Clinical relevance of current materials for cranial implants
Towards an optimal patient-specific implant material
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Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices

This chapter is based on the publication: Effects of sterilization on the mechanical properties of poly(methyl methacrylate)-based personalized medical devices

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ABSTRACT

**Background:** Nowadays, personalized medical devices are frequently used for patients. Due to the manufacturing procedure sterilization is required. How different sterilization methods affect the mechanical behavior of these devices is largely unknown.

**Materials and methods:** Three poly(methyl methacrylate) (PMMA) based materials (Vertex Self-Curing, Palacos R+G, and NextDent C&B MFH) were sterilized with different sterilization methods: ethylene oxide, hydrogen peroxide gas plasma, autoclavation, and γ-irradiation. Mechanical properties were determined by testing the flexural strength, flexural modulus, fracture toughness, and impact strength.

**Results:** The flexural strength of all materials was significantly higher after γ-irradiation compared to the control and other sterilization methods, as tested in a wet environment. NextDent C&B MFH showed the highest flexural and impact strength, Palacos R+G showed the highest maximum stress intensity factor and total fracture work.

**Conclusion:** Autoclave sterilization is not suitable for the sterilization of PMMA-based materials. Ethylene oxide, hydrogen peroxide gas plasma, and γ-irradiation appear to be suitable techniques to sterilize PMMA-based personalized medical devices.
INTRODUCTION

Poly(methyl methacrylate) (PMMA) has been widely used in different fields of healthcare. It is used as bone cement for fixation of knee and hip implants in orthopedics, as the base of dental prosthesis, for cranial reconstruction in neurosurgery, and for many other medical devices. PMMA is light, radiolucent, cost efficient, and easy to use. However, it is associated with complications such as infection. The exothermic polymerization of PMMA can cause burn injuries if applied directly onto tissues and there are indications that residual monomers are toxic to the body.

The mechanical properties of personalized medical devices are essential for long-term survival. These properties may be affected by storage time, pre-treatment, sterilization and the location of the inserted medical device in the body. PMMA demonstrates increased flexibility in a liquid environment compared to a dry environment, and storage at 37°C makes PMMA less resistant to fracture than storage at 21°C.

The most common sterilization methods for medical applications are ethylene oxide gas (EtO), hydrogen peroxide gas plasma (HPGP), autoclavation, and $\gamma$-irradiation. These sterilization methods are important as PMMA-based medical devices are not only prepared by powder and liquid mixing in the operating room, but pre-fabricated 3D-printed methacrylate-based materials and ex vivo polymerization are also used.

The advantage of 3D-printing is a better control on the shape and material properties of the medical device. Manufacturing the medical device before surgery reduces surgical times and removes limitations to the environmental conditions during polymerization, enabling optimizations that may lead to better clinical outcomes. However, the device then needs to be sterilized, this presents a challenge to retain optimal material behavior.

The sterilization of PMMA powder is usually performed by $\gamma$-irradiation, except for Palacos, which is sterilized using EtO. The liquid MMA monomer is sterilized through membrane filtration. $\gamma$-irradiation of PMMA results in chain scission, detectable through a decrease in molecular weight. This directly influences mechanical properties such as fracture toughness, fatigue, and flexural strength.
The effect of autoclave, EtO, and hydrogen peroxide (H₂O₂) sterilization, on the chemical structure and surface morphology of PMMA is previously described. However, it is still unknown how these sterilization methods affect mechanical properties of cured PMMA. Therefore, the aim of this study is to investigate the effect of sterilization methods: EtO, HPGP, autoclavage, and γ-irradiation on the mechanical properties of PMMA-based personalized medical devices.

MATERIALS AND METHODS

The effects of sterilization with EtO, HPGP, autoclavage, and γ-irradiation on the mechanical properties of PMMA-based personalized medical devices were investigated (Table 1). Since the mechanical properties of the PMMA-based materials may vary depending on the application, three different types were investigated: Vertex Self-Curing, Palacos R+G and NextDent C&B MFH (Table 2).

