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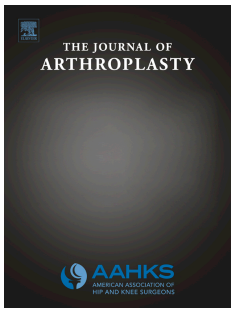

"Mechanical Integrity Assessment of Polymethylmethacrylate Bone Cement Incorporating Local Anesthetics: Implications for Joint Arthroplasty"

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TITLE: "Mechanical Integrity Assessment of Polymethylmethacrylate Bone Cement Incorporating Local Anesthetics: Implications for Joint Arthroplasty"

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TITLE:

Mechanical Integrity Assessment of Polymethylmethacrylate Bone Cement Incorporating Local Anesthetics: Implications for Joint Arthroplasty

ABSTRACT:

Background

Effective management of postsurgical pain following arthroplasty remains a challenge, lacking a definitive gold standard. As most knee and hip arthroplasties are cemented or hybrid, we used the property of bone cement as a drug carrier and added powdered local anesthetics (lidocaine hydrochloride and bupivacaine hydrochloride) to the polymethylmethacrylate (PMMA) as analgesics. However, the addition of drugs to bone cement may compromise its mechanical properties, necessitating a thorough analysis. Our objective was to assess the impact of added local anesthetics on the mechanical properties of PMMA bone cement.

Methods

Mechanical properties, including compressive strength, bending modulus, and bending strength, were evaluated following the procedure set by the International Organization for Standardization (ISO) 5833-2002 and the American Society for Testing and Materials (ASTM) F451-1 standards. There were three study groups compared: PMMA, PMMA with lidocaine hydrochloride, and PMMA with bupivacaine hydrochloride.

Results

Significant differences were observed between groups in compressive and bending strength, but not in bending modulus. Despite these differences, the mean compressive strength and bending modulus of all groups and the mean bending strength of the lidocaine group surpassed the minimum values set by the ISO 5833-2002 and ASTM F 451-08 standards for acrylic bone cement. However, the bupivacaine group fell short of the minimum bending strength value.

Conclusion

The addition of powdered local anesthetics to PMMA affects its mechanical properties, specifically compressive and bending strength, without compromising the bending modulus. While differences were noted, all groups surpassed the minimum standards for compressive strength and bending modulus. However, the bupivacaine group did not meet the minimum

bending strength requirement. This highlights the importance of considering mechanical properties when incorporating drugs into bone cement for implant fixation.

KEYWORDS: Knee arthroplasty, bone cement, local anesthetics, analgesia, mechanical properties, polymethylmethacrylate (PMMA)

INTRODUCTION

Arthroplasty is one of the most commonly used surgical procedures to treat knee and hip chronic refractory pain (1).

Post-surgical pain following arthroplasty is generally moderate to severe in almost a third of total hip arthroplasties and half of total knee arthroplasties (2) and can be challenging to manage, especially during the first three days following surgery (3). The main aim of postoperative care is pain alleviation to enhance functionality and prevent the transition from acute to chronic pain (4).

Currently, there is no gold standard for pain management following arthroplasty, prompting the exploration of various approaches. Present techniques include the administration of analgesics delivered in different ways that may cause adverse reactions and complications (3). An optimal delivery system of analgesics should provide non-toxic therapeutic doses at the surgical site, especially during the first 72 hours postoperatively (5). Polymethylmethacrylate bone cement (PMMA) is used to fix implants to the bone (6). Different health systems have reported cementation rates between 61.8% (7) and 83.7 to 91.5% (8,9) in knee arthroplasties and between 38.1 (7) and 72.7% (8,9) in hip arthroplasties, including hybrid and cement arthroplasties in the latter group. Bone cement is supplied as a two-component systems made up of a liquid component (monomer) and a powder component (polymer) (10). The main function of bone cement is the fixation of the implant to the bone by filling the space between the prosthesis and bone and transferring the load of the implant to the bone as evenly as possible (11). The long-term stability of the implant is dependent on the load distribution function (12).

A further function of the cement is its capacity to act as a drug carrier (12,13). Industrially manufactured cement containing low doses of antibiotics that range between 1.25 and 2.5% of the total weight of the cement (10) is available. Its use aims to reduce the incidence of perioperative infections by avoiding the toxicity associated with the use of systematic antibiotics (13–15).

