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Research Article

Mixing Technique of PMMA - Bone Cement Determines the Ideal Insertion Time Point in Cemented Arthroplasty

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Abstract

Background: The aim of this study was to assess the influence of different mixing techniques on handling properties of PMMA-bone cement.

Methods: Eighteen different mixing techniques which differ in mixing speed, use of vacuum, and storage temperature were performed and repeated five times. For each test group, the handling properties (doughing, working and setting time) were analysed.

Results: Vacuum and temperature had a significant influence on the doughing, working and setting time ($p<0.0001$). Mixing speed had a significant effect on doughing time ($p<0.0001$). It was statistically calculated (two-way ANOVA) that the interaction between the use of vacuum and the mixing speed, and the interaction between temperature and the mixing speed had a significant influence on doughing time ($p<0.0001$). The interaction between temperature and mixing speed had a significant effect on setting time ($p=0.0018$).

Conclusions: The mixing technique determines the viscosity of PMMA bone cement, thereby influencing the ideal time point for insertion.

Keywords: Bone Cement; Cemented Arthroplasty; Handling Properties; Mixing Speed; PMMA; Polymethylmethacrylate; Temperature; Vacuum

Introduction

Success of cemented arthroplasty is determined mainly by bone preparation, design of the implant, surgical technique and knowledge of the handling properties of acrylic bone cement. For about 60 years bone cement has been extensively used in medicine for the implantation of artificial joints. More recently, Polymethylmethacrylate (PMMA) - a glass-like, strong and hard plastic material- has also been well-established in clinical use in regard to techniques such as vertebroplasty and kyphoplasty [1-3]. In total joint replacement it is used [4] to build a solid connection between the metallic prosthesis and the living bone, and [5] to evenly transmit the energy exerted by the prosthesis to the bone [1,6]. To meet these demands, bone cement should have optimal viscosity during the application phase. If viscosity is too low during insertion, it can mix with blood, thereby increasing porosity of the cement. Consequently, this may lead to a higher fracture risk as well as a higher risk of aseptic loosening of the implant. On the other hand, if the viscosity is too high, a reduced intrusion into the interstices of cancellous bone may be observed. Untimely application can lead to impairment in the cement matrix, loss of function as an elastic buffer, and implant aseptic loosening [1,7]. Application of the correct mixing technique is a basic requirement to ensure the following: a homogeneous cement mixture, improved strength of the bone-cement-interface, optimal mechanical stability and increased longevity of cemented arthroplasties [2]. Besides bone preparation, design of the implant and surgical technique, knowledge of handling properties of acrylic bone cement is essential to perform a successful cemented joint replacement.

It is already known that the working properties of PMMA bone cement are influenced by the chemical composition of the components, the powder-liquid ratio, the molecular weight, the particle size distribution of the polymer powder, the chemical affinity of the monomers, the BPO-DmpT-ratio, the sterilization procedure of the powder component, the addition of antibiotics, the manner of mixing (vacuum mixing system vs. manual mixing), and especially the temperature and humidity [2,5,8-15]. Another little-reviewed factor is the mixing technique of the user (Operation Room [OR] staff) processing the cement in the OR. However, there are international standards regarding acrylic bone cement [10]. In order to sell PMMA bone cement, it has to correspond to the mechanical, physical, packaging and labelling requirements of the currently applicable ISO 5833: 2002 (E) standard. Information about temperature dependence of the processing of PMMA bone cement in the package insert is already required by the ISO 5833: 2002 (E) standard. But there is no obligation for the manufacture to demonstrate the influence of vacuum and mixing speed on the processing phases. For any type of available bone cement, manufacturer instruction exists. These instructions should act as reference. However, in the present non-interventional, experimental and prospective trial of a medical device, the mixing technique defined by various mixing speeds, temperatures, vacuum uses, and combinations of such factors was modified. The aim of this study was to determine the influence of the mixing technique on viscosity and the working properties. Therefore, we want to assess the clinical relevance of which method is best for optimal insertion time of the bone cement.

