

# **Do laboratory results concerning high-viscosity glass-ionomers versus amalgam for tooth restorations indicate similar effect direction and magnitude than that of clinical controlled trials? - A meta-epidemiological study [protocol]**

Steffen Mickenautsch<sup>a</sup>, Veerasamy Yengopal<sup>a</sup>

<sup>a</sup>SYSTEM Initiative / Department of Community Dentistry, Faculty of Health Sciences, University of the Witwatersrand, 7 York Rd., Parktown/Johannesburg 2193, South Africa, e-mail: [neem@global.co.za](mailto:neem@global.co.za).

## **ABSTRACT**

A large percentage of evidence concerning dental interventions is based on laboratory research. The aim of this meta-epidemiological study is to establish whether valid clinical inferences and recommendations can be made on basis of the current laboratory evidence concerning high-viscosity glass-ionomer cement (HVGICs) versus amalgam as materials for placing restorations in permanent posterior teeth for daily dental practice. HVGICs may offer a suitable clinical alternative to amalgam for placing permanent restorations in load-bearing posterior teeth. If such statement is true then invalid negative clinical inferences from poor in-vitro properties of the material may lead to erroneous rejection of HVGICs in clinical practice. However, if negative clinical inferences from in-vitro evidence against the material are valid then the rejection of HVGICs will be justified and consequently protects patients from unwarranted restoration failures, treatment expenses and discomfort. This meta-epidemiological study may assist in establishing the current evidence in regard to the question, whether valid clinical inferences and recommendations can be made on basis of the current laboratory evidence to this topic.

**Keywords:** Meta-epidemiological study protocol; amalgam; glass-ionomer; laboratory evidence; clinical evidence.

## **1. BACKGROUND**

A large percentage of evidence concerning dental interventions is based on laboratory research. A simple PubMed search (27 August 2014) of the dental literature published between 2009 - 2014, using the broad MeSH terms “Dental Amalgam” and “Glass Ionomer Cements” reveals a 2-3, as well as an over 7 times higher number of listed citations of laboratory (including in-vitro and animal based in-vivo) studies than of prospective clinical studies with control groups (including randomised controlled trials, non-randomised controlled trials, split-mouth trials and prospective 2-arm Cohort studies), respectively. The apparent wealth of laboratory evidence is sometimes used as basis for clinical inference and recommendations for daily dental practice. For example: In 2012, Ilie et al. recommended that selection of a suitable restorative material for clinical use in especially stress-bearing areas should be done with respect to in-vitro measured material properties, particularly in relation to its fracture toughness (KIC) [1]. Vichi et al. (2013) presumed that low in-vitro microleakage measurements for restorative materials translate into an adequate marginal seal when such materials are used for placing tooth restorations in the clinic [2], and based on laboratory shear bond strength (SBS) measurements, Ilie et al. (2014) suggested possible clinical advantages of using flowable bulk-fill resin composites for restoring deep, narrow cavities, with difficult access angles, and high-viscosity compounds for easier and faster restoration of larger tooth cavities [3].

In contrast, studies comparing the findings of both laboratory and clinical trials found only little correlation between the two. Papagiannoulis et al. (2002) established a lack of any correlation between in-vivo and in-vitro models in terms of artificial caries experiments and suggested that these may have only negligible clinical relevance in predicting the in-vivo effect [4]. Purk et al. (2004) established that the bonding of resin-based composite to teeth under in-vivo conditions yielded much weaker microtensile bond strengths than did bonding under in-vitro conditions and that bonding to dentin at the gingival wall under in-vivo conditions is weaker than that reported in-vitro studies [5]. In his review of dental literature, Heintze (2007) established that the quantitative marginal analysis of Class V fillings in the laboratory was

unable to predict the performance of the same materials in-vivo [6] and Heintze and Cavalleri (2010) found that retention loss of Class V tooth restorations in non-retentive cavities could not be simulated in the laboratory, even after prolonged water storage and mechanical loading and thus could not reflect the clinical findings [7]. In contrast, van Meerbeek et al. (2010) found some indications for correlation of laboratory bond strength with clinical retention rates of Class-V restorations [8]. However, the predictive strength of the laboratory findings was only expressed as linear correlation and not in line with full Prentice requirements [9], and appeared to be weak and of borderline significance ( $r = 0.5811$ ,  $p = 0.0475$ ), only. In addition, Heintze and Zimmerli (2011) stated that in-vitro dye penetration measurements have no clinical relevance for the clinical performance of restorative materials, that marginal gap analysis in the laboratory is clinically relevant only to a limited extent and that bond strength tests are useful as screening tests, only [10].

Traditionally, glass ionomer cements are considered as unsuitable for clinical use as a permanent filling material in the posterior dentition due to in-vitro measured poor mechanical properties [1,11]. Specifically, in-vitro measured low material strength and wear resistance have been stated as reasons why glass-ionomers cannot rival amalgam as truly universal posterior restorative material [12].

However, based on the demonstrated general lack of any observed correlations between laboratory and clinical evidence, particularly related to tooth restorations [6,7,10] the in-vitro measured poor mechanical properties of glass ionomers, including high-viscosity glass-ionomers (HVGICs), may not translate into poor clinical results.