For each material the flexural strength, flexural modulus, fracture toughness, and impact strength were determined after sterilization and compared to the unsterilized control. All test methods for determining the mechanical properties were taken from the appropriate standards, e.g. ISO 20795-1:2013 and ISO 179-1:2010.

Palacos R+G (Heraeus, Hanau, Germany) and Vertex Self-Curing (Vertex-Dental, Soesterberg, The Netherlands) were hand mixed and prepared according to the manufacturer’s instructions. These specimens were molded using a stainless-steel mold. Curing of Vertex Self-Curing followed in a water-filled pressure cooker for ten minutes at 55°C and 2.5 bar.

NextDent C&B MFH (NextDent, Soesterberg, The Netherlands) was 3D printed in a horizontal direction with a Rapidshape D30 (Rapidshape, Heimsheim, Germany) based on digital light processing (DLP). These specimens were washed in ethanol twice (three minutes and two minutes, respectively) under ultrasonic vibrations and dried for ten minutes prior to a 30 minutes post-cure in a LC3D-PrintBox (NextDent, Soesterberg, The Netherlands).
All specimens were wet grinded with standard metallographic grinding paper (P500, P1000 and P1200) and visually inspected for a smooth surface without porosities and irregularities. Sterilization was performed seven to ten days post-polymerization and the specimens were stored at least 72 hours under standard laboratory climate conditions (22 ± 1°C and 50 ± 2% humidity).

**Flexural strength and flexural modulus**

Eighteen series of ten rectangular specimens (64.0 ± 1.0 × 10.0 ± 0.2 × 3.3 ± 0.2 mm), one per material and sterilization method, were produced. The width and height of the specimens were measured by dial caliper before sterilization. After sterilization and prior to testing, the specimens were immersed in a water bath at 37.0 ± 1.0°C for 50 ± 2 h. The flexural strength was tested in a water bath at 37.0 ± 1.0°C, using a three-point-bending test (supporting bars span of 50.0 ± 0.1 mm) in a universal testing machine (Mecmesin Imperial 1000, West Sussex, UK) with a crosshead speed of 5.0 mm/min. Each specimen was tested until fracture or until the maximum curvature was reached. To calculate the ultimate flexural strength, \( \sigma \) and the flexural modulus, \( E \), Equation 1 and 2 were used.

\[
\sigma = \frac{3Fl}{2bh^2} \tag{1}
\]
\[
E = \frac{Fl^3}{4bh^3d} \tag{2}
\]

where \( F \) is the load [N], \( l \) is the distance between the supports [mm], \( b \) is the width and \( h \) is the height of the specimen [mm].

**Fracture Toughness**

Eighteen series of ten rectangular specimens (39.0 × 8.0 ± 0.2 × 4.0 ± 0.2 mm), one per material and sterilization method, were produced. The specimens were notched on the centerline with a sawing blade to a depth of 3.0 ± 0.2 mm. A pre-crack was made with a sharp blade with a thickness of 0.55 mm to a depth of 100 - 400 µm. An optical microscope was used to check the depth of the pre-crack. The width and height of each specimen was measured with a dial caliper. After sterilization and prior to testing the specimen were immersed in a water bath at 37 ± 1.0°C for 7d ± 2 h, followed by a water bath at 23.0 ± 1.0°C for 60 ± 15 min. The fracture toughness was measured using a three-point bending test (supporting bars span of 32.0 ± 0.1 mm) under dry conditions using the universal testing machine with a crosshead speed of 1.0 mm/min. The specimens were loaded until fracture. The maximum stress intensity factor, \( K_{\text{max}} \), in MPa m\(^{1/2}\) was calculated with Equation 3.
where $P_{\text{max}}$ is the maximum load exerted on the specimen [N], $h_t$ is the height and $b_t$ is the width of the specimen [mm], $l_t$ is the span [mm] and $f$ is a geometrical function, dependent on $x$ in Equation 4, where $a$ is the crack length consisting of the notch and the pre-crack [mm].

$$f(x) = 3x^{1/2}[1.99 - x(1 + x)(2.15 - 3.93x + 2.7x^2)]/[2(1 + 2x)(1 - x)^2]; \quad x = \frac{a}{h_t}$$

