentrations de vancomycine étaient respectivement de 2,5%, 5% et 10% de poudre ajoutée au ciment. L'échantillon de ciment Palamed G avec 5% de vancomycine et un mélange non standardisé ont été également testés. Les obligations ISO pour les test ont été suivies. Résultats: aucune des combinaisons testées ne présente de problèmes sur les forces en compression par rapport aux nécessités des données standards, néanmoins, Copal avec 10% et Palamed G avec 5% de vancomycine et les mélanges non standardisés ne semblent pas être en deçà de ces valeurs. Discussion: l'addition de vancomycine en poudre dans du Palamed G ou du Copal peut se faire en toute sécurité. Un soin particulier doit être réalisé lors du mélange de la poudre de façon à ne pas affecter de façon significative les caractéristiques du ciment en compression.

Introduction

Buchholz and Engelbrecht were the first to incorporate antibiotics in PMMA bone cements in 1970 [4]. The task was twofold: to prevent infection of the primary total hip replacement (THR) and to treat already infected THRs with gratifying results [5, 21]. The amount of antibiotic in the cement is proportional to its release to the surrounding tissues [20, 24]. Therefore, by adding large quantities of antibiotics to bone cement, sufficient levels of the drug in the tissues would be achieved and bacterial contamination avoided. The addition of antibiotics to bone cement, however, affects its mechanical properties. Clinically, the failure rate of prosthetic implants caused by infection has been observed to be far lower than that related to failure of the mechanical fixation of the cemented composite [8], demonstrating the importance of maintaining the cement's properties when using it as an antibiotic carrier.

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Various antibiotic agents have been tested as additives to bone cement, but the first and still most commonly used is gentamicin because is the most suitable from a bacteriological and physicochemical point of view [23]. Vancomycin has been the most commonly used agent for intravenous treatment in infected arthroplasties caused by resistant strains [3], and it was therefore also used as an additive to bone cement in revision surgery [1]. Combining an aminoglycoside with vancomycin in bone cement for revision cases of infected implants is common in surgical practice [9, 22].

The ISO standards for bone cements were first introduced in 1978 [12] and were updated in 1992 [13]. The compression strength was the only mechanical requirement set by the first ISO 5833–1 standard [12]. Two mechanical tests have been introduced into ISO 5833–2: the compression and the four-point bending test for the determination of the compression strength, the bending strength and the bending modulus (modulus of elasticity or Young's modulus), respectively. The standard ASTM F451 includes the compression test only [2]. The compression test, according to both standards, is a static method in which the compression strength is defined as the maximum strength that a material can withstand before failure in compression. The minimum requirement for compression strength in both standards is 70 MPa.

There are no studies, to the authors' knowledge, on the compression strength of antibiotic-loaded bone cement with the addition of vancomycin. The authors therefore wished to investigate the effect of the addition of various concentrations of vancomycin to the compression strength of proprietary cements with antibiotic.

Materials and methods

Palamed G, containing 0.55 g of gentamicin, and Copal, containing 1 g of gentamicin and 1 g of clindamicin per 40 g pouch, were the antibiotic-loaded cements that were chosen for the experiments. Palamed, which is the antibiotic-free equivalent of Palamed G, was also tested for reference purposes. The producer of all the antibiotics is Heraeus Kulzer GmbH & Co., Wehrheim, Germany. The cements used were provided in packages of two 40-g pouches.

Vancomycin hydrochloride in 500-mg vials of powder (Voncon, Eli Lilly, Indianapolis, IN) was used. The concentrations of vancomycin added were 2.5%, 5% and 10% per powder mass for Palamed G and Copal and 2.5% and 5% for Palamed. Specimens without antibiotic were also tested in all three formulations. The concentration of up to 2 g of antibiotic per 40 g of polymer powder (5%) is considered to be the gold standard in clinical practice [14], and it was decided to see the effect of up to twice that concentration. However, this was not done for Palamed, as research on the effect of admixing various concentrations of antibiotic, including vancomycin, in plain cements is quite extensive in the literature.

