Brazilian Dental Science

Subject: [BDS] Editor Decision

Dear Tijmen J.A.G. Münker, Sophie E.C.M. van de Vijfeijken, Cornelis J. Kleverlaan, Alfred G Becking:

Your submission Leachables from patient-specific implants produced by 3D printing compared to conventional PMMA-based alternatives to Brazilian Dental Science, has been revised, and according to reviewers' comments, there are questions to be addressed and/or points to be clarified/corrected.
Please address the reviewers' considerations point by point in a separate document, and also make all corrections to the text highlighted in yellow.

Deadline: 30 days

Thank you for considering Brazilian Dental Science for publishing your research.
We are looking forward the revised version of you manuscript.

Sincerely,

Reviewer A:
Recommendation: Revisions Required

Questionnaire

Does the manuscript contain new and significant information to justify publication?*

Yes

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Does the Abstract (Summary) clearly and accurately describe the content of the article?

Yes

Is the problem significant and concisely stated?

Yes

Are the methods or research design described comprehensively? Is the statistical analysis adequate?

Yes

Are the interpretations and conclusions justified by the results?

Yes

Is adequate reference made to other work in the field?

Yes

Is the language acceptable?

Yes

Manuscript Structure

Length of article is:*

Adequate

Number of tables is:

Adequate

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Number of figures is:

Adequate

Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable).

none

Rating

Interest*

Excellent

Quality

Excellet

Originality

Excellent

Overall

Excellent

Recommendation

Major Revision

Would you be willing to review a revision of this manuscript?

Yes

Comments

Comments to the Author

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This study investigated the monomer release of different PMMA-based materials, an important topic for understanding the potential risks associated with these materials. However, it requires major revision before it can be accepted for publication:

Introduction

1. The authors provide an extensive description of adverse reactions associated with (meth)acrylates. However, the reviewer recommends rephrasing this section to improve focus and coherence. Specifically, the introduction should better summarize the current literature on known monomer release and more clearly identify the existing knowledge gap, as well as the significance of the present study in addressing it.
2. "The amount of residual monomers is generally higher in the direct method due to its in situ environment," Reference is required to support this sentence.
3. There is an inconsistency in the study objectives: two objectives are presented in the introduction, whereas only one is stated in the abstract.

M&M

4. The first paragraph of M&M could be merged with the final paragraph of the Introduction to avoid repetition.
5. Referring to NextDent C&B MFH as a 'personalized medical device' is very general. The manufacturer has specified that the material is intended for dental crowns and bridges; this indication should be explicitly stated in the manuscript for accuracy.
6. 'All specimens were stored under standard laboratory climate conditions (22.0 ± 1.0 °C and 50 ± 10% humidity) in a dark environment for 20 ± 4 hours.' 'All the samples were stored at 7.0 ± 1.0 °C in a dark environment until further analysis.' Is there a specific rationale for using these different storage temperatures?

Result

7. The order of the group names in Figure 1 should be aligned with that used in the tables to improve readability.

Discussion

8. 'For the two bone cements, the amount of activator can explain the amount of residual monomers. Palacos R+G likely contains less activator than DePuy CMW-3 [7]. This results in a final PMMA product with longer polymer chains and thus a

higher molecular weight. Due to this structure, it should be more difficult for residual monomers in Palacos R+G to release into the water, resulting in a slower release pattern and a lower cumulative concentration of leached monomers.' This explanation appears to be an assumption but is presented in an assertive manner. The authors should either revise the writing style to reflect the underlying assumptions more cautiously or provide strong references to support this statement.

9. The statement 'The actual monomer exposure for the patient in a clinical setting, where the medical device is placed into the patient immediately upon cooling down, is thus likely to be higher than the values reported in this study.' requires further qualification. Materials such as NextDent C&B MFH, which are indirect restorations, are typically not placed immediately after fabrication. The authors should more clearly distinguish between the clinical workflows of direct and indirect materials and relate these differences to the laboratory protocols used in the present study. This would improve clinical relevance and interpretation of the results.

10. 'The efficacy of the addition of antibiotics to bone cements is still debated.[31] The research community started to investigate alternative antibiotic-free bone cements, containing Cu- Zn-, Mg-, and Ag-nanoparticles.[32] However, little or no attention is paid to the PMMA-based matrix.' These sentences appear somewhat disconnected from the current discussion. It may be more appropriate to move this content to the Introduction, where it can better contribute to significance of the study.

11. A discussion of the study's limitations should also be included (as always). For example, the evaluated materials are used in different clinical settings and are in contact with different tissues, resulting in varying environmental conditions (e.g., pH, fluid dynamics). Consequently, the actual amount of monomer release in vivo is likely to differ from the in vitro findings.

Conclusion

12. It was stated 'It is therefore advisable to develop specific compositions of PMMA-based materials for different applications in the medical field. Especially for neurosurgical applications an optimized material may prove to be advantageous due to the proximity to the cerebral meninges and the brain.' The authors may also consider extending this point by briefly addressing not only material composition but maybe also manufacturing and processing methods, as these can significantly

influence polymerization behavior, residual monomer content, and ultimately biocompatibility.

Reviewer B:
Recommendation: Revisions Required

Questionnaire

Does the manuscript contain new and significant information to justify publication?*

Yes

Does the Abstract (Summary) clearly and accurately describe the content of the article?

No

Is the problem significant and concisely stated?

No

Are the methods or research design described comprehensively? Is the statistical analysis adequate?

No

Are the interpretations and conclusions justified by the results?

No

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Is adequate reference made to other work in the field?

Yes

Is the language acceptable?

Yes

Manuscript Structure

Length of article is:*

Adequate

Number of tables is:

Too Short

Number of figures is:

Too Short

Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable).

none

Rating

Interest*

Average

Quality

Below Average

Originality

Brazilian Dental Science

Average

Overall

Average

Recommendation

Majo revisions

Would you be willing to review a revision of this manuscript?