The total fracture work, $W_f$, in J/m$^2$ was calculated using Equation 5.

$$W_f = \frac{U}{[2b_t(h_t - a)]} \times 1000$$

where $a$, $h_t$, and $b_t$ are the same as for Equation 3. $U$ [N mm] is the area under the load/displacement curve that is defined by Equation 6.

$$U = \int P_d \Delta$$

**Unnotched Charpy impact strength**

Eighteen series of ten rectangular specimens (62.0 ± 1.0 × 6.0 ± 0.2 × 4.0 ± 0.2 mm), one per material and sterilization method, were produced. The specimens were placed in a Karl Frank 53301 testing machine with a supporting bars span of 50.0 mm and a pendulum energy of 0.5 J for Vertex Self-Curing and Palacos R+G, and 1.0 J for NextDent C&B MFH. The Charpy impact strength, $a_{cU}$, was calculated in kJ/m$^2$ with Equation 7.

$$a_{cU} = \frac{E_c}{h_b} \times 10^3$$

where $E_c$ is the corrected energy absorbed by breaking the test specimens [kJ], $h$ is the height and $b$ is the width of the specimen [mm].

Data were statistically analyzed using one-way analysis of variance (ANOVA) followed by Tuckey’s post hoc test ($\alpha = 0.05$) in SPSS version 24.0 (IBM, Armonk, NY, USA).
RESULTS

The results of the mechanical tests and the statistical analysis are summarized in Table 3 and representative curves for the flexural strength and toughness are graphically depicted in Figure 1. The autoclave-sterilized specimens were excluded from the results and the statistical analysis due to deformation or exfoliation during the sterilization process.

Table 1: Specifications of the sterilization methods (autoclavation, ethylene oxide (EtO), hydrogen peroxide gas plasma (HPGP) and γ-irradiation).

<table>
<thead>
<tr>
<th>Sterilization Technique</th>
<th>Specifications</th>
<th>ISO norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoclavation</td>
<td>121 °C for 16 min or 134 °C for 3.5 min</td>
<td>17665:2006</td>
</tr>
<tr>
<td>EtO</td>
<td>-</td>
<td>11135:2014</td>
</tr>
<tr>
<td>HPGP</td>
<td>Sterrad</td>
<td>11737:2006</td>
</tr>
<tr>
<td>γ-irradiation</td>
<td>26.4 – 29.4 kGy from Cobalt-60</td>
<td>11137-1:2015</td>
</tr>
</tbody>
</table>

Figure 1: Force displacement graphs of representative flexural strength (left) and toughness (right) tested specimens of Vertex Self-Curing (dot), Palacos R+G (dot-dash) and NextDent C&B MFH (dash).

Flexural strength and flexural modulus

NextDent C&B MFH had a significantly higher flexural strength (σ) for each sterilization method compared to the other materials. Vertex Self-Curing had a significantly higher flexural strength for γ-irradiation and HPGP compared to Palacos R+G. The flexural strength of γ-irradiated specimens was significantly higher than the otherwise sterilized and control specimens for all materials.
NextDent C&B MFH had a significantly higher flexural modulus (E) than Vertex Self-Curing for control specimens. For HPGP sterilized specimens, NextDent C&B MFH showed a significantly higher flexural modulus compared to Vertex Self-Curing and Palacos R+G. EtO sterilized Palacos R+G showed a significantly higher flexural modulus than Vertex Self-Curing. For Vertex Self-Curing and Palacos R+G none of the sterilization methods showed a significant difference compared to the control specimens. However, NextDent C&B MFH showed a significantly reduction after EtO sterilization, and a significant increase upon HPGP sterilization.

Table 2: Specifications of the PMMA-based materials used in this study.

