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ORIGINAL ARTICLE

Modification of PMMA vertebroplasty cement for reduced stiffness by addition of normal saline: a material properties evaluation

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Abstract
Purpose Vertebral augmentation is an established treatment for patients with pathological vertebral compression fractures. These procedures typically employ a PMMA-based bone cement, which possesses a high compressive stiffness. Because of the increased risk of subsequent fractures after vertebral augmentations, there is a desire for reducing this stiffness. The goal of our study was to examine the influence of adding isotonic saline on the biomechanical properties of PMMA vertebroplasty cement.
Methods A PMMA-based vertebroplasty cement was prepared according to the manufacturer's recommendations after which isotonic saline was mixed into the cement at 10, 20, and 30% (volume:volume). Testing bodies were cast, and compression and bending tests were performed. Fracture surfaces were studied using SEM. Measurements of injectability, setting temperature, and radioopacity were also performed.
Results The addition of saline solution (of up to vol-30%) led to a pronounced reduction in the compression modulus of the cement from 3409 ± 312 to 1131 ± 127 MPa. In parallel, maximal compression strength was reduced from 86 ± 4 to 33 ± 3 MPa and bending strength from 40 ± 4 to 24 ± 3 MPa. The differences regarding injectability, setting temperature, and radioopacity were small and probably of no clinical relevance.
Conclusions The compressive stiffness of PMMA-based vertebroplasty cement can be reduced to almost a third by the addition of saline. The probable explanation is an increase in microporosity. Future simulator experiments will show whether the achieved reduction in stiffness is large enough to reduce the rate of subsequent vertebral fractures.

Keywords Material properties · PMMA · Poly-methyl-methacrylate · Saline solution · Stiffness reduction

Introduction

There is ongoing discussion about whether subsequent and adjacent vertebral fractures after vertebroplasty and kyphoplasty are due to the comparatively high compressive stiffness of the poly-methyl-methacrylate (PMMA) bone cement that is typically employed for these procedures. Recent publications clearly point to such a causal relationship, especially with high-grade osteoporosis [1–4]. Even though the anterior shift of the trunk superior to an osteoporotic vertebral fracture has been implicated as another factor [5], the stiffening of the treated vertebrae appears to play an important role. While there is evidence that the number of vertebrae fractured initially as well as the augmentation volume also are of relevance [4, 6], the characteristic biomechanical properties of the bone filler have great influence. There have been previous attempts to modify PMMA-based bone fillers to make them better suited for use in osteoporotic cancellous bone. Alternative cements have been tried that are not based on PMMA. These are primarily calcium phosphate-based bioresorbable cements, whose limited biomechanical properties have so far precluded a wider clinical use [7]. A recently introduced silicone-based bone filler exhibits greatly reduced

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compressive stiffness, but in initial clinical series had a comparatively high rate of pulmonary embolisms [8, 9]. Another alternative material based on bioglass appears to have a slightly reduced rate of subsequent fractures in initial trials [10–12]. The supportive data is still limited at present and there lies some contradiction in the fact that the material per se is actually stiffer than PMMA. It is claimed that the hydrophilicity of this compound and the resulting more finely structured distribution pattern within the vertebral cancellous bone are responsible for the reduced stiffness of the tamp generated with this bioglass. When looking at PMMA-based cements, the addition of various hydro- and lipophilic contrast media has been investigated since 2008, but as of yet has not led to a commercially available product with reduced stiffness [13, 14]. Autologous serum has been added experimentally with a resulting reduction in compressive stiffness as have hyaluronic acid [15, 16] and linoleic acid [17]. A more recent experimental study was able to demonstrate a significant reduction in cement stiffness by replacing 50% of the monomer volume with 1-methyl-2-pyrrolidone [18]. The addition of strontium hydroxylapatite nanoparticles as well as of linoleic acid has also resulted in significantly reduced compressive stiffness in laboratory experiments [19] and, more recently, mesoporous silica nanoparticles have been used to achieve similar modifications [20]. All these approaches have in common that they are limited in their clinical applicability: The addition of autologous patient serum requires the preparation of such serum prior to surgery. Any addition of a chemical or compound to bone cement prior to mixing the polymer powder with the monomer will inevitably lead to a modification of the polymerization process. The addition of substances such as strontium hydroxylapatite, 1-methyl-2-pyrrolidone or other foreign chemicals results in a new pharmacological compound or medical device, which in all consequence would require a renewed CE- or FDA-permissions process. This issue would not be as critical if a compound were to be used that is already present in the patient's biological system and which hence would come in contact with the bone cement anyway. Ahn et al. were able to show a significant reduction in cement compressive stiffness when mixing patient blood into the cement [21, 22]. Since patient blood is highly variable within an individual on different occasions and even more between different individuals, it is not well suited for a scientific investigation. Physiological sodium chloride solution, however, is an abundant and ubiquitous component of blood and of other human body fluids and can easily be standardized. We therefore decided to investigate the addition of normal saline to a PMMA-based high-viscosity vertebroplasty cement after initially mixing monomer liquid and polymer powder according to the manufacturer's recommendations.

