Failure rate of atraumatic restorative treatment using high-viscosity glass-ionomer cement compared to conventional amalgam restorative treatment in primary and permanent teeth: a systematic review of Chinese trials [protocol]

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1. Background

This protocol comprises an addition to an existing systematic review report that was first published in the *Clinical Oral Investigation* journal (online) in 2009 [1] and subsequently updated [2-4].

1.1. What is new?

This addition will provide a quantitative systematic review of the Chinese literature to the topic.

1.2. Description of the condition

Atraumatic restorative treatment (ART) failures may manifest as partial or complete material loss, caries related to restoration margins and material wear > 0.5 mm [5]. In contrast to other types of failures, the occurrence of caries on restoration margins has steadily decreased due to improvements in restorative materials and operator skills [6]. ART failures may occur in combination or lead to each other, e.g. material loss may promote occurrence of caries on restoration margins or partial defect may lead to complete loss [5]. Clinical factors related to ART failures are: material-, operator- and technique factors [5].

Material factors are directly related to material properties, such as its physical strength, flow rate and consistency. The flow rate of e.g. glass-ionomer cement (GIC) can be related to its adaptability to the cavity surface. Low adaptability may lead to partial defects on the restoration margin. Material flow rate can be related to small void formation (diameter > 0.1 mm, which also may be affected by type of material mix (capsule- or hand mix), which in turn may lead to higher material wear > 0.5 mm and material loss [7].

Operator factors relate to failures caused in areas of incorrect clinical indication, removal of carious general adherence to clinical protocols of restorative procedures [6]. Incorrect clinical indication of ART may lead to large restorations with constant exposure to masticatory forces that exceed material strength. In combination with material factors this may lead to material fracture and subsequent partial or complete material loss. Insufficient removal of carious bacterial infected tooth tissue on the cavity circumference may cause reduced material adhesion and higher residual bacterial count that may lead to further caries progression at the restoration margins in time [5]. In general, it has been shown that operator diligence regarding to the adherence to clinical protocols of restorative procedures, rather than operator experience are important for avoiding restoration failures [7].

Technique factors, such as hand-excavation and press-finger technique, are unique components of ART [6]. Hand excavation causes enamel fracturing and irregularities in dentine and this may manifest as challenges
to good marginal material adaptation [8]. Press finger technique causes a rough restoration surface with irregular margins that may support plaque and bacteria retention [9].

1.3. Description of the intervention

Atraumatic Restorative Treatment (ART) is a minimally invasive procedure that involves removing markedly softened carious enamel and dentine, using only hand instruments and then restoring the resulting cavity with an adhesive restorative material [10]. Although developed for use in the less industrialized parts of the world ART has now been accepted as part of the minimum intervention (MI) philosophy in developed countries [11-16]. At present the restorative material of choice for ART is high-viscosity glass ionomer cement (GIC) [17]. GIC is ideally suited to managing dental caries according to the principles of minimally invasive dentistry, as it can be applied in the very early stages of caries development or in the larger cavity. Additionally, it simplifies the restorative process and enables the dentine-pulp complex to react against the carious process [18].

1.4. How the intervention might work

During the ART procedure, the histological zone of caries-infected dentine is removed with hand instruments and, upon application of GIC, a seal is created between the GIC and the remaining enamel margin and caries-affected dentine lining the cavity surfaces. The glass ionomer adheres to this enamel and dentine primarily via calcium bonds to the mineral content of the tooth structure [19]. This adherence provides an adaptive seal and as the material slowly leaches fluoride ions into the adjacent tooth tissue, GICs are capable of halting or slowing the progression of carious lesions [20].

1.5. Specific definition of ART

For the purpose of this systematic review atraumatic restorative treatment (ART) was defined as a tooth restoration procedure including caries removal by hand instruments, using spoon excavators, and cavity restoration with a high-viscosity GIC [1]. This definition was based on the consideration that ART constitutes a synthesis of the concepts of:

(i) The retention of remineralisable affected dentine after caries removal by hand excavation [21];

(ii) The promotion of remineralisation of such affected dentine through the placement of a biomimetic restorative material [21].
Focus on hand excavation: Originally, ART was developed for use in underdeveloped regions [21], to address the need for inexpensive instrumentation. Other excavation techniques relying on specialized hand instruments in connection with a chemical agent [22] do not fulfill this criterion.