Materials

Palacos® R and the vacuum mixing and application system Palamix® (Heraeus Medical GmbH, Wehrheim, Germany) were used and stored at room temperature (24 +/- 0.5 ˚C) in the laboratory of the Department of Orthopaedics in Vienna. The test was performed in a fume cupboard. Before the investigation, a reference cement ball the size of 3x2x1.8cm was prepared. The cement was mixed according to the manufacturer's instructions. The doughing, working and setting time were determined following the usual OR procedure. The clock was started after adding the powder to the liquid component (beginning of the polymerization). The end of the doughing time and consequently the beginning of the application (working) time was determined using "doctor's finger test" according to ISO 5833; 2002 (E)-norm. The surface of the mixture was touched and observed to determine if fibres were formed between the cement and the finger as the finger left the surface. This process was repeated at an interval of 10 seconds. The time at which the fingers first separated cleanly from the cement was recorded as the doughing time [10]. Afterwards a cement ball the size and shape of the reference ball was modelled. A flat piece from the remaining cement was produced and a thermometer with an aluminium-foil-protection-cap was introduced into this modelled flat. As soon as the cement reached a temperature of 31˚C ± 1˚C, the end of the working time was recorded. The setting time was implemented to be as realistic as possible to real operating procedure, deviating from the ISO 5833: 2002 (E)-norm [10]. The sound of the cement ball when dropped into the kidney dish was evaluated and compared with the tone of the reference ball when it dropped in the same kidney dish. When the sounds matched, it was interpreted as the setting of the cement and the end of the hardening phase was documented [4,16-18].

In test group 1 the bone cement was prepared as recommended according to the manufacturer's instructions: After closing the mixing cartridge and before mixing, vacuum was enabled for 10 seconds (prevacuum). Afterwards, the cement was homogenized under vacuum for 25 seconds. n test group 2, the powder-liquid mixture was mixed with prevacuum as in test group 1, but without vacuum during stirring. In test group 3, vacuum (prevacuum and vacuum) was omitted entirely. Before investigation of test group 4, the Palacos® components (powder and liquid) as well as the Palamix® - system were stored in a fridge at a temperature of 4 ± 1 °C for at least 24 hours. The same treatment was applied in test group 5 but only for the Palacos® components, and in test group 6 only for the Palamix® - system. Thereafter, the liquid- and powder component were mixed according to the manufacturer's instructions until a homogenous mass was achieved. The analyses were executed as mentioned in the test groups above. The bone cement in all test groups was prepared with three different mixing techniques: sub groups a, b and c differ in the mixing speed. The cement in sub group a was blended with the recommended 25 strokes (one stroke/sec), while sub group b was blended with 50 strokes (two strokes/sec) and sub group c with 12.5 strokes ($\frac{1}{2}$ stroke/sec). (Table 1) shows the test group classification.

Test group	Temperature Palacos®	Temperature Palamix®	Prevacuum	Vacuum	Speed (stroke/sec)
Test group 1a	24°C	24°C	+	+	1
Test group1b	24°C	24°C	+	+	2
Test group 1c	24°C	24°C	+	+	$\frac{1}{2}$
Test group 2a	24°C	24°C	+	-	1
Test group 2b	24°C	24°C	+	-	2
Test group 2c	24°C	24°C	+	-	$\frac{1}{2}$
Test group 3a	24°C	24°C	-	-	1
Test group 3b	24°C	24°C	-	-	2
Test group 3c	24°C	24°C	-	-	$\frac{1}{2}$
Test group 4a	4°C	4°C	+	+	1
Test group 4b	4°C	4°C	+	+	2
Test group 4c	4°C	4°C	+	+	$\frac{1}{2}$
Test group 5a	4°C	24°C	+	+	1
Test group 5b	4°C	24°C	+	+	2
Test group 5c	4°C	24°C	+	+	$\frac{1}{2}$
Test group 6a	24°C	4°C	+	+	1
Test group 6b	24°C	4°C	+	+	2
Test group 6c	24°C	4°C	+	+	$\frac{1}{2}$

Table 1: Test group classification.