Materials and methods

Bone cement preparation

A PMMA-based high-viscosity vertebroplasty cement (Vertecem V + Cement Kit, Synthes, Oberdorf, Switzerland) was prepared according to manufacturer recommendations: The stopwatch started immediately when the liquid monomer was added to the powder, then the cement was mixed at a constant rate of approximately one beat per second for 20 s to ensure complete saturation of the powder with the monomer. Immediately after mixing, 10, 20 or 30 volume percent isotonic saline solution was added to the compound using an accordingly prefilled syringe. Cement without an additive was used as control group. Finally the cement of all groups was mixed again for 20 s. The injectability and the setting temperature tests were begun 120 s after starting the mixing, the other tests as specified.

Mechanical properties after setting

(a) Compression test

Compressive testing was performed according to the ISO 5833:2002(E) standard [23]. Forty-five cylindrical specimens (diameter 6 mm; height 12 mm) in each group were prepared in appropriate molds made from PTFE and stainless steel caps. Specimens were stored at 23 ± 2 °C and 50 ± 10% relative humidity until testing. The compression tests were started 24 ± 2 h after specimen preparation. Specimens were tested using a universal mechanical testing machine (Zwick Z010, Ulm, Germany) and a 10 kN force transducer. An extensometer (MTS Model Series 632.11B-20, Minneapolis, USA) was attached to the specimens to measure the compression strain in a fashion independent from the bending of the machine. Displacement controlled (20 mm/min) compressive loading was applied until a deflection of 3 mm was reached. Compression modulus, yield strength, and ultimate strength were calculated from the recorded load–displacement plots.

(b) Four point bending test

Bending stiffness was measured according to the ISO 5833:2002(E) standard [23]. Eight square bars (3.3 × 10 × 75 mm) were cast for each group and stored for 50 ± 2 h at 37 °C in distilled water. Subsequently, the bars were tested on a four point test rig with an outer distance of 60 mm and of 20 mm between the inner loading supports. The tests were run at room temperature (23 ± 2 °C) with dried specimens. These were loaded with a constant displacement of 5 mm/min until failure occurred. The bending modulus (slope between 10 and 50 N),

the ultimate bending strength, and the maximum deflection until failure were calculated from the recorded load–displacement plots.

To analyze qualitative changes in the microstructure, the fractured surfaces of the four point bending test specimens (one from each group) were examined by scanning electron microscopy (SEM). Prior to this, the fragments were sputtered with a thin layer of gold to ensure conductivity. Images were acquired at a magnification of 100×.

Parameters relevant for clinical application

(a) Injectability

The injection of the bone cement was simulated and the necessary injection force was recorded. The mixed cement (0 and 30% NaCl) was filled into 1 ml syringes and drained with a universal testing machine (Z010, Zwick, Ulm, Germany) through a gage 8 vertebroplasty cannula (Fig. 1). A 500 N force transducer measured the force necessary to apply the cement under a constant velocity of 3 ml/min (20 s/syringe). The test was repeated every 60 s with the same batch of cement and with subsequent syringes. The test was terminated when an application force of 70 N was reached or when 12 ml of cement had been applied. 70 N is the maximum force that according to previously published research can reasonably be applied to a syringe by healthy human thumbs [24]. In this fashion, the force necessary to apply the cement at a given and constant injection speed served as a surrogate parameter to compare the viscosity of the different cement preparations. Performing the measurements in this way also remains as close as reasonably feasible to the clinical situation.