<table>
<thead>
<tr>
<th>Material / Application</th>
<th>Ingredients powder</th>
<th>Ingredients liquid</th>
<th>Batch number</th>
<th>Expiration date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertex Self-Curing Denture</td>
<td>Poly(methyl methacrylate), benzoyl peroxide, various pigments</td>
<td>Methyl methacrylate, N,N-Dimethyl-p-toluidine, ethylene glycol, dimethacrylate</td>
<td>XN423P02 (shade 5)</td>
<td>04-2022</td>
</tr>
<tr>
<td>Palacos R+G Bone cement</td>
<td>Gentamicin, poly(methylacrylate), methyl methacrylate, zirconium dioxide, benzoyl peroxide, colorant E141</td>
<td>Methyl methacrylate, N,N-dimethyl-p-toluidine, hydroquinone, colorant E141</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH Personalized medical device</td>
<td>-</td>
<td>Methacrylate oligomer, methacrylate monomer, inorganic filler, phosphine oxides</td>
<td>XN305N01 (shade N3)</td>
<td>-</td>
</tr>
</tbody>
</table>

Fracture Toughness

Palacos R+G showed a significantly higher maximum stress intensity factor ($K_{max}$) compared to the other materials. For the HPGP sterilization specimens, it was significantly higher than NextDent C&B MFH. Following EtO sterilization, Vertex Self-Curing and Palacos R+G showed a significantly higher maximum stress intensity factor than NextDent C&B MFH. Upon HPGP sterilization NextDent C&B MFH showed a significant increase. Other sterilization methods had no significant effect on the maximum stress intensity factor of the materials.

Palacos R+G had a significantly higher total fracture work ($W_f$) compared to the other materials for each sterilization method. The sterilization methods had no significant influence on the total fracture work of the materials.
### Impact strength

NextDent C&B MFH showed a significantly higher Charpy impact strength ($a_{IC}$) after $\gamma$-irradiation and HPGP sterilization compared to the other materials. NextDent C&B MFH also had a significantly higher Charpy impact strength compared to Palacos R+G for the control. There was no significant difference found in the Charpy impact strength between the sterilization methods for Vertex Self-Curing and Palacos R+G. For NextDent C&B MFH there was a significant increase of the Charpy impact strength after $\gamma$-irradiation.

### Table 3: Flexural strength ($\sigma$) in MPa, flexural modulus ($E$) in MPa, maximum stress intensity factor ($K_{max}$) in MPa m$^{1/2}$, total fracture work ($W_f$) in J/m$^2$ and Charpy impact strength ($a_{IC}$) in kJ/m$^2$ of the different materials after sterilization with ethylene oxide (EtO), hydrogen peroxide gas plasma (HPGP) and $\gamma$-irradiation.