In clinical practice, at surgery, precise weighing is not possible either for the antibiotic or the polymer powder. Moreover, care is not always taken over the proper mixing of the two powder constituents before admixing them to the liquid. We tried to imitate these situations, creating specimens of Palamed G with 2 g per 40 g of polymer powder, but without standardised mixing conditions. The testing procedure was otherwise identical to the other specimens and is dictated in detail by the ISO 5833–2 requirements, which also set the standard for the minimum physico-chemical requirements of bone cements [16]. All three cements tested have mechanical properties fulfilling these standards.

Mixing was done without vacuum following the manufacturer's instructions, which were common to all three formulations: the liquid was first poured into a plastic bowl, and the powder was added. Components were mixed in a thermostatic chamber at 23±1° C and at a humidity between 40% and 60%. The mixture was stirred carefully with a spatula for no longer than 30 s to produce homogenous dough. When admixing antibiotic, the vancomycin powder was weighed in the precision scale and mixed together with the polymer powder in a separate bowl with a spatula, until the two powders formed a homogeneous powder, before admixing it to the liquid. Following the time requirements of each of the formulations, the dough was manually overfilled ('thumbed-in') into the drill holes of a special mold and allowed to harden.

The mold was a rectangular block made of brass, 63 mm by 63 mm and 12 mm high. Equidistant holes, 6 mm in diameter, were drilled in the mold in a 7×7 grid pattern, resulting in a total of 49 holes. Forty-nine cylindrical specimens, 6 mm in diameter and 12 mm high, were therefore produced for each cement–antibiotic pair. The mold was smeared on both sides with a metallographic polisher, to remove excess dough and to reduce the friction between the platen of the testing machine and the specimen. The specimens were then tapped out of the mold. Each specimen was measured with a precision calliper between 22 and 26 h after setting, and only specimens with a length of 11.9±1 mm and a diameter of 6 mm were used. The specimens were also inspected macroscopically, and those with flaws, such as voids or powder clots, were excluded, as numerous studies have indicated that antibiotic inclusions may propagate fracture in cement [8, 11, 18].

An Instron 5500-R universal testing machine (Instron Corporation, Norwood, MA) was used for the experiments. The machine was arbitrarily regulated to stop loading when a maximum compression deformation of 5 mm was achieved. The maximum load was set at 5000 N, as

preliminary calculations and data from the literature suggested that loads of approximately 2,500 N could be expected. The crosshead speed was fixed at 20 mm/min. The cylinders were placed upright in the loading device, and the compression load was applied. The maximum load F recorded by the machine was used for the calculation of the maximum nominal compression strength G of the cylinder, using the equation G=F/A, where A is the cross-sectional area before testing. Silicon spray lubrication was used between the specimen and the compression platens, following standard compression testing practice.

Ten specimens in each category were tested to achieve results with a 95% confidence interval. The results were analysed to identify the effect of the amount of vancomycin on the compression strength for every cement type. The compression strength of the three cement formulations and their vancomycin-containing subgroups were also compared with the ISO standard of 70 MPa, which is considered to be acceptable for clinical practice. Statistical analysis was carried out in SPSS 11.5 for Windows software (SPSS Inc. Chicago, IL). One-way analysis of variance (ANOVA) was used to compare mean values between groups. The confidence interval was set to 95%, and the level of significance at $p=0.05$. Post-hoc analysis with the Bonferroni test was used to identify the differences between the groups. The Wilcoxon signed rank test was used to compare the compression strength of the various subgroups with the value of 70 MPa.

Results

Palamed plain

The plain Palamed (Pal-0 group) had a mean compression strength of 88.8 MPa. With the addition of 2.5% (Pal-2.5) and 5% (Pal-5) vancomycin, the mean compression strengths were 87 MPa and 81.5 MPa, respectively, a reduction of 2% and 8.2%. Detailed results of mean strength, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range, are displayed in Table 1. One-way ANOVA showed that there was a significant difference between the groups ($F=27$, $p<0.001$). Post-hoc analysis showed that a significant difference existed between the mean strengths of the Pal-0 and Pal-2.5 groups compared with that of the Pal-5 group ($p<0.001$ in both instances).