(b) Setting temperature

Maximum temperature and setting time were measured using a custom protocol. Mixed bone cement (7 specimens each) with 0 and 30% saline solution added was filled into 2 ml syringes. A thermocouple (type K, class 1, diameter 0.25 mm) was placed into the center of each syringe and secured against dislodgement with a short stretch of sticky tape. The syringe was immediately submersed with only the luer connector penetrating the surface in a water bath with a controlled ambient temperature of 37 ± 1 °C (Instron Bio-Bath A100543.101). Thus, the thermocouples remained unsubmersed in their free trajectory. Temperature

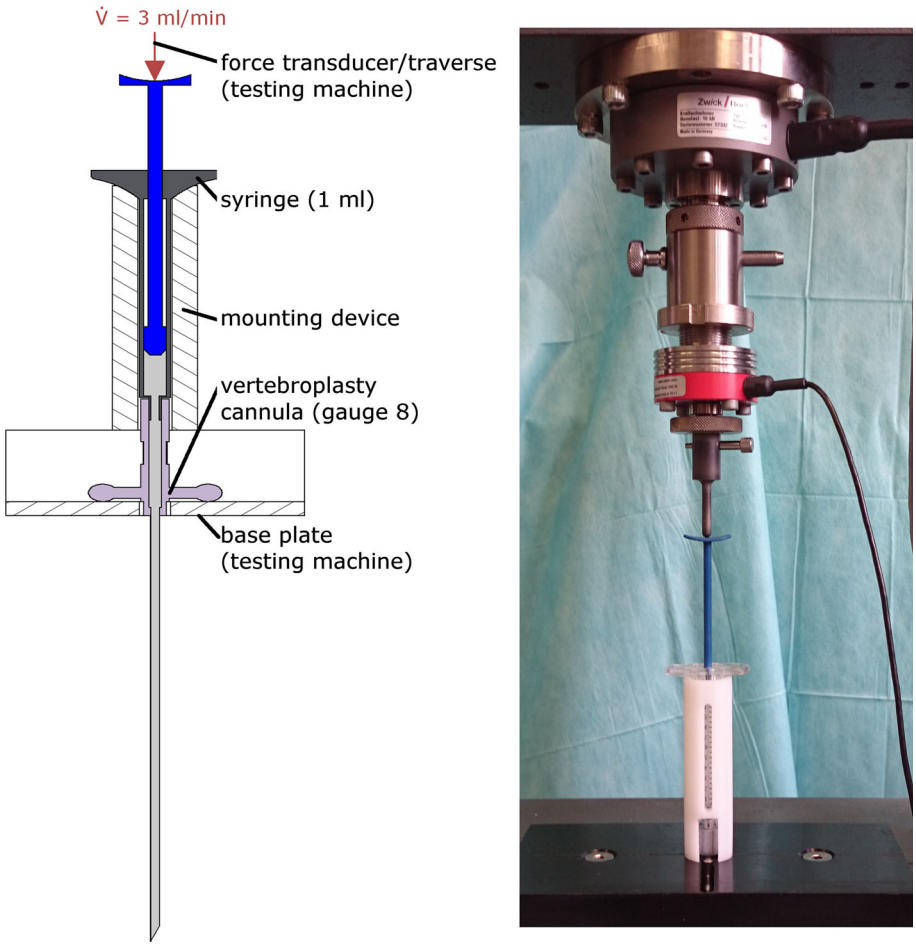

Fig. 1 *Left* Schematic drawing of the testing setup for measuring the force required to inject the cement under a constant flow rate through a gage 8 vertebroplasty cannula with prefilled 1 ml syringes attached. *Right* Corresponding photograph of the testing setup

was measured continuously at 0.5 Hz. Maximum temperature and setting time were recorded directly into a Microsoft Excel spreadsheet by means of a dedicated interface and software package (Testo 454, Testo, Lenzkirch, Germany).

(c) Radioopacity

This was examined in a qualitative fashion for fluoroscopic visualization. The cast cylinders (see "Mechanical properties after setting") were scanned with a digital C-arm (Veradius Neo, Philips, Germany) to assess alterations in radioopacity on a qualitative basis. In addition, specimens were studied using a CT scanner (Somatom Flash, Siemens, Germany). Hounsfield-Units distribution was measured in eight slices for each cylinder as a quantitative value of radio-density.

Statistics

All results are presented with the mean value and (±) standard deviation. Gaussian distribution was confirmed with a Kolmogorov–Smirnov-test before selecting the methods of inferential statistics. Material properties were compared within more than two groups using 1-way ANOVA with a Bonferrroni post hoc test while two groups were compared with a Student T Test. A $p < 0.05$ defines significant differences. Statistics were performed using Prism Version 5 (GraphPad Software, La Jolla, USA)

Results

Mechanical properties after setting

The compression modulus, yield compression strength, ultimate compression strength, bending modulus, and bending strength decreased consistently and significantly (each $p < 0.0001$) with increasing amounts of isotonic saline solution being added to the bone cement. This data is displayed in Table 1.