These 18 different mixing types were chosen because they are the modifiable parameters capable of being influenced by the mixing staff. Each examination of the 18 different test groups was repeated five times. The mean as well as the standard deviation of the doughing time, working time, the endpoint of working, the setting time and the endpoint of settings were calculated and compared. Analysis of Variance (ANOVA) was performed to analyse differences in means for doughing time, working time and setting time as independent variables respectively, accounting for the main effects of vacuum (no vacuum / prevacuum / prevacuum + vacuum), mixing speed (one stroke/sec ; two strokes/sec ; $\frac{1}{2}$ stroke/sec) and temperature (Palacos® 4°C + Palamix® 4°C / Palacos® 4°C + Palamix® 24°C / Palacos® 24°C + Palamix® 4°C / Palacos® 24°C + Palamix® 24°C). Additionally, two-way ANOVAs with interaction terms were calculated only for test groups 1 to 3 as well as for test groups 1, 4, 5 and 6. Results were considered statistically significant if $p < 0.05$. All calculations were performed using Microsoft Office Excel 2010 and the open source statistical program R version 3.1.1 [19].

Results

Influence of Mixing Speed

In test group 1, the doughing time in subgroup b (fast mixing) lasted 17 seconds on average less than in sub group a (normal mixing speed), and 43 seconds more on average in sub group c (slow mixing). The doughing time in fast mixing groups was reduced in almost every test group. Only in test group 3b was the bone cement sticky ca. two seconds longer than in test group 3a. An extension of the doughing time was observed in all six c subgroups (slow mixing groups) compared to the corresponding a sub groups. The main effects ANOVA showed that mixing speed had a significant influence on doughing time ($p<0.0001$). Regarding working time, the ANOVA showed that the mixing speed had no significant effect ($p=0.5578$), which is not surprising due to the rather large standard deviation of working times. Slow mixing caused a prolonged setting time of 4:04 minutes ± 25 seconds in test group 1c compared to test group 1a. In test group 1, the setting time was shortened by fast mixing to 1:55 minutes ± 18 seconds on average, and by slow mixing to 1:58 minutes ± 38 seconds on average compared to the setting time of 02:16 minutes ± 27 seconds resulting from blending the bone cement at a normal mixing speed. Also in sub group b of test group 2, 3 and 5 and in sub group c of test group 3 and 5, a shortening of the setting time could be demonstrated. In sub group b of test group 4 and 6 and in sub group c of test group 2, 4 and 6, an extended setting time was observed. However, an overall effect of mixing speed on setting time was not significant in the ANOVA ($p=0.4126$). (Figure 1) shows the influence of mixing speed on the processing properties of PMMA-bone cement in test group 1.

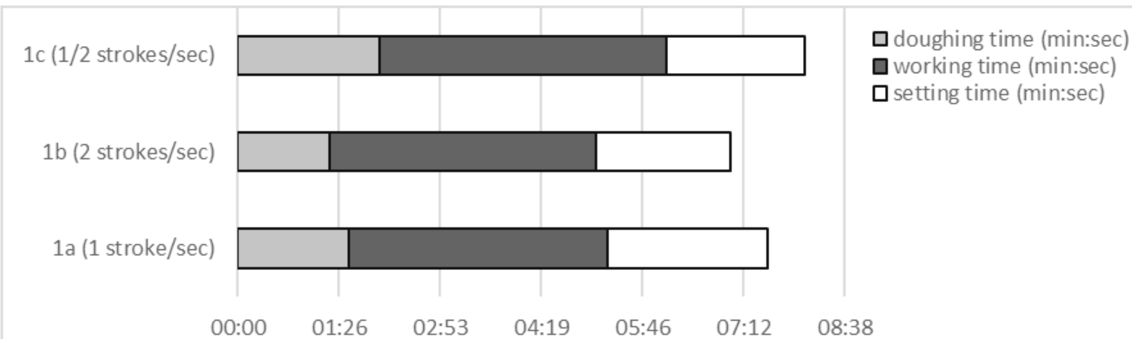

Figure 1: Influence of mixing speed on the processing properties of PMMA-bone cement.

