PROSPERO Registration Form

1. * Review title.

Dimethylsulfoxide pre-treatment strategy to overcome hydrolysis of dentin hybrid layers: a systematic review and meta-analysis of laboratory studies

2. Original language title.

Not Applicable

3. * Anticipated or actual start date.

15 December 2020

4. * Anticipated completion date.

1 March 2021

5. * Stage of review at time of this submission.

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

6. * Named contact.

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9. * Organisational affiliation of the review.

Instituto Universitário Egas Moniz (IUEM), Caparica, Almada, Portugal

Organisation web address: <https://www.egasmoniz.com.pt/>

10.* Review team members and their organisational affiliations.

Dr. Isabel Alcoforado, Dr. António HS Delgado, Dr. Tomas Amorim, Dr. Paulo Mascarenhas, Prof. José João Mendes and Prof. Ana Mano Azul, all authors are affiliated to Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), IUEM, Caparica, Portugal

11.* Funding sources/sponsors.

This systematic review did not receive any funding and is not related to any sponsorship.

12.* Conflicts of interest.

All of the authors involved in the project declare that they have no known conflicts of interest.

13.* Review question.

How does the application of dimethylsulfoxide, as a pre-treatment dehydration strategy, affect the short and long-term bond strength to dentin?

14.* Searches.

Bibliographic databases used for the electronic systematic search will be PubMed/Medline, Scopus, Mednar and Web of Science. Grey literature will also be searched through the OpenGrey platform. Furthermore, reference lists of eligible primary studies will be hand searched. A publication period without restrictions, from inception until Jan 2021, was chosen,

with no restrictions in language. An individualized search strategy for each database will be devised. Initial search results will be extracted to an appropriate software and later screened by two reviewers, working independently.

Searches will also be repeated prior to the final analysis and write-up/submission.

15.* Condition or domain being studied.

Hydrolysis of hybrid layers and polymers, in dentin, due to aging and degradation of restorative interfaces.

16.* Participants/population.

Inclusion: Permanent sound human molars

Exclusion: Bovine or deciduous teeth

17.* Intervention(s), exposure(s).

Interventions included are adhesive restorations, in dentin, which feature a dehydration pre-treatment of dimethylsulfoxide (DMSO).

18.* Comparator(s)/control.

Adhesive restorations, in dentin, without any pre-treatment strategy (control).

19.* Types of study to be included.

This systematic review will only include in vitro laboratory research studies. Any other study type will be excluded, no clinical trials are expected to be retrieved from the search, as the topic is essentially pre-clinical.

20.* Main outcome(s).

Microtensile bond strength measured at an immediate time-point, usually 24 h, and after aging periods. The values are expressed in megapascal units (MPa).

21.* Additional outcome(s).

None

22.* Data extraction (selection and coding).

- Two reviewers (I.A. and A.H.S.D.), working independently, will screen the data extracted by carefully separating included from excluded. In the end, a meeting will take place, where both reviewers converge their results.
- Disagreements will be resolved by consulting a third reviewer (A.M.A.).
- The software used to extract and screen data will be Mendeley Desktop for Mac.
- Data extracted from each eligible primary study includes: authors and publication date, intervention, sample size, experimental groups, materials used, bond strength results (immediate and aged), bond strength test characteristics and main conclusions
- Two people will independently extract data (I.A. and A.H.S.D.) and disagreements between individual judgements will be resolved by consulting another review team member (A.M.A.).
- Data extracted will be recorded in a Microsoft Excel spreadsheet previously built, approved and tested by all the review team members.
- Where full-texts cannot be retrieved online, researchers or their teams will be contacted via researchgate.net or e-mail

23.* Risk of bias (quality) assessment.

Risk of bias measurement will be conducted by adapting pre-specified risk of bias tools for in vitro studies in dentistry, as no formal tool exists. The following criteria will be assessed: randomization of samples, sample size calculation, presence of a control group, materials used according to manufacturer's instructions (composites and adhesives), reproducibility of aging method, standardization of the outcome assessment, blinding of the outcome assessment and correct reporting of outcomes.

This will be carried out in duplicate by two reviewers, working independently (I.A. and A.H.S.D.). Discrepancies will be resolved through consensus by reaching out to one or two additional review team members.

Plots will be constructed the robvis online tool (<https://www.riskofbias.info/welcome/robvis-visualization-tool>).

24.* Strategy for data synthesis.

Primarily, in regard to qualitative analysis, one table synthesizing qualitative and quantitative data extracted, organised chronologically, and divided by the studies will be included in the manuscript. This will allow an easy comparison of interventions, materials, aging methods, results and conclusions. Quantitative data will thus show bond strength means and standard deviations per experimental group, which will be further used in the quantitative analysis. Depending on data organization, two tables dividing qualitative/quantitative data extracted may be considered.

As for quantitative analysis, the quantitative data spreadsheet will be used to combine all results. Statistical analysis will be conducted using appropriate R Packages. A significance level of 5% will be set for inferential statistics. Meta-analysis will be considered for more than 8 studies. Depending on the treatments included, this may or may not be a network meta-analysis. Immediate bond strength results will be assessed using standard mean difference (SMD) against the control group. The long-term bond strength (HL anti-aging effect) will be evaluated by adjusting the SMD measured at the follow-up period (up to 3 months or longer) to the initial SMD, and to the aging period in months. Thus, a differential SMD will be obtained. Heterogeneity will be evaluated using the I^2 index (above 50% will be considered significative). Tukey's HSD with Holm's adjustment may be used for post-hoc multicomparison test. Bond strength reduction in percentage may also be featured in the results.

25.* Analysis of subgroups or subsets.

- ♦ There will be two main groups of data: immediate microtensile bond results and aged microtensile bond results
- ♦ For aged microtensile bond strength results, groups of different aging periods may require specific analysis, or different aging methods
- ♦ If multiple different treatments are included a network meta-analysis analytic approach is expected

- Sensitivity analysis may be required to determine study inclusion after risk of bias assessment

26.* Type and method of review.

Type of review

Network meta-analysis **Yes**

Pre-clinical **Yes**

Health area of the review

Dental **Yes**

27. Language.

English

28.* Country.

Portugal

29. Dissemination plans.

Do you intend to publish the review on completion? **Yes**

30. Keywords.

systematic review; meta-analysis; hybrid layer; aging; hydrolysis; hybrid layer degradation; adhesive interface; hybrid layer breakdown;

31.* Current review status

The review is currently ongoing.