Focus on GIC: In regard to the material of choice for ART, only GICs have been shown to have a (hyper-) remineralising (biomimetic) effect on hard tooth tissue [23-25]. GIC can therefore be considered as the only material currently proven to be capable of effectively remineralising the retained affected dentine.

Focus on high-viscosity: A previous meta-analysis reported higher restoration longevity with high-viscosity GIC than with low-viscosity GIC for ART [26].

1.6. Why it is important to do this review?

The last update of this systematic review [4] was assumed to be at risk of language bias, as it did not include the search of major Chinese medical databases [27]. It has been suggested that the exclusion of non-English trials may have little effect on summary treatment effect estimates [28,29]. Initial findings of non-English trials during the last systematic review update appear to confirm such point [4]. However, any falsification / verification of assumed language bias risk can only be based on systematic review results that include all possible evidence sources.

2. Objective

The objective of this quantitative systematic review update is to assess the failure rate of ART, versus amalgam fillings, in the permanent or primary dentition in single- or multi-surface cavities, with follow-up periods from more than 1 to exceeding 3 years.

PICO question:

<table>
<thead>
<tr>
<th>Problem / patients:</th>
<th>All patients with carious cavities of any class in primary and permanent teeth.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>ART (as defined per section 1.5)</td>
</tr>
<tr>
<td>Comparison:</td>
<td>Amalgam restorations placed using conventional rotary instruments in tooth cavities of the same size, type of dentition and follow-up period</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Restoration failure (as per section 1.2)</td>
</tr>
</tbody>
</table>

This systematic review seeks to answer the PICO question as to whether, in patients with carious cavities of any class in primary and permanent teeth, ART restorations have a higher failure rate than amalgam restorations placed using conventional rotary instruments in tooth cavities of the same size, type of dentition and follow-up period?
3. Methods

3.1. Systematic literature search

The following electronic databases will be searched by two reviewers independently:
Chinese Biomedical Literature Database (CBM), Chinese Medical Current Content (CMCC), China National Knowledge Infrastructure (CNKI, formerly China Academic Journals), VIP Information and WanFang Data [30].

Strings of search terms will be constructed in simplified Chinese. In addition, the English search term “atraumatic restorative treatment” will be used for database search and reference lists of accepted trial reports and systematic reviews, as well as narrative reviews, if found of importance to the topic, checked for further suitable trials.

3.2. Criteria for trial consideration

3.2.1. Trial inclusion criteria

From the produced search results, trials will be selected based on the following criteria:

- Clinical trials (trials on animals, in-situ, in-vitro trials not included);
- Controlled trials: including control- and test group(s) (1-arm longitudinal trials not included);
- Trial focus relevant to PICO question;
- Prospective trials (retrospective trials not included)

3.2.2. Trial exclusion criteria

From the included trials, trials will be excluded based on the following criteria:

- No computable dichotomous or continuous data reported;
- Test and control groups not evaluated the same way;
- Any outcomes measured not in line as per section 3.2.5.;
- ART procedure not in line with adopted ART definition as per section 1.5.
- Control procedure not in line with description as per section 3.2.4.

3.2.3. Types of trial participants

Trial participants will include all patients of any age, gender or place of origin with carious cavities in either primary or permanent teeth.
3.2.4. Types of interventions

Test group: Atraumatic restorative treatment as described in sections 1.3. and 1.4. and as defined in section 1.5.

Control group(s): Restorative tooth treatment including the use of rotating instruments for caries removal and cavity preparation; placement of any material excluding any form of GIC as liner or base followed by tooth restoration using amalgam.

Amalgam has been used successfully as a universal posterior restorative material for over a century. Its operative advantages of being relatively simple to place, its intrinsic strength and the longevity of the final restoration has led to amalgam being considered the “gold standard” against which all new materials are measured for outcomes such as the effectiveness and durability of the restoration.