Other drugs, such as local anesthetics (LA), have been experimentally added to bone cement to study the elution profile of these drugs and how their addition can affect the workability properties of the cement (5,16).

However, adding drugs to bone cement may reduce its mechanical performance due to the interference of the drug particles with the setting process (10,17), compromising its main

function of implant fixation and load distribution. If the mechanical stress imposed is greater than the load-carrying capacity of the cement, the latter may fracture and lead to implant failure (18).

When adding drugs to cement, several factors should be considered, such as the type and amount of drug added (18–20). Drugs cannot be added to PMMA cements as aqueous solutions (17) as these interfere with the process of polymerization, thus reducing compressive strength (CS) (21). Although the proportion of added drugs has not been conclusively established (12), several authors agree that it should not exceed 10% of the total weight of the cement (10).

Other factors that may alter the mechanical properties of bone cement are related to the technique of incorporation and mixing of the drugs as well as to the preparation, storing, and chemical composition of the bone cement (12,19).

For joint arthroplasty, the mechanism of loading *in vivo* is especially complex because of interaction on different interfaces with different materials and properties. The total load affecting the cement layer is a mixture of compressive loading combined with bending, impact, tension, torsion, and shear (10). The minimum requirements are defined by the International Organization for Standardization (ISO) 5833-2002 (22) and the American Society for Testing and Materials (ASTM) F 451 – 08 (23) standards, which serve as benchmarks for evaluating the clinical relevance of changes in mechanical properties. Compliance with these thresholds is critical for ensuring the functionality and safety of bone cement in clinical applications.

This study aims to analyze the mechanical properties of PMMA bone cement when local anesthetics (lidocaine hydrochloride and bupivacaine hydrochloride) are manually added. The investigation includes compressive and bending tests, reported in the ISO 5833-2002 (22) and ASTM F 451 – 08 (23) standards.

MATERIALS AND METHODS

This is an experimental *in vitro* study. Institutional review board approval was not required.

The PMMA bone cement used in this study was PALACOS® R+G (Heraeus Medical GMBH, Germany), a fast-setting, high-viscosity PMMA composite bone cement containing gentamicin.

The LAs used in the study were powdered lidocaine hydrochloride and bupivacaine hydrochloride (Fagron®, Spain).

There were three study groups compared: PMMA (control), PMMA with lidocaine hydrochloride (lidocaine) and PMMA with bupivacaine hydrochloride (bupivacaine). For the preparation of the PMMA specimens, the powdered LAs were mixed with the powdered component of the cement using the geometric dilution method. The LAs doses used in the study were 3.5 grams of lidocaine hydrochloride for a commercial presentation of 40.8 grams of PMMA, and 3.5 grams of bupivacaine hydrochloride for a commercial presentation of 40.8 grams of PMMA.

Subsequently, the liquid component of the PMMA cement was added to this mixture and manually mixed.

The effect of adding local anesthetics on the mechanical properties of bone cement was assessed through compression and bending analysis. Following the ISO 5833:2002 and ASTM F 451-08 standards, specimens were tested 24 +/- two hours from starting the mixing process. For the compression studies, cylindrical specimens with a diameter of six mm (+/- 0.1) and a height of 12 mm (+/- 0.1) were molded. While bending studies utilized rectangular specimens with dimensions of 75 mm in length (+/- 0.1), 10 mm in width (+/- 0.1), and 3.3 mm in height (+/- 0.1).

Compression studies were performed using the Shimadzu AGS-X universal testing machines equipped with compression plates PC.r/156-Af30-St Techlab Systems (Figure 1) featuring a 10 KN force-load cell and a constant speed of 25 mm/minute. The cylinders were placed into the machine without any padding between the cylinder and the testing machine plate. The machine was operated to produce a load-displacement curve, halting either upon cylinder fracture or when the upper limit was surpassed. For each cylinder, the ultimate load was determined as the load at 2% offset strain or as the upper yield point, whichever occurred first. This force was then divided by the original cross-sectional area of the cylinder in mm^2 and was defined as compression strength (CS) in MPa. The results obtained are expressed as the mean CS of the specimen in each group in MPa, standard deviation (SD), and minimum and maximum values.