We observed a two-thirds reduction in bending stiffness when adding 30% isotonic saline solution to the cement and in parallel; the compressive strength decreased from 85.9 ± 4.1 to 33.4 ± 2.5 MPa (61% relatively). No significant difference was measured between 20 and 30% isotonic saline solution groups for bending modulus and for bending strength (Bonferroni post hoc: $p > 0.05$).

The ultimate deflection during bending was increased by adding 10% isotonic saline solution from 5.2 ± 1.1 to 7.5 ± 0.7 mm. Beyond this concentration, there was no detectable difference between both 20 and 30% (both 7.0 ± 0.7 mm; Bonferroni post hoc: $p > 0.05$) and 10%.

The higher the concentration of the additive, the higher was the observed porosity of the cured cement at the fracture sites (Fig. 2).

Parameters relevant for clinical application

The maximum setting temperature of the cement with 30% saline solution (57.8 ± 0.8 °C) was slightly lower than that of the control group (61.0 ± 1.6 °C; $p = 0.0004$) while the setting time with saline solution decreased from 27 min and 39 s (±57 s) to 24 min and 13 s (±28 s; $p < 0.0001$; Fig. 3).

An injection force of 66.4 ± 5.8 N was measured after the 11th syringe in the group with no additive, while with 30% saline solution added, a similar application force (67.6 ± 5.9 N) was reached already after 10 syringes (Fig. 4).

The radio-density of the cement decreased with increasing amounts of saline solution being added (Fig. 5). Significant differences in the Hounsfield-units (Table 2) were found between each group except between 0 and 10%.

Discussion

Our results demonstrate that the simple addition of between 10 and 30 vol.% of physiological saline to this specific commercially available PMMA-based vertebroplasty

Table 1 Material properties of the different cement modifications measured by means of compression and four point bending tests

Vol.% saline solution	Compression test ($n = 45$)			Bending test ($n = 6$)		
	Compression modulus (MPa)	Ultimate compression strength (MPa)	Yield compression strength (MPa)	Bending modulus (MPa)	Ultimate bending strength (MPa)	Maximum deflection (mm)
0	3409 ± 312	85.9 ± 4.1	69.1 ± 3.3	1153 ± 95	39.9 ± 3.6	5.2 ± 1.1
10	2127 ± 251	61.6 ± 3.6	48.1 ± 2.4	745 ± 28	30.8 ± 1.4	7.5 ± 0.6
20	1844 ± 171	48.8 ± 2.2	37.4 ± 2.1	553 ± 24	25.4 ± 1.1	7.0 ± 0.7
30	1131 ± 127	33.4 ± 2.5	28.0 ± 2.0	484 ± 103	23.6 ± 2.8	7.0 ± 0.7