3.2.5. Type of outcome measure

Acceptable outcome measures will be the number of failures (n) from the total number of evaluated units (N) for dichotomous data and the statistical mean (X) of outcomes with standard deviation (SD) or standard error (SE) from the total number of evaluated units (N) for continuous data. Only primary outcomes with either the patient or the tooth as unit of analysis will be accepted. Only clinical failure reasons as described in section 1.2 are considered primary outcomes. The number of failures (n) / statistical mean (X) of outcomes will comprise of the sum of all failures types due to the reasons as per section 1.2.

3.3. Trial selection process

Titles and abstracts of identified articles from data sources (see section 3.1) will be scanned by two reviewers (NJ and CX) in duplication, for possible inclusion in line with the inclusion criteria. Articles with a suitable title but without listed abstract will be retrieved in full copy. All included articles will be judged separately by authors for possible exclusion with reason or for acceptance, in line with the exclusion criteria. Disagreements between authors will be solved through discussion and consensus.

3.4. Data collection from accepted trials

Two reviewers will extract data from accepted trials independently without being blinded to authors, institutions, journal name and trial results. Disagreements between authors concerning data extracted will be
solved through discussion and consensus. All extracted data will be entered in specifically designed data sheets in MS Excel. The following data will be extracted:

3.4.1. General important information

- Article first author; year of publication and full article reference;
- Place of trial;
- Age, gender of trial participants;
- Participant characteristics, inclusion/exclusion criteria;
- Study design;
- Per test- and control group:
  - Type of restorative material used;
  - Type of dentition;
  - Type of tooth restored;
  - Type of cavity;
  - Number of participants at beginning of trial (BSL);
  - Assessment method used;
  - Assessment criteria followed;
  - Number of evaluated units (N);
  - Number of failures (n) for dichotomous data;
  - Statistical mean (X) of outcomes with standard deviation (SD) or standard error (SE)* for continuous data;
  - Length of trial (follow-up period);
- For ART group: cavity conditioning before GIC placement (yes / no).

* Any SE will be converted into SD.

3.4.2. Verbatim quotes relevant to intervention integrity

- Article first author; year of publication and full article reference;
- Per test- and control group:
  - Patient adherence;
  - Patient exposure;
o Quality of delivery;
  o Patient responsiveness;
  o Any adverse outcomes.

3.4.3. Information concerning methodological trial quality

Any information provided in the trial report concerning: Article first author; year of publication and full article reference; reporting guidelines followed; sample size calculation used; ethical approval obtained.

3.4.4. Information concerning research gaps related to trial precision: Imprecision of results; Inconsistency of results; Lack of right information

- Article first author; year of publication and full article reference;
- Imprecision of results: e.g. Confidence intervals; sample size;
- Inconsistency of results: e.g. Direction of effect size;
- Lack of right information: e.g. Length of follow-up period;
- PICOS information (Population; Intervention; Comparison; Outcomes; Setting):
  o Population: Age; gender, ethnicity clinical characteristics;
  o Intervention / Comparison: name of treatment;
  o Outcome: measured clinical outcomes;
  o Setting: Type of clinical setting.

3.4.5. Verbatim quotes relevant to selection-, performance- and detection bias risk

- Article first author; year of publication and full article reference;
- Selection bias:
  o Random sequence generation;
  o Concealment of the sequence allocation;
- Performance bias:
  o Operator blinding;
  o Patient blinding;
- Detection bias:
  o Evaluator blinding.
3.5. Assessment of clinical and methodological heterogeneity

In order to fulfill criteria of clinical and methodological homogeneity datasets from trials should not differ in the following minimum set of characteristics: Outcome measure; control intervention; assessment method and length of follow-up period. If in-between-dataset differences are identified, heterogeneity is assumed.

3.6. Data analysis

3.6.1. Calculation of point estimates per dataset

A dichotomous dataset is defined as any extracted set of n / N for test- and control group. For each dataset the Risk ratio (RR) with 95% Confidence intervals (CI) and p-values will be computed. A continuous dataset is defined as any extracted set of N, X, SD or SE for test- and control group. For each dataset the Mean difference (MD) with 95% Confidence intervals (CI) and p-values will be computed.