<table>
<thead>
<tr>
<th>Material</th>
<th>Control</th>
<th>EtO</th>
<th>HPGP</th>
<th>$\gamma$-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertex Self-Curing</td>
<td>66.8 (4.3)</td>
<td>66.4 (2.7)</td>
<td>68.3 (3.3)</td>
<td>80.0 (3.4)</td>
</tr>
<tr>
<td>Palacos R+G</td>
<td>61.6 (2.8)</td>
<td>63.8 (1.8)</td>
<td>60.2 (2.5)</td>
<td>70.6 (3.2)</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH</td>
<td>91.8 (6.3)</td>
<td>89.2 (3.5)</td>
<td>94.0 (3.4)</td>
<td>109.3 (2.6)</td>
</tr>
<tr>
<td>Vertex Self-Curing</td>
<td>2166 (160)</td>
<td>2165 (68)</td>
<td>2212 (104)</td>
<td>2265 (87)</td>
</tr>
<tr>
<td>Palacos R+G</td>
<td>2256 (85)</td>
<td>2307 (76)</td>
<td>2226 (90)</td>
<td>2244 (49)</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH</td>
<td>2374 (118)</td>
<td>2221 (78)</td>
<td>2521 (96)</td>
<td>2238 (55)</td>
</tr>
<tr>
<td>Vertex Self-Curing</td>
<td>1.70 (0.34)</td>
<td>1.87 (0.35)</td>
<td>1.98 (0.21)</td>
<td>1.83 (0.21)</td>
</tr>
<tr>
<td>Palacos R+G</td>
<td>2.18 (0.31)</td>
<td>2.40 (0.20)</td>
<td>2.24 (0.35)</td>
<td>2.31 (0.22)</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH</td>
<td>1.42 (0.09)</td>
<td>1.63 (0.12)</td>
<td>1.80 (0.14)</td>
<td>1.77 (0.20)</td>
</tr>
<tr>
<td>Vertex Self-Curing</td>
<td>476.7 (163.2)</td>
<td>562.9 (193.2)</td>
<td>579.9 (93.2)</td>
<td>494.5 (97.6)</td>
</tr>
<tr>
<td>Palacos R+G</td>
<td>940.0 (151.3)</td>
<td>981.1 (123.7)</td>
<td>948.6 (135.7)</td>
<td>832.0 (74.8)</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH</td>
<td>331.4 (34.1)</td>
<td>421.8 (51.0)</td>
<td>443.5 (77.5)</td>
<td>405.3 (66.4)</td>
</tr>
<tr>
<td>Vertex Self-Curing</td>
<td>7.6 (1.8)</td>
<td>7.8 (2.5)</td>
<td>7.3 (1.1)</td>
<td>6.5 (2.5)</td>
</tr>
<tr>
<td>Palacos R+G</td>
<td>4.7 (0.0)</td>
<td>4.5 (1.4)</td>
<td>4.5 (0.9)</td>
<td>4.0 (1.1)</td>
</tr>
<tr>
<td>NextDent C&amp;B MFH</td>
<td>10.5 (4.0)</td>
<td>7.3 (1.9)</td>
<td>11.1 (2.3)</td>
<td>14.2 (3.8)</td>
</tr>
</tbody>
</table>

Values given as mean and standard deviation (SD). Identical letters indicate no significant difference between the groups. Capital letters indicate differences between the materials (split by sterilization method), the lowercase letters indicate differences between the sterilization methods (split by material).

†: n<10 because maximum strength could not be calculated, since some specimens did not fail during testing.
‡: Test was repeated because of an inordinate high standard deviation, both tests are combined in this result.
¶: n=9 because one specimen was broken during the sterilization process.
DISCUSSION

PMMA-based polymers have been used for many years in medical devices with their specific formulations and applications. No reports on a systematic investigation of the mechanical properties using the same ISO standards are available (bone cement (ISO 5833) or dental (ISO 20795-1:2013 and ISO 179-1:2010)), making comparison between the reported values difficult. Literature reports the flexural strength (56.3 MPa), flexural modulus (2213 MPa), the toughness (2.03 MPa m$^{1/2}$), and total fracture work (897 J m$^{-2}$) of Palacos R+G. The impact strength reported for Palacos R without gentamicin was 4.1 kJ m$^{-2}$. For Vertex Self-Curing the flexural strength (79.6 MPa) and flexural modulus (2.38 GPa) are reported. Currently, there is no data available on the mechanical properties of NextDent C&B MFH. These values reported in literature are in line with the findings presented in this study.

From the measured mechanical properties of the different materials the following trends were observed (I) an increase in flexural strength ($\sigma$) resulted in decreased toughness ($K_{max}$ and $W_f$), (II) an increase in flexural strength ($\sigma$) resulted in increased impact strength ($A_{cu}$) and (III) an increase in toughness ($K_{max}$ and $W_f$) resulted in decreased impact strength ($A_{cu}$). The latter is contradicting with finding of Lewis and Mladsi, where a positive correlation was found between the toughness ($K_{max}$) and impact strength ($A_{cu}$). The toughness and impact strength are two independent properties, which are related to the ductile or brittle nature of the material. Brittle polymers fail through nucleation of voids and initiation and propagation of brittle cracks resulting in catastrophic failure. The polymers have yield strengths higher than their ultimate or breaking strengths, and thus a low crack initiation and low crack propagation energy in impact. Ductile polymers fail by crazing or matrix shear yielding. Both mechanisms lead to high crack initiation energy, but to a low propagation energy at impact. As a result one can expect a high unnotched impact strength, but a low notched impact strength.
In this study Palacos R+G and Vertex Self-Curing have a comparable flexural strength and flexural modules, however, Vertex Self-Curing is more brittle compared to Palacos R+G (Figure 1). According to Perkins and Lewis et al., one should expect that the unnotched impact strength of Palacos R+G exceeds the impact strength of Vertex Self-Curing. However, the experiments showed a decrease of impact strength, suggesting that Palacos R+G fails at impact by a brittle polymer mechanism, e.g. voids in the material. This seems plausible because Palacos R+G has macroscopically visible voids in the material and contains 10% zirconium dioxide as filler for radio opacity, which are most probably not chemically incorporated in the matrix and can act as a void.