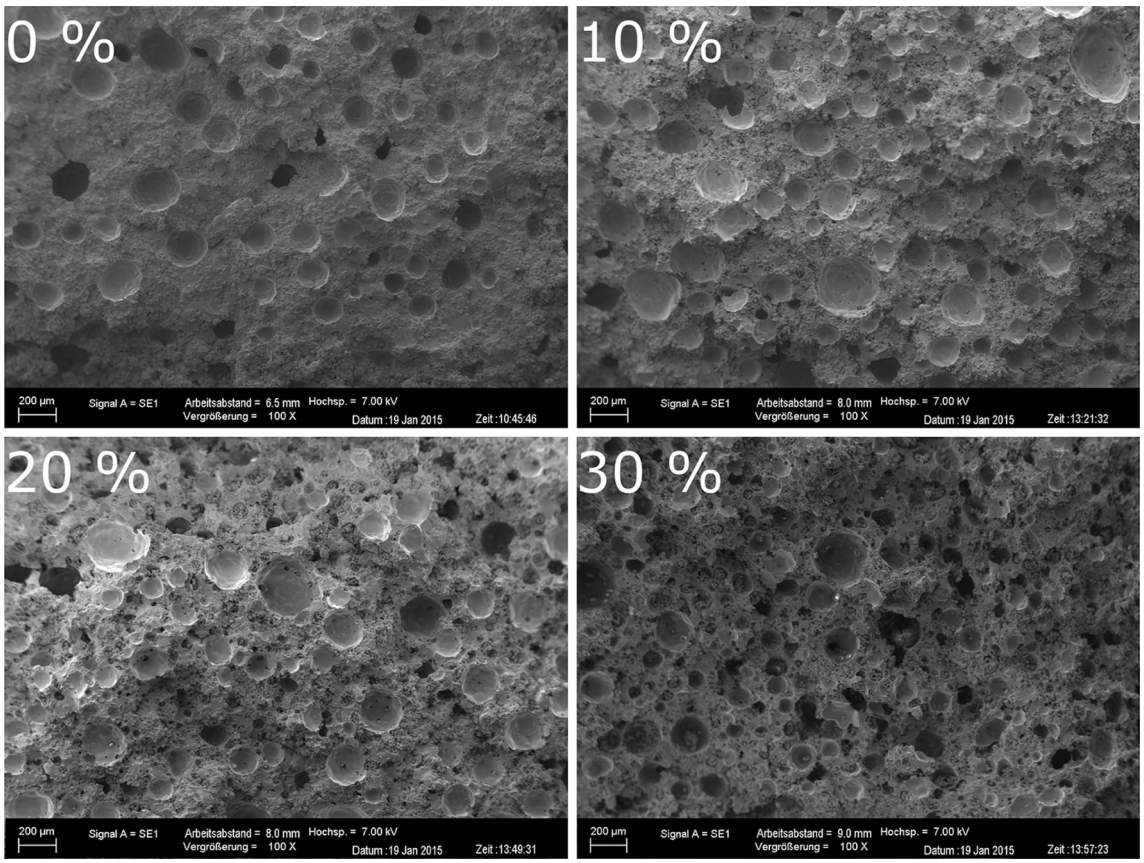

Fig. 2 SEM-Images of the fractured specimens after the four point bending test. All four subimages are marked according to the amount of normal saline mixed into the cement (volume:volume). In the group without saline solution, only a few larger pores are visible at the fracture surface. This changes gradually with the addition of saline solution. Smaller pores can be seen with increasing concentration on the fracture surfaces of the specimens with saline solution as an additive

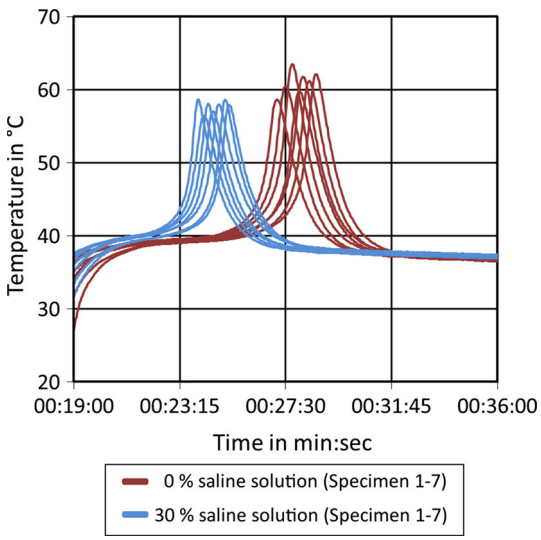

Fig. 3 Temperature-time plots recorded during cement curing; the temperature was measured in the center of 2 ml syringes placed in a water bath with an ambient temperature of 37 °C

cement induces significant alterations of that cement's physical properties. In particular, we were able to show that the compression modulus was reduced by about one-third with 10% of saline added and reduced to about one-third of the original value with 30% of saline added. While we cannot be sure that such a reduction is large enough to reduce the risk of adjacent and/or subsequent vertebral fractures after augmentation, we believe that it is impressive enough to warrant further investigation in a fracture model. It should be noted as an aspect of caution that a recent experimental study augmenting fractured single cadaveric vertebrae with normal and with low modulus cement found only small differences in post-augmentation compressive stiffness [25].