In addition, the point estimate of each dichotomous dataset will be computed into an absolute measure (Risk difference – RD) with 95% Confidence intervals (CI) and p-values, as well as an illustrative comparative risk, i.e. number of failures out of 100, for both test- and control intervention will be generated with help of the Visual Rx - Statin Calculator by Cates [31,32].

Statistical significance is set at alpha 5%. For computation of all point estimates the statistical software programme RevMan 4.2 will be used.

3.6.2. Assessment and investigation of statistical heterogeneity

The $I^2$ – test with 95% CI will be used to establish, whether any statistical heterogeneity exists between datasets that were assumed to be clinically and methodologically homogenous (as per section 3.5). Thresholds for $I^2$ point estimates (in %) and its upper confidence values will be used in order to interpret the test results [33]:

- 0-40% = might not be important;
- 30-60% = may represent moderate heterogeneity;
- 50-90% = may represent substantial heterogeneity;
- 75-100% = considerable heterogeneity.

Dataset outliers as potential sources for heterogeneity between datasets will be identified using Galbraith plot and potential effect modifiers as reasons for heterogeneity explored using regression analysis.

For computation of all $I^2$ point estimates with 95% CI and generation of Galbraith plots the software programme MIX 1.7 will be used [34]. Biostat 2009 statistical software will be used for regression analysis.
3.6.3. **Data synthesis (meta-analysis)**

Identified (clinically/methodologically/statistically) homogenous datasets will be pooled using fixed-effects model meta-analysis with RevMan 4.2. A pooled Risk ratio (RR) and a Weighted mean difference (WMD) with 95% CI and p-values for dichotomous and continuous data, respectively, will be computed.

In addition, the point estimate of pooled dichotomous data will be computed into an absolute measure (Risk difference – RD) with 95% Confidence intervals (CI) and p-values, as well as an illustrative comparative risk, i.e. number of failures out of 100, for both test- and control intervention will be generated with help of the Visual Rx - Statin Calculator by Cates [31,32]. Statistical significance is set at alpha 5%.

Should the number of homogenous datasets be small, i.e. < 5, a random-effects model meta-analysis will be used, instead. Should events be rare (failure rate < 1%), trials show moderate effect sizes and effect sizes are similar in both groups then Peto Odds ratio (OR) meta-analysis will be used.

3.6.3. **Sensitivity analysis per dataset and meta-analysis result**

In order to test the robustness of dataset and meta-analyses results to the type of analysis chosen, all results will be recomputed:

- Dichotomous dataset results: as Odds ratios (OR);
- Dichotomous meta-analysis results: as Odds ratios (OR) using both fixed- and random-effects models;
  - as Risk ratios (RR) using either fixed- or random-effects models (depending on which type of model was used as main method);
- Continuous meta-analysis results: using either fixed- or random-effects models (depending on which type of model was used as main method).
3.7. Assessment of selection-, detection- and performance bias risk

Selection-, detection- and performance bias risk will be assessed using the following set of criteria:

### 3.7.1. Assessment criteria for selection bias risk

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate randomisation method reported¹</td>
<td></td>
</tr>
<tr>
<td>Prevent its direct observation²</td>
<td>N</td>
</tr>
<tr>
<td>Prevent its correct prediction³</td>
<td>N</td>
</tr>
<tr>
<td>Evidence is given in some form of statistical test result that indicates the allocated random sequence was adhered to throughout the trial⁴</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>NA</th>
<th>A</th>
</tr>
</thead>
</table>

¹ The following methods are considered as inadequate: cluster randomisation, fixed block randomisation with block size 2, minimization, alternation, randomisation of teeth, use of date of birth or patient record number, “quasi”-randomisation, split-mouth, generation of the random sequence before patient recruitment.

² Central randomisation or sequence allocation by other than the operator(s) who apply the allocated intervention and who informs the operator(s) which (test- or control) intervention has been allocated to a particular patient only at moment of start of intervention (e.g. by phone), are considered to be adequate.