Influence of Vacuum

Mixing only with prevacuum caused a reduction in mean doughing time, depending on the mixing rate. In test group 2a, the bone cement was no longer sticky after 1:18 ± 4 seconds, which means 17 seconds earlier than by mixing the cement under vacuum and normal speed. When vacuum was omitted entirely in test group 3a, doughing time was shortened by an average of 40 seconds compared to test group 1a. Using only prevacuum and normal mixing speed (test group 2a), the duration of the processing phase was prolonged to mean 1:26 minutes compared to the reference group. In case of total absence of vacuum (test group 3a), the working time was extended to mean 2:00 minutes. Furthermore, the setting time in test group 2a lasted 41 seconds, and in test group 3a 35 seconds less. It was shown that the factor vacuum had a highly significant effect on doughing, working and setting time ($p<0.0001$). In (Figure 2), the handling properties of test group 1a are compared to the doughing, working and setting time of test group 2a and 3a. It represents the impact of vacuum on the handling properties of PMMA- bone cement.

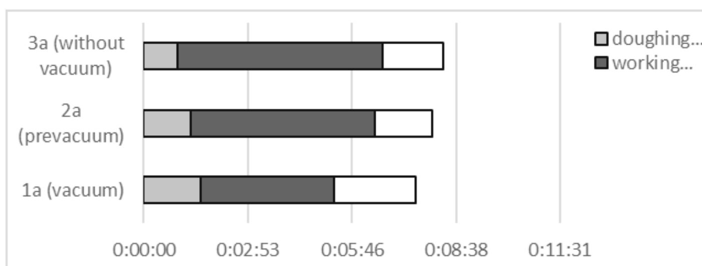

Figure 2: Influence of vacuum on the processing properties of PMMA-bone cement.

Influence of Temperature

The cooling of the components resulted in a total prolonged processing time. When cooling both components and mixing at normal speed (one stroke/sec), the dough was no longer sticky after a mean time of 4:09 minutes ± 12 seconds. For cooling of Palacos®, the application phase was reached after 4:32 minutes ± 6 seconds, and for cooling Palamix®, the application phase was reached after 2:38 minutes ± 6 seconds. Cooling the liquid and powder components to 4°C resulted in doubling of the working time. In test group 5a the application phase was extended to an average time of 5:04 minutes ± 10 seconds and in test group 6a to an average time of 4:52 minutes ± 6 seconds. No strong influence on the setting time was evident when cooling the components. When the Palacos® components were cooled exclusively, the setting time was prolonged by three seconds. If only the Palamix® - system was cooled, the setting time was shortened by four seconds. And if both the Palacos® components, as well as the Palamix®-system were cooled to 4°C, an average setting time of 1:08 minutes ± 36 seconds was determined. Overall, the temperature had a significant effect on doughing time and working time ($p<0.0001$) as well as on setting time ($p=0.0057$). For test groups 1 to 3, where Palamix® and Palacos® temperatures were both 24°C, we calculated two-way ANOVAs for each of the times separately, taking into account the effects of vacuum and mixing speed as well as the interaction of the two. It showed that both factors and the interaction term had a significant effect on doughing time ($p<0.0001$). (Figure 3) shows the different handling properties of PMMA-bone cement in test group 1a, 4a, 5a and 6a.

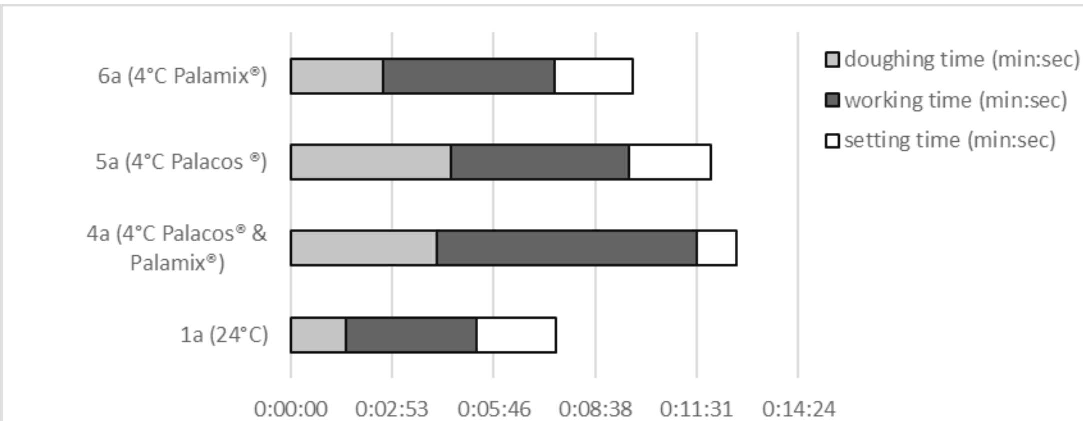

Figure 3: Influence of temperature on the processing properties of PMMA- bone cement.

