BIOMECHANICAL EVALUATION OF ORTHOPAEDIC CEMENT COMBINED WITH ANTIBIOTIC AND METHYLENE BLUE

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ABSTRACT

Objective: Acrylic cement has been used for years on orthopaedic surgeries, especially on knee arthroplasties, deserving special attention when added to antibiotics (for treatment of deep bone infections) or stains (to facilitate its removal). The present study was conducted in order to evaluate potential mechanical differences between the orthopaedic cement itself and when this is added to antibiotic

and/or stains. Methods: Surgical bone cement Simplex®P Stryker, vancomycin and methylene blue were used, and the mixtures were submitted to physical and mechanical tests according the ABNT NBR ISO 5833 rule. The parameters studied here were: time for mass formation, intrusion capability, resistance to compression, resistance to flexion and maximum temperature reached by the mixtures. Results: The evaluated mixtures were approved as to mass formation, maximum temperature, intrusion capability and resistance to compression. Only the one containing pure cement was approved on the flexion essay. Conclusion: The addition of vancomycin and/or methylene blue to Surgical Simplex®P Stryker bone cement reduces its resistance to flexion, being unacceptable by the ABNT NBR ISO 5833 rule.

Keywords: *Bone cements. Polymethylmetacrylate. Arthroplasty.*

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INTRODUCTION

Orthopaedic cement was introduced in joint replacement surgeries in mid 20th Century, with the use of polymethylmetacrylate compounds for fixating total hip arthroplasties. The technique has been disseminated by Sir John Charnley, one of the key authors in modern orthopaedic surgery.[1,2]

Total arthroplasty with cement is regarded by many authors as the golden standard for knee joint replacement.[3-5] Despite of the widely spread use of non-cemented components for the hip, providing excellent results, the non-cemented technique still lead to inconsistent results on the knee.[4,5] Thus, the study of orthopaedic cement in arthroplasties is still a matter of strong attention.

One of the disadvantages of the use of cement in arthroplasties is its difficult removal, which is required in occasions such as prosthesis review or in cases of infection. In this sense, some studies investigated the addition of methylene blue to the cement, making its identification and removal easier. However, those studies did not identify significant biomechanical changes in cement's characteristics following stain addition.[6-10]

Another aspect to be considered when using cement is the addition of antibiotic agents for the treatment and prophylaxis of infections. Recent studies suggest that the prophylactic use of antibiotics on cement in primary arthroplasties reduces the rate of deep infections.[7,8] There are also evidences that the biomechanical features of cement in its pure state are comparable to those of cement with antibiotics, such as vancomycin and gentamicin.[9,10] However, studies correlating the mechanical characteristics of cement added by antibiotics and/or stain have not been found.

The physical properties of acrylic cement, polymethylmetacrylate, can be assessed by the ABNT NBR-ISO 5833 policy, which describes mechanical tests of compression, folding (flexion) and intrusion, as well as the assay to monitor the temperature raise caused by an exothermal response of the mixture of its powder and fluid contents. The policy also establishes the minimum limits for the safe use of the cement.

In this context, we have proposed a set of assays to test the mechanical characteristics of orthopaedic cement when simultaneously added by vancomycin and methylene blue, assessing potential changes in its feasibility, once a successful arthroplasty also depends on cement quality.

OBJECTIVE

To assess eventual differences on mechanical characteristics of orthopaedic cement concerning preparation time, intrusion ability, maximum reached temperature, compression resistance and folding (flexion) resistance – in its pure state and when added by antibiotics, stains, or both.

MATERIALS AND METHODS

The following have been used: a) 20 units of radiopaque acrylic cement Surgical Simplex®P brand Stryker (donation), containing, in

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each box, an envelope with 40 g of sterile copolymer powder and barium sulfate, and a ampoule with 20 ml of a monomer; b) ten ampoules with the powder antibiotics vancomycin at a dosage of 500 mg, c) 5 ampoules containing 5 ml of 1% methylene blue.