[INSERT FIGURE 1 HERE]

For the bending tests, the specimens were placed in a Shimadzu AGS-X universal testing machine (Figure 2) equipped with a bending test fixtureTH238-4P-200-CR1.5-AF159, a 10KN load cell, and a constant speed of dive of mm/minute. The force on the main load-bearing points was gradually increased from zero at a constant speed, registering the displacement according to the force applied until the specimen ruptured, rounding the result to the nearest 0.05 mm. For the determination of the Young's Modulus of each specimen (also called bending modulus), the displacement was registered when applying 15 and 50 N, rounding the result to the nearest 0.5 N. Bending strength (BS) in MPa and Bending Modulus in MPa were calculated for each

specimen accordingly to the expressions indicated in the ISO standard. Results are expressed as the mean BS and Young's Modulus of bending for the specimens in each group in MPa, along with standard deviation (SD) and minimum and maximum values.

[INSERT FIGURE 2 HERE]

Data analyses

The results obtained are expressed as mean, standard deviation (SD), minimum, and maximum values. The groups with added local anesthetics were compared to the control group in compression strength, bending strength, and bending modulus using the independent-samples Mann-Whitney U test, performed with Statistical Package for Social Sciences (SPSS) 27.0 for Mac (IBM SPSS, Chicago, Illinois, USA). A *P*-value less than 0.05 was considered statistically significant.

The mean curves of the three study groups are graphically displayed for compression strength and bending strength. These curves were obtained by calculating the mean of the curves of the five specimens registered for the study group.

RESULTS

Table 1 shows the mean, SD, and minimum and maximum resistance to compression strength (MPa) of the study groups.

[INSERT TABLE 1 HERE]

The results show significant differences between groups, both between the control and lidocaine groups ($P = 0.01$) and between the control and bupivacaine groups ($P = 0.01$).

Compared with the control group, a decrease of 14.4% in compression strength (CS) was observed in the lidocaine group and 9.2% in the bupivacaine group.

In Figure 3, the stress-strain curve represents the behavior of single, representative specimens from each group, illustrating their maximum stress at fracture. The figure also shows the minimum of 70 MPa established by the ISO 5833-2002 guidelines (22) regarding CS (red line).

[INSERT FIGURE 3 HERE]

Table 2 shows the mean, SD, and minimum and maximum bending strength (BS) for the study groups for the bending strength results.

[INSERT TABLE 2 HERE]

The results show significant differences, both between the control and lidocaine groups (P = 0.03) and between the control and the bupivacaine groups (P = 0.01).

Compared with the control group, a decrease of 10.7% in BS was observed in the lidocaine group and 18.9% in the bupivacaine group.

In Figure 4, the stress-strain curve represents the behavior in bending of single, representative specimens from each group, illustrating their maximum stress at fracture. The figure also shows the minimum of 50 MPa established by the ISO 5833-2002 guidelines (22) regarding BS (red line).

[INSERT FIGURE 4 HERE]

Regarding BS, the mean for the bupivacaine group (49.2 ± 2.6 MPa) falls below the ISO 5833 threshold of 50 MPa, despite individual specimens, such as the one shown in Figure 4, achieving higher maximum stresses. This difference reflects the influence of variability across the group and highlights the importance of evaluating both individual and group-level data when interpreting mechanical performance.

Table 3 shows the mean, SD, and minimum and maximum bending modulus (BM) of the different study groups for the Young's Modulus obtained from the bending strength tests.

[INSERT TABLE 3 HERE]

No significant differences were noted between groups, neither between the control and the lidocaine groups (P = 0.55) nor between the control and the bupivacaine groups (P = 0.42).

DISCUSSION

Currently, there is no gold standard for managing postoperative pain following arthroplasty. All available procedures are associated with certain limitations and/or adverse effects. Our hypothesis is that the elution of local anesthetic (LA) from the cement could provide an analgesic effect that would minimize the use of systemic analgesics, including opioids, facilitating early initiation of physical therapy. This would likely result in greater patient satisfaction and, potentially, earlier hospital discharge, ultimately reducing healthcare costs associated with prolonged hospital stays. We believe that this novel analgesic method aligns with the outpatient

surgery programs and fast-track protocols commonly employed in the postoperative management of hip and knee arthroplasty.