Influence of Mixing Type on Doughing, Working and Setting Time

Regarding working time, only the effect of vacuum was significant ($p<0.0001$). Mixing speed ($p=0.5031$) and the interaction between vacuum and mixing speed ($p=0.7021$) showed no significant effect on working time. Both vacuum ($p<0.0001$) and mixing speed ($p=0.0162$) factors showed a significant effect on setting time, and no significant interaction effect was revealed ($p=0.4256$). The interaction plots (Figure 4) show the effects for all combinations of the two factors.

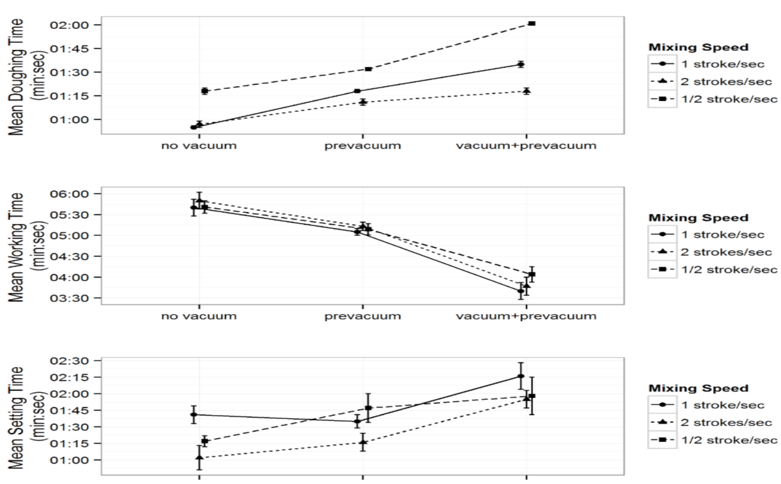

Figure 4: Effects of vacuum and mixing speed when Palamix® 24°C and Palacos® 24°C. Error bars give the standard error.

Similar analysis was done for test groups 1, 4, 5 and 6, where prevacuum and vacuum were used. The effects of temperature, mixing speed and the interaction of temperature and mixing speed were considered. The results showed that both factors and their interaction had a significant effect on doughing time ($p<0.0001$). On working time only, the temperature had a significant influence ($p<0.0001$). Mixing speed and the interaction between temperature and mixing speed showed no significant influence on working time ($p=0.3702$ and $p=0.3638$, respectively). The factor temperature showed a significant effect on setting time ($p=0.0021$), and mixing speed had no significant influence ($p=0.9522$), however there was a significant interaction effect ($p=0.0018$). The interaction plots in (Figure 5) show the effects for all combinations of the two factors.