Palamed-G

The mean compression strength of plain Palamed G (GPal-0) was 91 MPa. With the addition of 2.5% (GPal-2.5), 5% (GPal-5) and 10% (Gpal-10) vancomycin, the mean compression strengths were 79.8, 82.3 and 74.6 MPa, respectively, a reduction of 12.4%, 9.6% and 18.1%. The mean compression strength of the roughly prepared Palamed G specimens (GPal-rough) was 72.9 MPa, a 19.9% reduction. Detailed results of mean strength, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range, are displayed in Table 2. There was a significant difference between the groups ($F=31.1$, $p=0.0002$). Post-hoc analysis showed that significant differences existed between the GPal-0 group compared with all other groups ($p<0.001$ in all cases), the GPal-2.5 group and the GPal-rough group ($p=0.004$), and, finally, the GPal-5 group compared with the GPal-10 and GPal-rough groups ($p=0.001$ and $p<0.001$, respectively).

Copal

The mean compression strength of the plain Copal (Cop-0) was 86.3 MPa. With the addition of 2.5% (Cop-2.5), 5% (Cop-5) and 10% (Cop-10) vancomycin, the mean compression strengths were 76.6 MPa, 78.9 MPa and 71.2 MPa, respectively, a reduction of 11.2%, 8.5% and 17.5% respectively. Detailed results of mean strength, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range, are displayed in Table 3. There was a significant difference between the groups ($F=36.9$, $p<0.001$), which the post-hoc analysis identified to exist between the Cop-0 group and all other groups ($p<0.001$ in all cases), the Cop-2.5 group and the Cop-10 group ($p=0.004$), and, finally, the Cop-5 group and the Cop-10 group ($p<0.001$).

ISO standards

The subgroups of Palamed bone cement, with any concentration of vancomycin, had mean compression strengths that

Table 1 Mean compression strengths of the Palamed subgroups in MPa, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range

	Mean	SD	SE	95% CI		Range	
PAL0%	88,817	1,950	0,616	87,422	90,213	85,407	92,056
PAL2.5%	87,028	1,709	0,540	85,805	88,250	83,333	89,152
PAL5%	81,512	3,065	0,969	79,319	83,705	74,527	84,428

Table 2 Mean compression strengths of the Palamed G subgroups in MPa, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range

	Mean	SD	SE	95% CI		Range	
GPAL0%	91,087	2,326	0,735	89,423	92,750	87,289	94,873
GPAL2.5%	79,824	4,828	1,526	76,370	83,277	68,237	84,550
GPAL5%	82,299	3,876	1,225	79,526	85,072	76,155	87,260
GPAL10%	74,555	3,484	1,101	72,063	77,048	69,665	81,234
GPALROUGH	72,875	5,284	1,671	69,095	76,656	64,338	81,500

were significantly superior to the ISO standard of 70 MPa ($Z=-2.80$, $p=0.005$ for all three groups). The GPal-0 group ($Z=-2.80$, $p=0.005$) as well as the GPal-2.5, GPal-5 and GPal-10 groups ($Z=-2.70$, $p=0.007$, $Z=-2.80$, $p=0.005$ and $Z=-2.70$, $p=0.007$, respectively) had mean compression strengths significantly exceeding 70 MPas. The Palamed G-rough specimens had mean compression strength that was not significantly superior to the ISO standard ($Z=-1.58$, $p=0.114$). The formulations of Copal bone cement without vancomycin and those with 2.5% and 5% vancomycin had strengths significantly greater than 70 MPa ($Z=-2,80$, $p=0.005$). The addition of 10% vancomycin to Copal bone cement produced specimens with a compression strength not significantly greater than the ISO standard.

Discussion

The purpose of the study was to investigate the effect of the addition of vancomycin on the compression strength of antibiotic-containing proprietary bone cements. Palamed G and Copal were the formulations tested, while Palamed was also tested for reference purposes.