The methylene blue stain was selected because it is used in some orthopaedic services for a better visualization of the cement when performing arthroplasties or when removing prosthesis. This is an aromatic heterocyclic water-soluble organic compound with fusion point between 100 and 110° C, which decomposes when its ebullition point is reached.

Vancomycin was the antibiotic agent selected for the assay because it is available as powder, is shown to keep stable when submitted to temperature raises occurring at cement polymerization, and because it is the antibiotics of choice for covering the key infectious agents found in infected arthroplasties, especially the multiple-resistant *Staphylococcus aureus*.

The equipment used in the assay, as well as the contents of cement units, vancomycin and methylene blue, were submitted to a temperature of 23±1 °C and minimum air relative humidity of 40% for 2 or more hours before the experiments. All assays were carried out at a temperature of 23±1 °C and minimum air relative humidity of 40%.

The physical and mechanical assays were conducted according to the ABNT NBR–ISO5833 policy[10] for assessing acrylic resin cements, and they were divided into: a) identification of the time for preparing the fluid-powder mixture (Annex B of the policy); b) identification of the maximum temperature and time for introducing the fluid-powder mix (Annex C); c) identification of the intrusion of the fluid-powder mix (Annex D); d) identification of the mixture resistance to compression (Annex E); e) identification of mixture's folding module and folding resistance (Annex F).

Four groups were built for the assays, namely: 1) PURE group – containing cement free from other substances; 2) BLUE group – cement added by methylene blue 1 ml at the moment of fluid-powder blending; 3) BLUE-VANCOMYCIN group –cement added by methylene blue 1 ml and vancomycin 1 g at the moment of fluid-powder blending; 4) VANCOMYCIN group – cement added by vancomycin 1 g at the moment of fluid-powder blending.

The time for preparing fluid-powder mixtures for cements used on the four groups was the first parameter to be assessed. The components of a single cement unit were mixed and the time device activated. After about 1 minute, the cement was touched with a gloved finger, assessing fiber formation between the finger and the cement. From this point on, the touch was repeated at each 15 seconds. The time when, for the first time, the gloved finger did not stick to the cement was recorded. The described procedure was repeated for a second cement unit. The mean time for preparing both cement units was, then, calculated. The described procedure was repeated twice for all groups, totaling two cement units for each group. All cements assessed in this first assay were employed for the next following experiments.

On the second phase, the intrusion of the cement fluid-powder mixture designed to be used as a mass was determined, and the results achieved on the four groups were compared. For this assay, the following were used: 1) a cylindrical polytetrafluorethylene cast with four 4 mm-wide holes on its base; 2) a polytetrafluorethylene plunger (Figure 2); 3) a weight with a 5 kg mass for applying compressive force to the cast; 4) a digital Mitutoyo pachymeter, with 0.01 mm resolution.

The components of one cement unit were blended and, after the mixture preparation time was completed (according to the procedures described on the first phase), carefully poured into the cylindrical cast, and immediately followed by the plunger. After 1 minute ± 10 seconds of the mixture time, a 49±1 N force was applied to the plunger for a period of 1 minute ± 2 seconds. Force was removed and the cement was allowed to harden. The hardened cement was removed from the cast, and the extensions of the four cement cylinders produced by intrusion through the holes on the polyfluorethylene cylinder were measured with the pachymeter. The described procedure was repeated for all groups.

The third assay identified the polymerized cement's resistance to compression. The following were used: a) a 12-mm high cylindrical aluminum cast with 6-mm wide holes; b) support boards; c) bench vise; d) removal pin, targeting to produce 12-mm high and 6-mm wide hardened cement cylinders each. (Figure 3) A Kratos 5002 universal assay machine for mechanical assays with built-in load cell of 5000 kgf, adjusted for the 500 kgf scale, and equipped with a computer interface able to register the "load versus deformation" graph was employed.

The components of a single cement unit were blended, and, one minute after mass preparation time, each of the cavities of the aluminum cast was slightly overfilled with the mixture, and the cast was placed between two support boards and compressed at the bench vise for one hour. After that period, cylinders were removed from the cast. After 24 ± 2 hours, 18 cylinders were selected, and its width and height were measured with the digital Mitutoyo pachymeter.