Yes

Comments

Comments to the Author

Leachables from patient-specific implants produced by 3D printing compared to conventional PMMA-based alternatives

This study aims to investigate the release patterns of residual monomers from different compositions and fabrication methods of four PMMA-based materials, where it was examined by reversed-phase high-performance liquid chromatography (HPLC), and was measured the residual monomer leached and release patterns. The topic is relevant and timely, particularly given the increasing use of additive manufacturing for patient-specific medical and dental devices.

However, several methodological limitations, issues in data interpretation, and inconsistencies between the study design and conclusions significantly limit the strength of the findings.

Major revisions

The title emphasizes patient-specific implants produced by 3D printing; however, the study evaluates bulk materials without clearly demonstrating their application as patient-specific implants.

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Abstract:

- The abstract does not clearly reflect the “patient-specific implants” aspect stated in the title. Please clarify whether actual implant geometries or only bulk materials were investigated
- The abstract should include sample sizes and statistical significance where relevant. Please include key indicators (e.g., p-values)
- I suggest focus on what matters for the study as mention the biological risk and the link to clinical safety or toxicity, instead mention information that is well know: “PMMA is formed through the polymerization...”

Introduction

- The introduction provides extensive background information; however, the specific research gap is not clearly articulated, is slightly unfocused, which is difficult see the aligned with the study’s core question.
- No clear statement why this comparison is needed now. The authors should explicitly define what is currently unknown, particularly regarding 3D-printed PMMA-based materials compared to conventional alternatives,
- The introduction should better reflect the focus on patient-specific and 3D-printed materials introduced in the title. Currently, this aspect is underdeveloped and only briefly mentioned. For example, it was focused broadly on acrylics, allergies, cosmetics and mentioned 3D printing only at the very end.
- The statements on cosmetic applications (e.g., manicure products) appears disproportionately detailed and may distract from the primary focus on dental and medical implant materials. Consider condensing this section.
- The explanation of allergic contact dermatitis could be clarified, as sensitization may occur both from unpolymerized monomers and residual monomers after curing:
“ACD is caused by this resin being applied on nails or teeth in an unpolymerized stage, after polymerization, so-called 'residual monomers' remain in the material”.
- Reference [7] does not correspond to the statement and appears to be incomplete. Please verify and correct the citation
- The study aim should be more specific and ideally include a hypothesis or expected outcome. Why 3D printing matters?

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Materials & Methods

- Table I should include appropriate references or manufacturer information for each material composition.
- Critical 3D printing parameters (e.g., layer thickness, exposure time, print orientation) are not reported and should be included, as they influence polymerization and monomer release.
- Clarify which post- polymerization unit was used and report the light wavelength, irradiance, and temperature conditions during post-polymerization. These parameters, along with the type of light-curing device, are important methodological details that should be clearly described.
- More detailed information on the polymerization procedures is required to ensure reproducibility.
- The additional post-processing steps applied to the 3D-printed material (ethanol cleaning and ultrasonic treatment) were not applied to the other materials.
- The sample size (n=3) is limited. Please justify the sample size.
- Statistical methods should be clearly described, including group comparisons and not only curve fitting approaches. Provide appropriate statistical comparisons.
- The rationale for specimen geometry should be justified with literature or relevant ISO standards.
- Storage conditions (time, temperature, and medium) should be clearly referenced and described.
- References for HPLC and LC-MS methodologies should be included.
- The statistical analysis section should specify the tests used and clarify how significance was determined.
- Provide images of specimens and 3D-printed models to improve methodological transparency.

Results

- The small sample size (n=3, and n=2 for some data points) raises concerns regarding the reliability of the results and the robustness of the kinetic modeling. Please justify the sample size and discuss this limitation.
- Statistical analysis is insufficiently described. The manuscript should specify the tests used and report p-values where claims of significance or non-significance are made (e.g. p-values, ANOVA / post hoc).

- The interpretation that NextDent C&B MFH does not release monomers beyond the first hour appears inconsistent with Table II and should be clarified.
- This statement: “µg/g monomer per product”, µg/g of What exactly?. Clarify whether values are expressed as µg of monomer per gram of material.
- The LC/MS analysis is described briefly and lacks sufficient detail. Please provide more information on the identified compounds and their relevance (e.g. identification, chemical names, quantification, etc)

Discussion

- Several statements are not sufficiently supported by data or literature and should be revised or properly referenced. For example:

“PMMA-based materials which can be dual-cured (chemical- and light-curing), can be a solution for reducing the amount of free monomers…”

“This is especially the case when the resin is in direct contact with metal or bone while polymerizing….”

“For dentures, craniofacial reconstructions, and other personalized medical devices, the amount of leached monomers can be reduced easily and effectively. Storing the material in water…”

“Palacos R+G likely contains less activator than DePuy CMW-3 [7]. This results in a final PMMA product with longer polymer chains and thus a higher molecular weight. Due to this structure, it should be more difficult for residual monomers in Palacos R+G to release…”

- Key methodological limitations (sample size, surface area control, and sampling protocol) should be more explicitly discussed.

Conclusion

- The conclusion regarding 3D-printable materials should be tempered, as only one such material was evaluated.

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- The statement to neurosurgical applications appears speculative and is not directly supported by the data presented in this study.

Minor revisions

- Several grammatical and typographical issues are present throughout the manuscript. For example, punctuation after citations should be corrected (e.g., “dentistry has been reported [5].” instead of inconsistent formatting).

- Terminology should be used consistently throughout the manuscript (e.g., (meth)acrylates, acrylics, PMMA). Define terms once and maintain consistency thereafter.