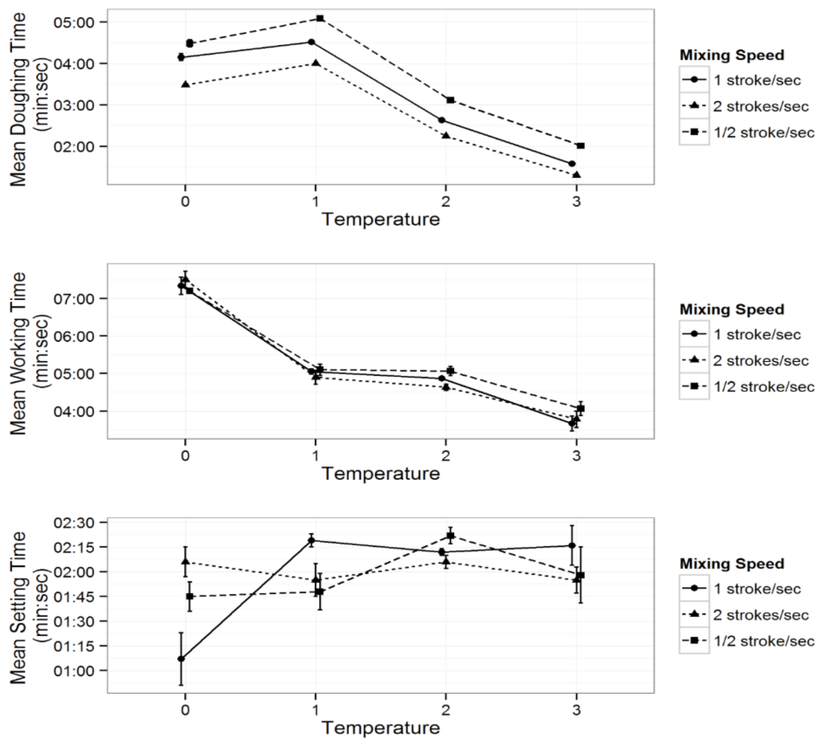

Figure 5: Effects of mixing speed and temperature, when vacuum+prevacuum was used. Temperature is coded as 0: Palamix® 4˚C + Palacos® 4˚C, 1: Palamix® 24˚C + Palacos® 4˚C, 2: Palamix® 4˚C + Palacos® 24˚C, 3: Palamix® 24˚C + Palacos® 24˚C. Error bars give the standard error.

Discussion

The mixing technique, mixing system, corresponding ambient and components temperature have an impact on the processing of PMMA bone cement. Using the example of Palacos® mixed in Palamix®, we were able to show the significant effect of mixing techniques on the handling properties of bone cement. It is well known that the influence of temperature on the handling properties is immense [1,5,6,9,14,18,20,21]. In the literature, the additional influence of mixing speed and vacuum on the handling properties has not been extensively studied [22].

Mixing Speed

The present examination reveals mixing speed (during the processing of bone cement) to have a significant influence on doughing time, but no significant effect on working and setting time. However, a fast mix (two strokes/sec) caused a shortened doughing time compared to mixing with the recommended one stroke/sec. This could be explained by the additional energy input, which leads to an accelerated polymerization. Based on these results, it can be assumed that fast-mixed cement had a premature applicable viscosity (no stickiness). Therefore, it can be introduced into the bone earlier and the surgeon can shorten the operation time or use the gained time for further steps of the operation. The deviation of the doughing time in test group 3b is probably caused by delayed measurement. The doctor's finger test could not be performed before the cement was completely squeezed out of the mixing cartridge. The complete extrusion of the bone cement took 55 seconds on average in this group. So, the doctor's finger test was performed after this time period. If the test was performed earlier, shortened doughing time was possible. Exactly the opposite effect

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was demonstrated by (too) slow mixing ($\frac{11}{22}$ stroke/sec). In almost every test group c in comparison to every test group a, doughing time was achieved at a later time point. Consequently, the surgeon has to wait longer until the cement can be applied into the bone. Such an overall prolonged processing time results in an extended operation time. In addition, the risk from introduction of the cement too early is clearly increased. (Figure 1) shows the influence of mixing speed on the processing properties of PMMA-bone cement in test group 1.

As only a small modification of the mixing speed in the manufacturer's instruction leads to a strong variability of the handling properties, the user cannot rely on the recommended times documented in the package insert of the cement producer alone. These additional factors can be minimized by constant instructional courses for the OR staff. If PMMA bone cement is inserted too late into the bone e.g. in the high viscous phase, which happens by mixing at a high speed the result can be low moulding and thereby insufficient intrusion into the cancellous bone. In such case, the prosthesis cannot be pressed into the bone optimally and the risk of an inadequate connection between bone and cement, and cement and implant are increased. If bone cement is mixed (too) slowly which can happen by mixing with less strokes viscosity can be too low. This is a consequence of still being in the doughing phase during the recommended application phase described in the package insert. So, there is increased risk that the cement mixes with blood, substantially weakening the cement matrix resulting in high porosity and impairment of the cement matrix. Furthermore, the longevity of the cemented implant could be reduced.