Each cement cylinder was submitted to compression at the assay machine, at a deformation speed of 20 mm/min. The machine was shutdown when a cylinder fractured or when the maximum drainage limit was exceeded.

Figure 1 – *Evaluation of the time for mass formation*

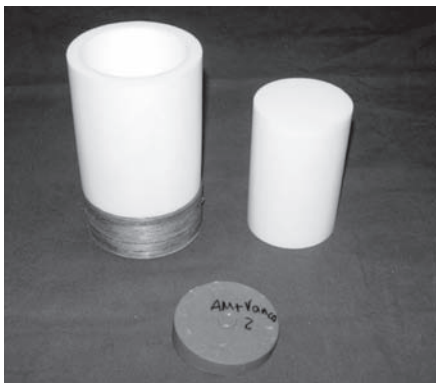

Figure 2 – *Cast, plunger and hardened cement used on the intrusion assay.*

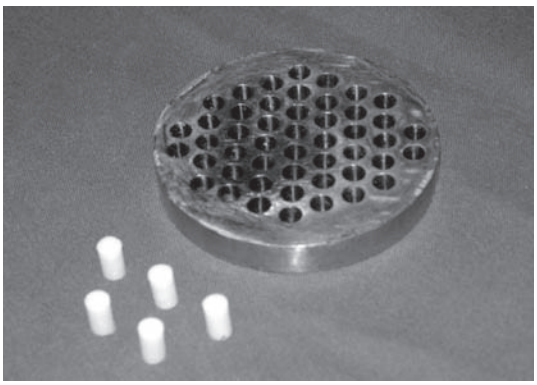

Figure 3 – *Cast and cement cylinders used on the compression assay*

From the graph register "load versus deformation" (Figure 4), we could determine one of the following situations for each cylinder: a) applied force required to fracture it; b) load corresponding to 2% of permanent deformation of the cylinder; c) load of the maximum limit of cylinder drainage.

The graph has also enabled the calculation of tension, defined as the ratio of the force obtained by the original cross-sectional area of the cylinder. The result of such division, named as resistance to compression, was expressed as megapascals (MPa). The described procedure was repeated for all groups.

On the fourth assay, the folding module and the cement's resistance to folding were determined. The following were used: a) an aluminum cast with seven prismatic cavities (Figure 5), 75-mm long, 3.3 mm high and 10 mm wide each; b) a mechanical device for folding or flexion assay at four points (Figure 6); c) a comparator analogical clock; d) a universal mechanical assay machine Kratos 5002 described on the previous procedure, but with a load cell of 100 kgf adjusted for a 20 kgf scale; e) bench vise; f) support boards; g) digital Mitutoyo pachymeter, with 0.01 mm resolution; h) a Sony DCR-HC26 video camera synchronized with a desktop PC.

The components of one cement unit were blended, and, one minute after the time for preparing the mass, the mixture was poured into the cast cavities. The cast was then positioned between both support boards, and the set was compressed in a bench vise for one hour. After that period, the samples were removed with approximately 75 mm in length, 3.3 mm in thickness and 10 mm in width. After 24 ± 2 hours, the seven bodies of evidence were measured with the digital pachymeter, with length, thickness and width parameters being recorded.

Each sample was then submitted to folding assay, at a speed of 5 mm/min. Deflexion was measured at the sample center by the comparator analogical clock and recorded by the video camera Sony DCR-HC26, synchronized with the computer and focused on the clock display. The assay was shutdown at the moment a sample was fractured.