³ Use of the Maximal randomisation procedure [35] is considered to be adequate.

¹³ Fulfilment of these criteria indicates adequate attempt of effective randomisation but not that the attempt was indeed successful.

⁴ Any statistical test that includes the use of the Reverse Propensity Score (RPS) [35] is considered to be adequate. Fulfilment of this criterion indicates that the attempt of effective randomisation was indeed successful, i.e. sufficient proof of low selection bias risk.
In addition, trial reports will be checked for any differences in baseline covariates between groups using the following criteria:

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
<th>Impact on bias risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Baseline data collected before randomisation and reported for both treatment groups / Data shows no significant differences between both groups</td>
<td>Evidence is given that randomisation has lead to equal groups in the selected covariates*</td>
</tr>
<tr>
<td>B</td>
<td>Baseline data collected before randomisation and reported for both treatment groups / Data shows significant differences between both groups but has been statistically adjusted appropriately</td>
<td>Differences have been adjusted, thus the influence of possible selection bias appears to be reduced</td>
</tr>
<tr>
<td>C</td>
<td>Baseline data collected before randomisation and reported for both treatment groups / Data shows significant differences between both groups without being statistically adjusted</td>
<td>Reported differences may be due to ineffective randomisation, thus indicate risk of selection bias</td>
</tr>
<tr>
<td>0</td>
<td>Trial does not comply with criteria A - C</td>
<td>No evidence is given whether randomisation has indeed lead to equal groups with differences beyond chance, thus differences may exists indicating selection bias</td>
</tr>
</tbody>
</table>

* However, difference between other, not measured covariates may still exists (thus no proof for lack of bias risk)

### 3.7.2. Assessment criteria for detection- and performance bias risk

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate method of masking/blinding of patients and clinicians and evaluators reported¹</td>
<td>0 C B A</td>
</tr>
<tr>
<td>No reasons for doubt discerned from the report text that masking/blinding was not successful</td>
<td>N N Y Y</td>
</tr>
<tr>
<td>Evidence is given in some form of applied test* result that shows the masking/blinding was successful throughout the trial²</td>
<td>N N N Y</td>
</tr>
</tbody>
</table>

**Conclusion**

| NA | A |

¹ Fulfilment of this criterion indicates adequate attempt of effective masking/blinding of effective masking/blinding but not that the attempt was indeed successful.

² Fulfilment of this criterion indicates that the attempt of effective masking/blinding was indeed successful, i.e. proof of lack of detection/performance bias

* E.g. Application of a questionnaire during the trial that assesses believes as to which test- or control intervention was given/received to/by a particular trial participant, followed by statistical comparison of the questionnaire results with the true allocation sequence. A non-significant result (alpha set at 5%) should sufficiently indicate successful attempt of masking/blinding and subsequent low detection- and performance bias risk.
3.8. Assessment of attrition bias risk

In order to assess attrition bias risk a worst- and best-case scenario will be assumed. These will be calculated for both dichotomous and continuous data, if the number of lost trial participants per intervention group is reported in the trial reports. The results may then be compared to the intervention outcomes computed for participants available to follow-up and on this basis conclusions concerning attrition bias risk been drawn: i.e. high risk of attrition bias will be assumed if the computed outcomes between worst- and best-case scenario and the intervention outcomes computed for participants available to follow-up differ significantly. Where the number of lost trial participants per intervention group is not reported a high risk of attrition bias will be assumed by default.

3.8.1. Dichotomous data

The worst-case scenario for dichotomous data will be calculated by adding the number of lost-to-follow-up participants in the test group to the failures of that group and adding the number of lost-to-follow-up participants in the control group to the successes of that group. The best-case scenario will be calculated by adding the number of lost-to-follow-up participants in the test group to the successes of that group and adding the number of lost-to-follow-up participants in the control group to the failures of that group.