Vacuum

Vacuum is an essential part of modern cementing techniques. Use of vacuum improves handling characteristics making mixing easier. Also, mechanical strength which includes the fracture strength, maximum deflection, modulus of elasticity and hardness increases because of the reduction of porosity [5,22,23]. Lindgren, et al. [22] described that mixing under vacuum gave a delay in setting time by about one minute in comparison with hand mixing, but no detailed statement concerning the handling properties were given. In the present study, we verified the hypothesis of the influence of vacuum on the handling properties, which has been presumed in the literature for some time. Our examination shows a significant influence of vacuum on the doughing, working and setting phase. Even the mere use of 10 seconds prevacuum resulted in an extension of the doughing time and shortening of the working time. Setting was also reached earlier. By mixing with prevacuum and under vacuum, the application phase started even later, and the end of the application and setting was achieved at an even shorter time. Obviously, the bone cement remains at a low viscous state longer by eliminating air in the cartridge. Therefore, vacuum mixed cement should be applied later. A possible cause could be the faster superficial drying of the polymer beads by mixing without vacuum, which makes the cement appear tack-free at an earlier time. The data seems to suggest that vacuum leads to faster moistening and thereby to a shortened working time. For using it is important to know the difference between mixing with or without vacuum in order to introduce the cement at the desired viscosity into the bone. (Figure 2) shows the influence of vacuum on the processing properties of PMMA bone cement by mixing it with the recommended mixing speed (one stroke/sec).

Temperature

In order to achieve a lower initial viscosity and thereby facilitated homogenization in the mixing phase [1,5,18,22], in many hospitals bone cement is stored in a fridge before surgery. Due to the temperature dependence on the free-radical polymerization of PMMA bone cement, the handling properties are influenced significantly by ambient- and component-temperatures [1,5,6,9,14,18,21,22]. In the collected data the effect of the temperature could be confirmed. By cooling the monomer liquid and powder to 4°C, an approximate three minutes prolonged doughing time could be shown. The average processing time was extended by one minute. Since the setting time was approximately comparable to the setting time of the reference group, total processing was delayed by about four minutes. If both Palacos® and the vacuum mixing and application system Palamix® are pre-cooled, the total processing time was extended even further. However, because of the possible formation of condensation water on the plastic cartridge inside the sterile packaging, the mixing system should not be stored in a fridge. Figure 3 shows the influence of temperature on the processing properties of PMMA bone cement by mixing it at the recommended mixing speed (one stroke/sec).

Recommendation

If a surgeon needs a fast doughing time and thereby fast usability, the bone cement should be stored at room temperature and mixed without vacuum at a high mixing speed according to the present results. However, a higher porosity must be expected [5,22]. If a longer working time is desired, the OR staff can cool the components, however this is associated with overall extended processing. The collected data suggests that the processing and consecutively the operation time will be extended by mixing the bone cement at a low speed, without vacuum and by cooling the components. However, based on our study we advocate for the manufacture's guidance. Precooled PMMA bone cement should be mixed in vacuum in an airtight mixing system with a mixing speed of one stroke/sec for 25 seconds to obtain easy application and bone cement with a reduced number of air inclusions.

There are few limitations to this study. First, only one type of bone cement was examined. It can be assumed that the processing phases and handling properties differ in cements with varying viscosity and chemical composition of the components. Hence, tests for all available cements on the market would be necessary. Additional instructions in the package insert would be advisable. Second, only one person mixed the cement under a fume cupboard. Thus, we did not have quite the same conditions as in the operating room. It is known that in the OR cement is mixed by a huge number of different people. So clear instructions for the surgeon and OR staff are necessary. Next, there were only five repeated measurements for one group. Despite the small sample size of the individual test groups, our results show an enormous impact on the processing phases of Palacos R®. A clear limitation is the subjectivity of the "sound test", but we attempt to perform the tests to be as realistic as possible to real operating procedures.

Conclusion

Before using PMMA bone cement, detailed knowledge of handling properties is necessary to ensure insertion of the cement at the right viscosity. Furthermore, it is advisable to provide clear instructions to the surgeon and surgical staff.

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