Deflexions occurred when 15 N and 50 N forces were applied were recorded, as well as the force when the body of evidence was broken. Then, the folding module was calculated, E, as megapascal (MPa), by the expression $E = \Delta F \times (L - a)^3 / 4 \times f \times b \times h^3$, where :

f – is the difference between deflexions under 15 N and 50 N loads, as millimeters

b – is the mean width measured on the sample, as millimeters

h – is the mean thickness measured on the sample, as millimeters

l – is the distance between external loading points (60 mm)

ΔF – is the load range (50N-15N=35N)

A – is the distance between internal and external loading points (20 mm)

For each sample of the assay, the resistance to folding was calculated, B, as megapascal (MPa), by the expression $B = (3 \times F \times a) / (4 \times b \times h^2)$, where:

F – is the force measured at fracture, as Newtons

b – is the mean width measured on the sample, as millimeters

h – is the mean thickness measured on the sample, as millimeters

a – is the distance between internal and external loading points (20 mm).

For the 7 samples of the assay, the mean value and the standard deviation for the folding module and resistance to folding were calculated and expressed as MPa. The same procedure was repeated for the other studied groups.

On the fifth and last assay, maximum temperature and the time for inserting the fluid-powder mixture were determined. The insertion time is defined as the time elapsed to reach a mean temperature between room temperature and the maximum temperature reached by mixture reaction.

For this assay, the following have been used: a) cylindrical cast and plunger, both made of polytetrafluorethylene; b) a T-type 1.5 mm wide thermocouple positioned at the center of the cast base, attached at 3 ± 0.5 mm above the inner surface of the cast base; c) a signal conditioner for the thermocouple, Salvi Casagrande brand (Figure 7); d) a computer-based data acquisition system model ADS-2000, Lynx brand, able to transform thermocouple exit signal into a continuous temperature reading, with an accuracy of ±0.5 °C and temporal accuracy of ±0.1 s; e) software for recording temperature as a function of time.

First, room temperature was recorded from the thermocouple on the cast. All components of a cement unit were blended, and the data acquisition software was activated. Immediately by the completion of blending, the cast was filled with approximately 25 g of cement. The plunger was then seated on the cast using a weight of 49 N to assure a constant volume. The exothermal reaction, which occurs when powder and fluid components are blended, was monitored until the maximum temperature was reached.

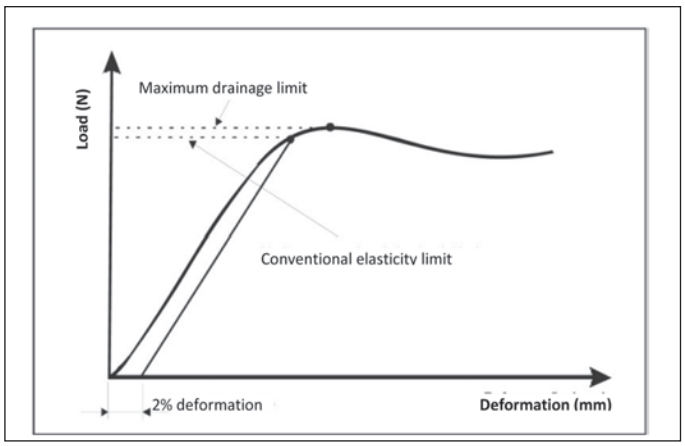

Figure 4 – *Typical curve for load versus deformation in a cement compression assay*

Figure 5 – *Cast and bodies of evidence used on the cement folding assay*

Figure 6 – *Assay device for folding at four points and comparator clock*

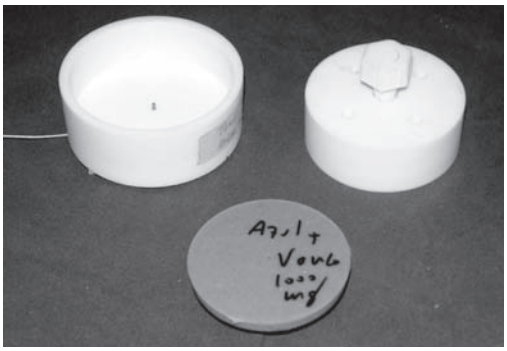

Figure 7 – *Thermocouple inserted on the cast base and cement removed after the assay in order to determine the maximum temperature.*