The addition of drugs to bone cement may affect its mechanical properties, jeopardizing its functionality and the obtained results (10,12,20). The use of antibiotic-loaded bone cement (ALBC) is widely widespread. Numerous studies have examined how the technique of addition, type, and quantity of drug can affect its performance (12,19,24–26).

The incorporation of drugs reduces the mechanical stability of bone cement because their molecules interfere with the curing process of the cement and may form clusters that become embedded within the PMMA matrix. During drug elution, these clusters dissolve, leaving voids in the cement (27). Consequently, the increased porosity can impair the mechanical stability of the bone cement, as any form of void can serve as a starting point for cement breakage (28). The more drug is added, the more the stability of the cement will be reduced (12). Although the maximum proportion of the drug is not well established, a dose of 5 to 10% of the drug with respect to the total weight of the powder component of the cement is considered adequate for the construction of temporary cement spacers (19,24–26). This evaluation aligns with the ISO standard requirements for the permanent fixation of implants, establishing minimum values of 70 MPa in compression strength (CS), 50 MPa in bending strength (BS), and 1,500 MPa in bending modulus (BM). In the present study, the dose of local anesthetics (lidocaine hydrochloride and bupivacaine hydrochloride) added was 8.6% of the total weight of the cement powder. We chose PMMA for being the most commonly used cement powder. Our choice of anesthetics was guided by their thermal stability, duration of effects, and use in loco-regional nerve blocks in orthopaedic surgery.

We opted to add the LA to the powder component of the bone cement, as it has been reported that in high-dose ALBC (greater than 10% volume), the addition of drugs in the dough phase of the cement reduces CS below 70 MPa compared to its addition to the powder component (29). In contrast, with low-dose ALBC (up to 3% volume), the mixing technique does not affect CS or BS (30,31).

Our study focused on analyzing the influence of adding LA (lidocaine hydrochloride and bupivacaine hydrochloride) on the mechanical properties of PMMA bone cement included in the ISO standard. We decided to reproduce the ISO standard because during prosthetic implantation, high localized stresses arise from factors like applied surgical force, cement shrinkage, uneven load distribution, and stress concentrations at interfaces. These stresses, compounded by the cement's viscosity and thickness variations, make static mechanical

properties like compressive and bending strength essential for immediate fixation and early stability. Furthermore, the ISO 5833 standard emphasizes static mechanical properties as critical benchmarks for bone cement performance, reinforcing their importance in clinical applications. While fatigue crack propagation is crucial for long-term performance, static properties take precedence in ensuring functionality and patient safety during implantation and the early postoperative phase. They provide the critical baseline that complements fatigue resistance.

The results showed significant differences between groups in CS and BS, but not the BM. Despite these differences, all study groups had CS values over 70M Pa and BM over 1,500 MPa, meeting the minimum values outlined by the ISO 5833 guidelines. However, in BS, the bupivacaine group fell short of the 50 MPa requirement. While statistically significant differences in bending and compressive strengths were observed between groups, these do not always translate into clinical relevance. In our study, the lidocaine group showed a statistically significant reduction in bending strength compared to the control group (P = 0.03), but its mean value (54.2 MPa) remained above the ISO 5833 minimum threshold, indicating limited mechanical importance. Conversely, the bupivacaine group not only showed a statistically significant reduction (P = 0.01) but also failed to meet the ISO minimum threshold of 50 MPa, which has clear clinical implications for implant stability *in vivo*.

These results are conducted under *in vitro* conditions, and the clinical relevance of these differences in mechanical properties would need to be determined in an *in vivo* environment.

Literature on the impact of these substances on the mechanical properties of bone cement is limited. Giordano et al. (32) reported that the addition of LA to bone cement improves its impact resistance. They attributed their results to the alteration of the powder/liquid cement ratio and its influence on cement polymerization.

In contrast, numerous studies have investigated the effect of the addition of antibiotics on the mechanical properties of bone cement (24,33–37), but comparability is hindered by variations in approaches, adherence to ISO 5833 guidelines, and differences in antibiotic type, proportion, and brand, as well as study conditions (12). Our study aimed to address these limitations by conducting all the mechanical tests outlined in the ISO 5833 guidelines under controlled study conditions and specifying the type of cement used as well as the brand and proportion of antibiotic added. To our knowledge, this is the first study assessing all the mechanical requirements listed in the ISO 5833 guidelines regarding LA-loaded bone cements.