The obtained desirable changes in physical properties do not come at the cost of a greatly reduced radioopacity, as our investigations by means of fluoroscopy and computed tomography demonstrate. So we feel confident that the application safety in the context of visibility in any

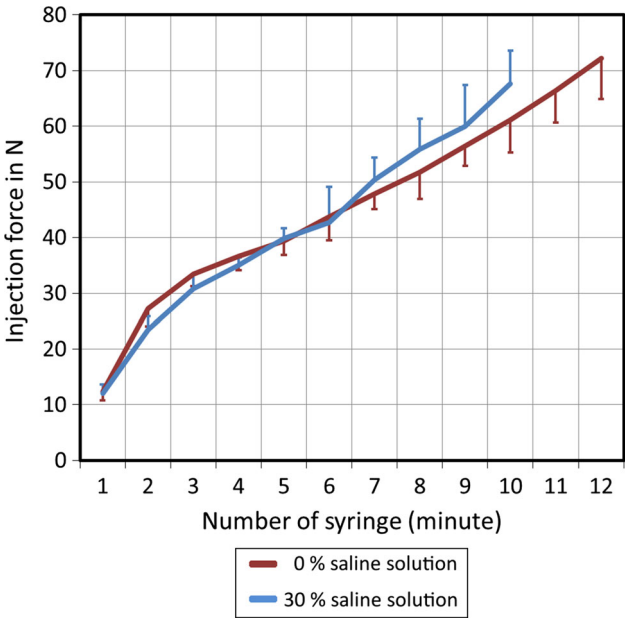

Fig. 4 The effects of cement modification with saline solution on the required injection force through an 8 gage vertebroplasty cannula with a cement-filled 1 ml syringe attached. In respect of comparable maximum application forces, there was a reduction by one applied syringe in the saline group. Data are displayed as means and standard deviations

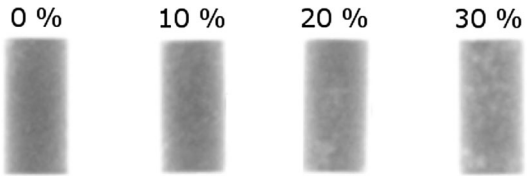

Fig. 5 Fluoroscopic images of the cast cylinders with increasing concentrations of saline solution. Qualitatively, there is a slightly reduction in radioopacity with increasing saline contents, but all cylinders remain clearly visible

Table 2 Mean Hounsfield-units of the cast cylinders extracted from the CT-data

Vol.% saline solution	Radio-density (Hounsfield-units)
0	3041 ± 21
10	3040 ± 17
20	2968 ± 29
30	2850 ± 64

potential clinical application should not be reduced by a clinically important margin. The same applies to the alterations in viscosity and hence applicability, as we were able to demonstrate by means of the simulated application test. Rather than making the cement more liquid and hence more prone to extravasation as we had expected, we reached comparable application forces somewhat earlier during the application test when saline had been added, implying a slight increase in viscosity. This was paralleled by a reduced setting time and, contrary to our original expectations, by a reduced peak temperature during polymerization that was reached slightly earlier than with the unmodified cement. In our view, these phenomena are best interpreted as an accelerated polymerization process. It appears likely that at the same time, the added saline and the generated increase in porosity are responsible for preventing an increased peak temperature during setting. While a reduced maximum temperature has also been observed by other groups working on modifying the modulus of pure PMMA vertebroplasty cements, these researchers found an increase in setting time, which is contrary to our observations with this biphasic cement [26].

The decreased setting time reduces the time window for cement application and needs to be pointed out as a disadvantage of this procedure. In a clinical situation, this effect could lead to fewer vertebrae being augmented with one batch of cement and in consequence, to increased treatment cost in certain situations.

From the data generated in this study, we have no indication that the PMMA cement per se was altered in its chemical properties and in our eyes, the observed increase in microporosity constitutes an adequate explanation for the changes in biomechanical properties. This aspect, however, certainly warrants further investigation. Physiological saline, just like patient blood in earlier experiments by other investigators [21, 22] does not constitute a pharmacological compound or another medical device but rather is native to the human body. Therefore, this approach is fundamentally different from most other attempts to modify PMMA-based bone cements for reduced stiffness as it does not generate a new chemical substance, pharmacological compound or medical device. It merely modifies the microstructure of an existing PMMA-based vertebroplasty cement and any potential future clinical application could therefore be considered as being less critical with regards to labeling aspects than if additional chemicals or compounds were to be added that are not natural components of the human body. However, despite these encouraging results in a laboratory setting, it must be noted that our study examined only one specific product and that we cannot be sure about whether other cements will behave in a similar fashion. It should also be remembered that the PMMA modification studied in this project would constitute an off-label application in a clinical setting, even though a chemical modification appears very unlikely, based on these results. In addition, we have not yet performed formal fatigue testing on the modified cement, which is another important aspect to study prior to considering any potential clinical application. These initial results are therefore not to be interpreted as a suggestion for clinical application of this modification process at this time.

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Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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