Temperatures were graphically depicted as a function of time, recording the maximum temperature value *(Tmax)* and the insertion temperature *(Tcol)*, defined as *Tcol = (Tmax + Tamb) / 2* , where:
***Tmax* is the maximum temperature reached by the reaction**
***Tamb* is the recorded room temperature.**
The insertion time was then determined by the graph "temperature versus time", at the curve point referent to insertion temperature (Figure 8). The assay was repeated for a new cement unit and the mean values for maximum temperature and insertion time were calculated. The described procedure was repeated for the other groups, totaling two cement units for each group.
All collected data were gathered and compared to the standards of ABNT NBR ISO 5833 policy, and, subsequently, the groups were classified into "PASSED" or "FAILED". The values found between the different groups have also been statistically compared to each other by the Variance Analysis test with Tukey's discriminating test.

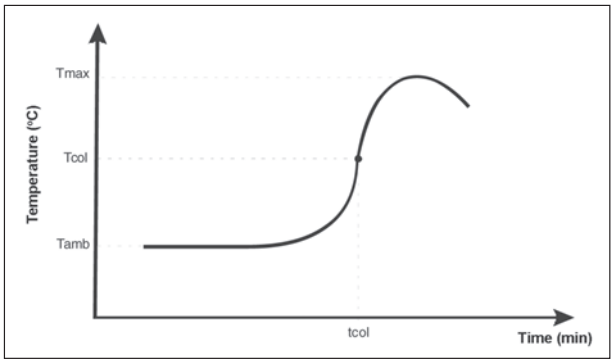

Figure 8 – *Typical curve for determining maximum temperature and insertion time.*

RESULTS

After the statistical analysis, we found the results presented on Tables 1,2,3,4,5,6,7:

Table 1 – *Time for preparing the mixture fluid-powder for the studied samples. Mean, adjusted mean for multiples of 15, maximum mean deviation values and the approval status (passed or failed) are presented here – based on the ABNT NBR ISO 5833 policy.*

	Time for mixture			
	PURE	MB	MB + V	VANCO
Sample one	120	120	120	135
Sample two	150	150	135	150
Mean	135.00	135.00	127.50	142.50
Adjusted mean	135.00	135.00	120.00	135.00
Maximum mean deviation	15	15	7.5	7.5
Approval status	Passed	Passed	Passed	Passed

According to the ABNT NBR ISO 5833 policy, samples with mean values for preparation time below 300s (5 min.) and maximum mean deviation below 90 s (1.5 min.) are regarded as passed.

Table 2 – *Maximum temperature reached by assessed samples. Mean, standard deviation, maximum mean deviation values and the approval status (passed or failed) are presented here – based on the ABNT NBR ISO 5833 policy.*

	Maximum temperature [ºC]				
Group	Sample one	Sample two	Mean	Maximum mean deviation	Approval status
PURE	47	44	45.50	1.5	Passed
MB	45	50	47.50	2.5	Passed
MB + V	48	50	49.00	1.0	Passed
VANCO	47	51	49.00	2.0	Passed

According to the ABNT NBR ISO 5833 policy, samples with mean values for temperature below 90ºC and maximum mean deviation below 5°C are regarded as passed.

Table 3 – *Time for inserting the studied samples. Mean, adjusted mean for multiples of 15 values and the approval status (passed or failed) are presented here – based on the ABNT NBR ISO 5833 policy.*

	Insertion time					
Group	Sample(s) one	Sample(s) two	Mean	Adjusted mean		Approval status
				[s]	[min]	
PURE	530	625	577.50	585	9.75	Passed
MB	410	545	477.50	480	8.00	Passed
MB + V	385	445	415.00	420	7.00	Passed
VANCO	625	650	637.50	630	10.50	Passed

According to the ABNT NBR ISO 5833 policy, samples with mean values for insertion time between 3 and 15 minutes are regarded as passed.