3.8.2. Continuous data

The worst-case scenario will be calculated for continuous data by adding the standard deviation (SD) value to the mean value (X) of the test group (assuming that the higher the mean value the worse the outcome*). This adjusted mean value will be assumed to be the statistical mean for the number of participants (N) lost-to-follow-up in this group. The SD for these lost trial participants will be zero because all lost participants are assumed to have the same extreme outcome value and the total number of participants will be the number of participants lost-to-follow-up. In the control group, the SD value will be subtracted from the mean value of the control group. Like for the test group, this adjusted mean value will be assumed to be the statistical mean for the number of participants lost-to-follow-up in the control group. The SD for this group will be zero and the total number of participants will be the number of participants lost to follow-up.

The best-case scenario is calculated by subtracting the standard deviation value (SD) from the mean value of the test group (assuming that the lower the mean value the better the outcome*). This adjusted mean-value will be the statistical mean for the number of participants lost-to-follow-up in this group. The SD for this
group will also be zero and the total number of participants will be the number of participants lost-to-follow-up. In the control group, the SD value will be added to the mean value of the control group. Like above: for the test group, this adjusted mean value will be assumed to be the statistical mean for the number of participants lost-to-follow-up in this group. The SD for this group will be zero and the total number of participants will be the number of participants lost-to-follow-up.

Once the number of participants (N), mean value (X) and standard deviation (SD) for the lost-to-follow-up participants are so established per group, these will be pooled with the number of participants (N), mean value (X) and standard deviation (SD) for test- and control group that were available to follow-up. The combined group values are then re-computed for both worst- and best-case scenario and compared with the results for participants available to follow-up.

* If assuming that the lower the mean value, the worse the outcome then SD needs to be subtracted and added for the worst- and best-case scenario, respectively.

3.9. Assessment of publication bias risk

The $I^2$ point-estimate with 95% CI of all extracted datasets will be computed. High statistical in-between-datasets heterogeneity as per thresholds (see section 3.6.2) will be taken under consideration when assessing publication bias risk by graphical and statistical methods.

Graphically a funnel plot will be generated, using a fixed-effects model with the Risk ratio (RR) as effect size estimate from all extracted dichotomous datasets and the MD for continuous datasets and examined for potential scatter asymmetry. The graphical findings will be statistically verified using Egger’s regression [36]. Statistical significance is set at alpha 5%.

The $I^2$ point-estimate with 95% CI, funnel plot generation and Egger’s regression analysis will be computed using MIX 1.7 statistical software [34]. Both, funnel plot and Egger’s regression will not be conducted if the number of extracted datasets is < 10.

3.10. Assessment of reporting bias risk

The method and results sections of each accepted trial report will be compared for potential discrepancies.
5. Reporting of results

5.1. Summary of results table

The final report will contain a summary of results table including the following information:

- Title/Header including PICO information;
- Outcomes per dataset and group:
  - Illustrative comparative risk (number of failures in 100);
  - Relative effect (in RR with 95% CI and p-value for dichotomous data and MD with 95% CI and p-value for continuous data);
  - Absolute effect (in RD with 95% CI and p-value for dichotomous data).

5.2. Anticipated start date

01 August 2012

5.3. Anticipates completion date

01 August 2013

5.4. Language editing of final report

The final report will be produced in English and handed for correction of any shortcomings to a professional language editor.

5.5. External expert input

Before publication, the final edited version of the report will be distributed to members of the external SYSTEM Advisory Group of Experts (SAGE) for review and comments.

5.6. Dissemination plans

In order to avoid months of dissemination delay and subsequent content redundancy of the systematic review update (e.g. due to the emerging of further new evidence to the topic), the final version of the full-length report will be published immediately after completion in the *Journal of Minimum Intervention in Dentistry - JMID* (www.jmid.org) of the SYSTEM Initiative [37].
After JMID publication, the results of the report will be combined with existing evidence [4] and an overview of reviews in line with Cochrane recommendation [38] prepared for submission in a peer-reviewed journal in English language. In addition, a systematic review summary in simplified Chinese will be prepared for publication in a suitable Chinese journal.

6. Funding / sponsors

No funding provided.

7. Conflict of interest

None known.

8. References