Regarding the influence of drug addition on the mechanical properties of PMMA bone cement, other authors (35,38) conclude that adding up to 2 grams of antibiotic powder to 40 grams of

PMMA does not affect the BM of the cement. In our study, no differences were found in BM with the addition of 3.5 grams of lidocaine or 3.5 grams of bupivacaine. Regarding BS, Kuhn et al. (10) conclude that the addition of 2 grams of antibiotic powder to 40 grams of PMMA reduces the ISO BS by approximately 20% and that the addition of 5 grams of antibiotic reduces it by 38%. In our study, the addition of 3.5 grams of lidocaine and 3.5 grams of bupivacaine reduced BS by 10.7 and 18.9%, respectively. Also, regarding CS, other authors (24,34,35,38,39) conclude that CS is reduced by 10% with the addition of 2 grams of powder antibiotic to 40 grams of PMMA. In the present study, the addition of 3.5 grams of lidocaine and 3.5 grams of bupivacaine reduced CS by 14.4 and 9.2%, respectively.

In conclusion, changes in mechanical properties induced by drug addition depend on several factors, such as the brand and type of cement, the type and proportion of antibiotic, and the loading method. Thus, when considering the manual loading of any drug into bone cement for permanent implant fixation, its *in vitro* mechanical properties should be studied in order to ensure that they meet the minimum standards set by the regulations governing the use of such cement. One of the main functions of bone cement is the load transference of the implant to the bone. Reduced flexural and compressive strength may result in the fracture of the cement mantle, leading to an aseptic loosening of the implant. Thus, it is critical that the cement is able to withstand a wide array of biomechanical forces.

While our study contributes valuable insights, it is essential to acknowledge its limitations. The number of samples used for each test and study group is limited, adhering to ISO 5833 guidelines. Furthermore, although the specimens included in each group met all the conditions contemplated by the guidelines, we did not analyze the porosity of the specimens. Therefore, we cannot guarantee that the porosity of all specimens is the same. This information would be particularly relevant because AL addition and cement mixing method may affect the porosity of the material and thus modify the mechanical properties of the cement, including fracture toughness (40,41). Fatigue-crack initiation in bone cement is related to the size of the pores. Analyzing fracture toughness is particularly relevant, as it may be reduced in LA-loaded bone cement, following what some authors have reported for antibiotic-loaded bone cement (38,42–44). The role of PMMA bone cement porosity on its fracture toughness remains a subject of debate. While some researchers consider pores as defects (44–46), others argue they are crucial for drug elution, bone ingrowth, and even for mitigating crack propagation (47,48).

As the aim of our study was to reproduce the mechanical tests outlined in the ISO 5833 guideline under the conditions detailed therein, the mechanical properties of samples subjected to cyclic

stress, especially fatigue strength, were not analyzed. During normal daily activities, the cement is subjected to cyclical mechanical stress when used in load-bearing applications that can lead to the formation of microcracks and pores. Previous studies of the fatigue properties of PMMA-containing antibiotics are contradictory depending on the antibiotic type, antibiotic dose, PMMA cement brand, and mixing technique (49–54). Additionally, neither porosity nor static strength was a consistent predictor of bone cement fatigue life.

It would be of interest to analyze the mechanical properties of aged samples. Other authors have reported differences in the behavior of bone cement before and after aging (55,56).

Furthermore, maximum doses of LA were used in our study, and the possibility of using lower doses of bupivacaine in order to reach the minimum values established by the regulations regarding BS should be considered.

To bring everything together, compliance with the minimum values established by ISO standards validates that the material possesses the mechanical properties required for clinical applications under standard conditions, providing a robust framework for safety. Our results highlight the importance of not only achieving statistical significance but also ensuring compliance with ISO thresholds to address the clinical relevance of mechanical properties when incorporating drugs into bone cement for implant fixation. However, these standards represent minimum criteria that may not fully capture the complexities of the *in vivo* environment, such as fatigue under cyclic loads, porosity induced by drug elution, or the effects of material aging. Therefore, while our results ensure the functionality of bone cement within international standards, its performance in specific applications may require further studies to evaluate long-term behavior under more demanding clinical conditions.