Table 4 – *Intrusion depth of samples, measured for the four holes of the cast. Mean, adjusted mean for multiples of 0.5 mm, standard deviation values and approval status (passed or failed) are presented here – based on the ABNT NBR ISO 5833 policy. Statistical comparison between groups by the Variance Analysis test and by Tukey's discriminating test.*

	Intrusion depth measurement [mm]			
	PURE	MB	MB + V	VANCO
Hole one	10.1	6.7	3.2	3.8
Hole two	10.4	5.4	2.7	6.6
Hole three	7.5	4.7	1.9	8.8
Hole four	9.8	5.6	2.7	9.8
Mean	9.5	5.6	2.6	7.3
Adjusted mean	9.5	5.5	2.5	7.5
Standard deviation	1.3	0.8	0.5	2.7
Approval status	Passed	Passed	Passed	Passed

ANOVA p= 0.0004*

Tukey				
	P x AM	p < 0.05*	AM x AM+V	p > 0.05
	P x AM+V	p < 0.001*	AM x VANCO	p > 0.05
	P x VANCO	p > 0.05	AM+V x VANCO	p < 0.01*

According to the ABNT NBR ISO 5833 policy, samples with mean values for intrusion above 2 mm are regarded as passed.

Table 5 – *Samples' resistance to compression. Mean (M), standard deviation (SD), mean standard error (MSE), minimum resistance (Min), maximum resistance (Max) and sample size (N) values are presented here. Comparison between mean values and those established by the ABNT NBR ISO 5833 policy. Statistical comparison between groups by the Variance Analysis test with Tukey's discriminating test.*

	Resistance to compression [Mpa]			
	PURE	MB	MB + V	VANCO
M	96.24	94.20	94.85	90.26
SD	3.92	2.79	2.43	2.58
MSE	0.92	0.66	0.57	0.61
Min	87.01	87.62	90.90	86.83
Max	102.19	99.44	98.66	95.95
N	18	18	18	18
Approval status: Policy (≥ 70 MPa)	Passed	Passed	Passed	Passed

ANOVA p= 0.0001*

Tukey				
	P x AM	p > 0.05	AM x AM+V	p > 0.05
	P x AM+V	p > 0.05	AM x VANCO	p < 0.01*
	P x VANCO	p < 0.001*	AM+V x VANCO	p < 0.001*

According to the ABNT NBR ISO 5833 policy, samples with mean values for resistance equal or higher than 70 MPa are regarded as passed.

Table 6 – *Folding module (E) according to the samples assessed. Mean (M), standard deviation (SD), mean standard error (MSE), minimum module (Min), maximum module (Max) and sample size (N) values are presented here. Comparison between mean values and those established by the ABNT NBR ISO 5833 policy. Statistical comparison between groups by the Variance Analysis test with Tukey's discriminating test.*

	Folding module [MPa]			
	PURE	MB	MB + V	VANCO
M	2451.03	1887.33	2062.19	2236.73
SD	83.28	70.82	63.13	43.09
MSE	34.00	26.77	23.86	16.29
Min	2392.17	1809.93	1969.99	2158.85
Max	2616.32	2018.66	2127.51	2292.13
N	6	7	7	7
Approval status E ≥ 1800 Mpa	Passed	Passed	Passed	Passed

ANOVA p= 0,0001*

Tukey	P x AM	p < 0.001*	AM x AM+V	p < 0.001*
	P x AM+V	p < 0.001*	AM x VANCO	p < 0.001*
	P x VANCO	p < 0.001*	AM+V x VANCO	p < 0.001*

According to the ABNT NBR ISO 5833 policy, samples with mean values for folding module equal or above 1800 MPa are regarded as passed.