Beside the composition of the material, the effect of the sterilization procedure was investigated. In general, autoclave sterilization is one of the most common sterilization methods. In this study it caused specimens to deform or exfoliate due to the high temperatures and pressurized steam, which exceed the glass transition temperature ($T_g$) of Palacos R (100°C). A material that deforms or exfoliates during sterilization is not desirable for medical devices, therefore autoclave sterilization was excluded from further analysis. HPCP and EtO did not tend to significantly change material properties. In contrast, the flexural strength of all three materials increased significantly following $\gamma$-irradiation. Literature reports a decrease in molecular weight of PMMA upon $\gamma$-irradiation due to chain scission, this directly relates to worsening of the mechanical properties. $\gamma$-irradiation increases the amount of scission, it follows therefore that it may also increase side-group scission. An increase in flexural strength originating from additional crosslinking thus seems unlikely, instead it could originate from a change in wettability of the material. These materials show a significant reduction in flexural strength when immersed in water. A reduction in hydrophilic side-groups due to $\gamma$-irradiation induced side-group scission may thus effectively increase the flexural strength compared to the control when both are incubated in water following sterilization, even though the molecular weight is lower.
Most related research regarding bone cements is performed in the field of orthopedics, which use the ISO 5833 norm to determine mechanical properties. Since Vertex Self-Curing and NextDent C&B MFH are mostly used as dental acrylics, which have different demands compared to bone cement applications, ISO 20795-1:2013 and 1791:2010 norms were applied in this study. ISO 5833 would allow better comparison to the available literature, however, the bone cements are tested in dry conditions after 24 hr. This results in over estimation of the mechanical properties. The current ISO 5833 standard does not mimic the conditions or environment in which the material is used clinically and should be revised and preferably harmonized with more realistic dental ISO standards, which use 37°C in water (2 – 7 days).

When comparing the above mentioned materials, NextDent C&B MFH performs better than the other materials on flexural strength and modulus, as well as impact strength. However it also has significantly lower toughness and shows a more brittle behavior, especially compared to Palacos R+G which appears more ductile. This is in line with literature, as an increase in crosslink density lowers the fracture toughness and limits the total crack-tip strain. NextDent C&B MFH is a poly(dimethacrylate) and therefore has significantly more crosslinks than the other two materials. Due to crosslinking in the materials tested, thermoset polymers with similar chemical compositions may show similar trends to the results presented in this study, although this requires further investigation.

There is no influence of EtO on the molecular weight of PMMA reported in literature, suggesting that EtO does not influence the mechanical properties of PMMA. The results reported in this study show no significant difference between unsterilized and EtO sterilized specimens. However, EtO is a toxic gas and requires a long period - up to fifty days - of degassing.

This study did not take into consideration the effect of sterilization on biocompatibility of the materials and leaching of potential harmful substances, i.e. unreacted monomer and activator. It should be noted that the powder and liquid components of PMMA used in the operating room are sterilized before use, γ-irradiation is often used to sterilize the powder component. These properties are crucial for clinical use and should be investigated in future studies.
CONCLUSION

This study provides an overview of the influences of different sterilization methods on the mechanical properties of PMMA-based personalized medical devices. Autoclave sterilization is not suitable for the sterilization of PMMA-based materials. EtO, HPGP, and γ-irradiation appear to be suitable techniques to sterilize PMMA-based personalized medical devices. γ-irradiation could even increase the effective flexural strength in a wet environment.
REFERENCES