CONCLUSIONS

The incorporation of powdered local anesthetics into PMMA bone cement affects its mechanical properties, specifically compressive and bending strengths, but does not compromise the bending modulus. Despite the differences observed, all the groups exceeded the minimum values set by the ISO guidelines in compressive strength and bending modulus. However, in bending strength, the bupivacaine group falls short of meeting the established minimum value.

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516 Figure 1. Compression tests. Shimadzu AGS-X universal testing machine with compression
517 plates PC.r/156-Af30-St Techlab Systems

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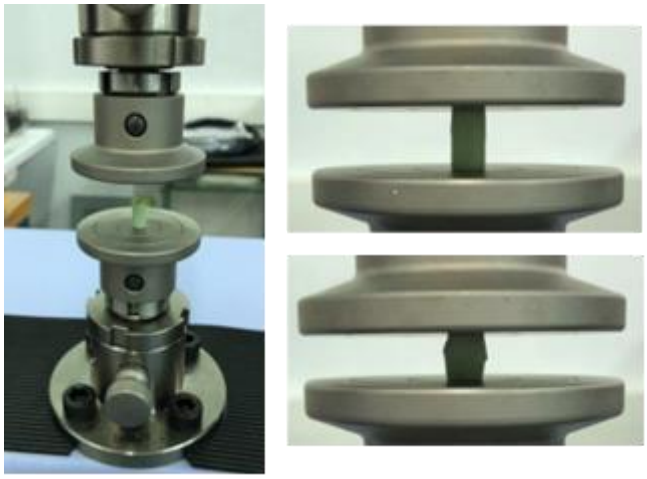

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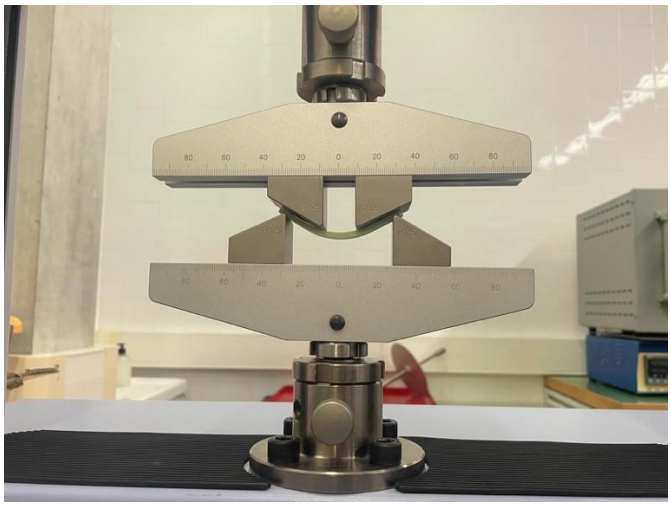
521 Figure 2. Bending tests. Shimadzu AGS-X universal testing machine with the bending test
522 fixture TH238-4P-200-CR1.5-AF159



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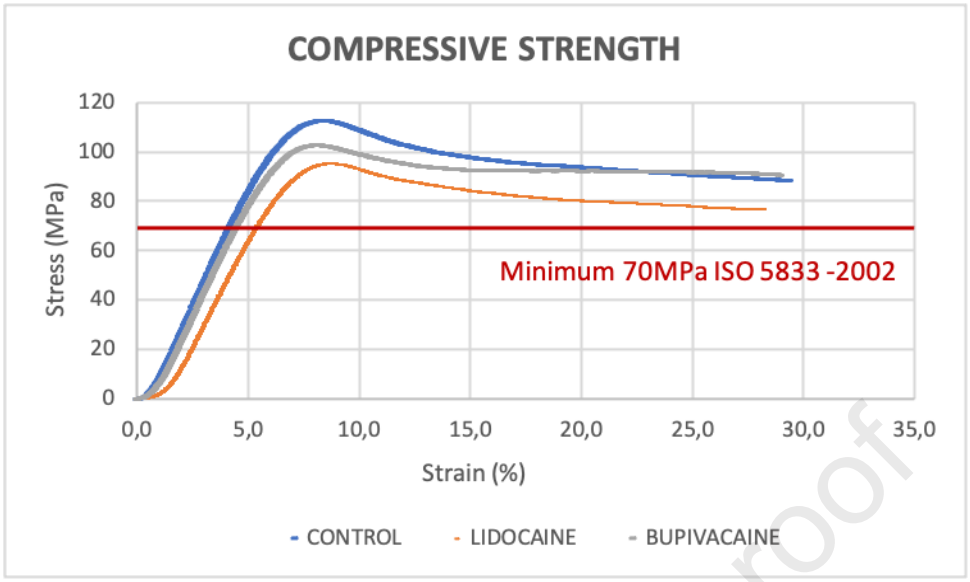
526 Figure 3. Compressive strength curves