Table 7 – *Assessed samples' resistance to folding (B). Mean (M), standard deviation (SD), mean standard error (MSE), minimum resistance (Min), maximum resistance (Max) and sample size (N) values are presented here. Comparison between mean values and those established by the ABNT NBR ISO 5833 policy. Statistical comparison between groups by the Variance Analysis test with Tukey's discriminating test.*

	Resistance to folding [MPa]			
	PURE	MB	MB + V	VANCO
M	59,79	49,50	49,11	47,24
SD	4,20	1,94	6,15	1,84
MSE	1,72	0,73	2,33	0,69
Min	53,83	45,60	40,35	45,18
Max	64,18	51,23	55,71	49,81
N	6	7	7	7
Approval status B ≥ 50 Mpa	Passed	Failed	Failed	Failed

ANOVA p= 0.0001*

Tukey	P x AM	p < 0.001*	AM x AM+V	p > 0.05
	P x AM+V	p < 0.001*	AM x VANCO	p > 0.05
	P x VANCO	p < 0.001*	AM+V x VANCO	p > 0.05

According to the ABNT NBR ISO 5833 policy, samples with mean values for resistance equal or higher than 50 MPa are regarded as passed.

DISCUSSION

After the analysis of results, we found that all pure cement samples passed the tests established by ABNT NBR ISO 5833 policy for "insertion time", "maximum temperature", "intrusion depth", "resistance to compression", and "folding module".

Despite of being approved by the ABNT NBR ISO 5833 policy, when added to antibiotics, stain or both, cement samples showed a reduced intrusion depth by up to 73% ($p < 0.001$) compared to those containing only cement. This fact suggests that the increased number of particles in the mixture substantially impairs its intrusion into the bone, which is an essential factor for a good cement-bone fixation. For presenting a mean intrusion value much superior to the minimum required amount, the studied cement ultimately offsets that reduced intrusion ability of the samples added by antibiotics and/or methylene blue.

A slight reduction of the resistance to compression has also been proven for the combined samples when compared to those containing cement in its pure state. That reduction was as high as 6.21% for the mixture containing vancomycin, 4.18% for the one containing methylene blue, and 4.84% for the mixture with methylene blue and vancomycin ($p<0.001$). However, such reduced resistance was not enough to determine failure of the mixtures in this parameter.

On the assay addressing resistance to folding, only the samples containing pure cement passed the tests established by the ABNT NBR ISO 5833 policy, with the others being regarded as failed. Data presented here show that the reduced resistance to flexion was as high as 17.2% for the sample containing methylene blue, 17.86% for the sample containing methylene blue and vancomycin, and 20.99% for the sample containing vancomycin.

This assay, at first, can contraindicate a combination of the studied substances (vancomycin and methylene blue) with the surgical cement, as the samples did not reach the minimum value for resistance to folding – the ability to withstand maximum compression and traction forces acting on the surface of the bodies of evidence – as recommended by the policy.

Nevertheless, the cement used in this assay was found to present, alone, resistance to folding close to the minimum recommended limit (50 MPa), while the other mixtures, although failed, presented mean resistance to flexion values that are very close to the acceptable limit, namely: a) 49.5 MPa for the sample containing methylene blue; b) 49.11 MPa for the sample containing methylene blue and vancomycin; c) 47.24 MPa for the sample containing vancomycin. These data suggest that the use of cement with stronger resistance to folding may allow the approval of all samples. However, the statistically significant negative effect of the mixture combining vancomycin and/or methylene blue with orthopaedic cement in unquestionable, making this practice unsafe.

Another factor to be considered is that the pure cement samples and those added by antibiotics and/or methylene blue were manually prepared. Maybe a vacuum blending, for reducing the number of micro particles, may provide stronger resistance[9] to samples to be regarded as passed.

Therefore, the cement employed in this study, which was manually prepared, shows a lower tensile strength when added by stain, antibiotics or both, making the mixture improper for use – as established by the ABNT NBR ISO 5833 policy.

Should the use of acrylic cement with antibiotics or stain is necessary, it is recommended that the mixture is available through the manufacturer, delivering a product that has been properly tested by regulatory agencies. Thus, a surgeon mixing these substances at the moment of surgery is not recommended.

CONCLUSION

The addition of methylene blue 1 ml, vancomycin 1 g, or both to Surgical Simplex P orthopaedic cement (Stryker Howmédica®), associated to a manual preparation of the mixture, reduces cement's resistance to flexion to be regarded as failed by the current ABNT NBR ISO 5833 policy.

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