The compression strength of Palamed G was found to be 91.1 MPa, a value comparable with 89.3 MPa, found by Kuehn [17]. There was a significant difference between the two groups containing 5% antibiotic, which should be attributed to the inappropriate manufacture of the specimens in the GPal-rough, which presumably resulted in big voids and antibiotic inclusions. Care should be given to the mixing and manufacturing conditions when admixing antibiotic to bone cement in clinical practice, especially in concentrations greater than 2.5% per polymer powder [6]. This is an issue that has often been highlighted in the literature, [7, 8, 15, 21]. The compression strength of Copal was found to be 86.3 MPa, greater than the 78.9 MPa found by Kuehn [16]. Again this difference may be interpreted by variations between pouches or, more possibly, may be the result of the specimens' selection that was performed in this study.

Lautenschlager et al. [18] advised that the addition of up to 4.5 g (approximately 10%) of antibiotic is safe. However, the highest safe combination they tested was 5%. They did not actually test the 10% ratio of antibiotic–cement, making their recommendation by extrapolating from a graph. Klekamp et al. [15], found that a concentration of up to 7.5% vancomycin to plain cements had no significant effect on the compression strength; however, this concentration is not addressed in our study. Similarly, Chohfi et al. [7] also reported that such a concentration is safe; however, they used an industrially prepared cement containing only vancomycin, and this was the only concentration tested. He et al. [11], on the other hand, although having also tested a different cement–antibiotic combination (Palacos–gentamicin), presented results very similar to this study's. Investigation of sufficient dosage increments is needed to define that concentration.

The final aim of the study was to compare the results with the ISO standard of 70 MPa. All plain and antibiotic-containing subgroups of Palamed, Palamed G and Copal cements had compression strengths above the ISO standard of 70 MPa, similar to all published studies for cement–antibiotic combinations of similar ratios [11, 17, 18]. However, when the results were statistically analysed and compared with the value of 70 MPa, the GPal-rough and the Copal 10% specimens did not significantly exceed that value. This is a statistical analysis not conducted in any of

Table 3 Mean compression strengths of the Copal subgroups in MPa, including standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the mean and range

	Mean	SD	SE	95% CI		Range	
COP0%	86,268	2,549	0,806	84,444	88,092	82,231	90,217
COP2.5%	76,589	3,988	1,261	73,736	79,443	70,440	83,210
COP5%	78,917	2,862	0,905	76,869	80,964	74,000	83,366
COP10%	71,188	3,433	1,085	68,732	73,644	65,540	76,386

the above studies. These combinations are therefore not recommended in clinical practice as they may exhibit an unexpected pattern of behavior in compression. This conclusion is further reinforced by the fact that in this study specimens with macroscopically visible flaws, voids and inclusions were excluded.

The findings of our study coincide with those in the literature, where the addition of 5% antibiotic is considered to be the gold standard [11, 14]. Several limitations exist, however. Compression strength is only one of the mechanical properties of bone cement. This study did not address other characteristics of acrylic cement such as tensile strength and fatigue properties. Furthermore, the addition of vancomycin to the specific bone cements examined in this study does not guarantee its sufficient release, as the elution properties of these combinations have not been tested.

In conclusion, Palamed G and Copal bone cements and their formulations with 2.5% and 5% vancomycin should be considered as safe, whereas the addition of 10% vancomycin alters their mechanical properties in compression in such a way that it renders them unsafe for clinical use. Moreover, specific care should be given to the mixing procedure when adding antibiotic to bone cement, as specimens with the same antibiotic to polymer powder ratios, but with different manufacturing procedures, exhibited significantly different mechanical properties.

Acknowledgements The authors wish to thank Miss Sarah Vowler (Medical Statistician, Centre for Applied Medical Statistics, Department of Public Health and Primary Care, University of Cambridge) for her invaluable contribution to the statistical analysis of the results. They are also indebted to Biomet Hellas Inc. for kindly supplying free units of cements and to the NIMTS Hospital, Athens, Greece, for generously supplying free vials of vancomycin.

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