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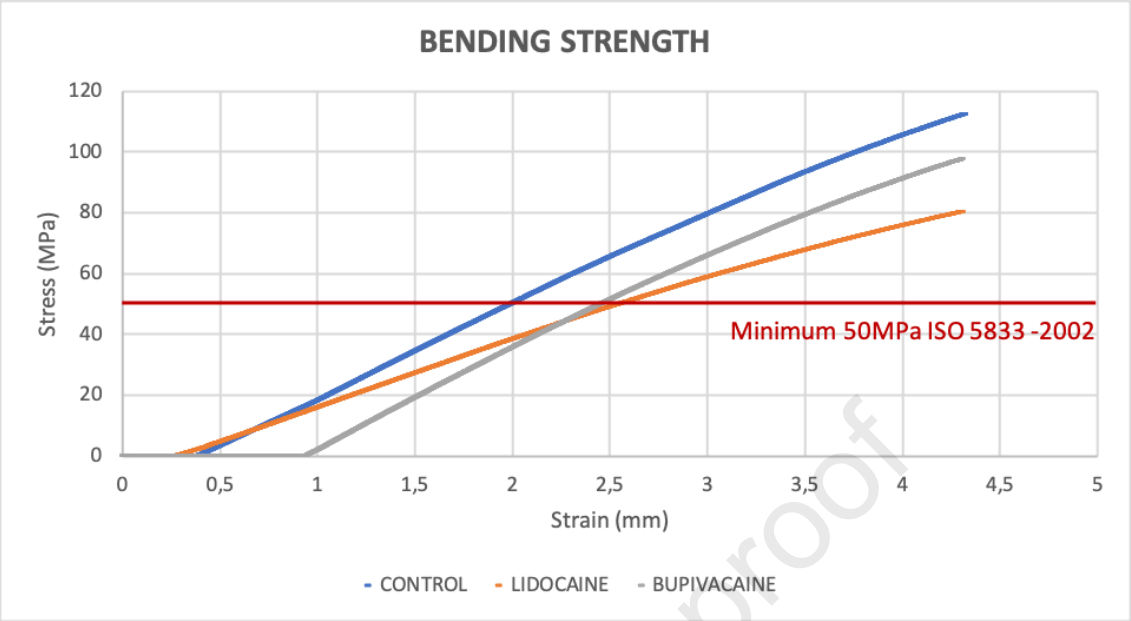
528 International Organization for Standardization (ISO)

529 Figure 4. Bending strength curves



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531 International Organization for Standardization (ISO)

532 Table 1. Compressive strength test results (MPa)

Study group	N	Mean	SD	Minimum	Maximum	*P*-value
Control	5	112.8	2.7	109.1	115.5	
Lidocaine	5	96.6	6.9	87.1	104.6	0.01
Bupivacaine	5	102.4	3.1	99.1	105.9	0.01

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536 Table 2. Bending strength (MPa)

Study group	N	Mean	SD	Minimum	Maximum	*P*-value
Control	5	60.7	4.5	56.8	68.2	
Lidocaine	5	54.2	3.6	49.0	59.0	0.03
Bupivacaine	5	49.2	2.6	45.7	52.6	0.01

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Table 3. Bending modulus (MPa)

Study group	N	Mean	SD	Minimum	Maximum	*P*-value
Control	5	3,069.2	146.3	2,943.6	3,275.5	
Lidocaine	5	3,100.0	120.2	2,988.8	3,250.1	0.55
Bupivacaine	5	3,181.7	313.2	2,742.3	3,567.3	0.42

TITLE: "Mechanical Integrity Assessment of Polymethylmethacrylate Bone Cement Incorporating Local Anesthetics: Implications for Joint Arthroplasty"

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