Against this general background, the aim of this meta-epidemiological study is to establish whether valid clinical inferences and recommendations can be made on basis of the current laboratory evidence concerning HVGICs versus amalgam as materials for placing restorations in permanent posterior teeth for daily dental practice.

### *1.1. What is new?*

To our knowledge, this will be the first meta-epidemiological study with the purpose to test whether the results from current laboratory trials concerning HVGICs versus amalgam indicate similar effect direction and similar effect magnitude as results from current clinical controlled trials concerning HVGICs versus amalgam restorations placed in permanent posterior teeth.

### *1.2. Description of the condition*

Failures of HVGIC may manifest as partial or complete material loss, caries related to restoration margins and material wear  $> 0.5$  mm. Failures may occur in combination or lead to each other: material loss may promote occurrence of caries on restoration margins or a partial defect may lead to complete loss. Clinical factors related to failures are: material-, operator- and technique factors [13].

Material factors are directly related to the properties of materials - such as physical strength, flow rate and consistency. The flow rate of glass-ionomer cement, for example, may be related to its adaptability to the cavity surface and low adaptability may lead to partial defects on the restoration margin. Material flow rates may be related to small void formations (diameter  $> 0.1$  mm), which may also be affected by the type of material mix (capsule- or hand-mix), which in turn may lead to higher material wear  $> 0.5$  mm and material loss [14]. In addition, low physical strength may lead to material fracture and subsequent partial or complete material loss.

### *1.3. Description of the intervention*

The definition of HVGICs according to laboratory/material characteristics such as powder/liquid ratio or compressive strength may prove to be difficult due to conflicting and inconclusive in-vitro evidence [15]. Instead, the distinction between low and high-viscosity conventional GICs, on a clinical rather than chemical basis, seems to be empirically supported: When used for tooth restorations, HVGICs appear distinct from other (low) viscosity GICs (including Cermets) in their comparative better survival rate to that of conventional amalgam restorations [16]. Therefore, it may be reasonable to assume that GICs labeled as 'high-viscosity', i.e. Fuji IX and Ketac Molar [16], share other non-disclosed characteristics, which make them clinically distinct to GICs labeled as 'low-viscosity'.

#### *1.4. How the intervention might work*

Upon placement of HVGIC into the tooth cavity, a seal is created between the HVGIC and the cavity surfaces. The glass ionomer adheres primarily via calcium bonds to the mineral content of the tooth structure [17]. This adherence provides an adaptive seal and as the material may slowly leach fluoride ions into the adjacent tooth tissue, thus HVGICs appear capable of halting or slowing the progression of carious lesions [18].

#### *1.5. Why it is important to do this review?*

HVGICs may offer a suitable clinical alternative to amalgam for placing permanent restorations in load-bearing posterior teeth. If such statement is true then invalid negative clinical inferences from poor in-vitro properties of the material may lead to erroneous rejection of HVGICs in clinical practice. However, if negative clinical inferences from in-vitro evidence against the material are valid then the rejection of HVGICs will be justified and consequently protects patients from unwarranted restoration failures, treatment expenses and discomfort. This meta-epidemiological study may assist in establishing the current evidence in regard to the question, whether valid clinical inferences and recommendations can be made on basis of the current laboratory evidence to this topic.

## **2. OBJECTIVE**

The aim of this meta-epidemiological study is to establish whether laboratory trial results can be indicators for clinical efficacy of HVGIC tooth restorations. Therefore, the objective of this study is to test the two null-hypotheses:

H01: The results from laboratory trials concerning HVGICs versus amalgam indicate similar effect direction as results from clinical controlled trials concerning HVGICs versus amalgam restorations placed in permanent posterior teeth.

H02: The results from laboratory trials concerning HVGICs versus amalgam indicate similar effect magnitude as results from clinical controlled trials concerning HVGICs versus amalgam restorations placed in permanent posterior teeth.

The scope of this study excludes:

- (i) Validation of treatment efficacy for either type of restorative material from either laboratory or clinical evidence;
- (ii) Clinical validation of specific laboratory outcome measures;
- (iii) Investigation of laboratory or clinical effect estimates for clinical guidance or recommendation, including the investigation of precision and validity of effect estimates on basis of trial methodology.

## **3. METHODS**

### *3.1. Systematic literature search*

Two reviewers will search the following electronic databases independently:

[1] General international databases:

- CENTRAL accessed via Cochrane Library;
- MEDLINE accessed via PubMed;

[2] Open access sources:

- Biomed Central;
- Database of Open Access Journals (DOAJ);

[3] Regional databases:

- IndMed;

[4] Grey-Literature sources:

- OpenSIGLE;
- Google Scholar.

Suitable strings of search terms will be constructed in English for database search. In addition to the search of databases, reference lists of accepted trial reports and systematic reviews, as well as narrative reviews, if found of importance to the topic, will be checked for further suitable trials.

### *3.2. Criteria for trial consideration*

#### 3.2.1. Trial inclusion criteria

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

- Articles published in English;
- Full reports of prospective clinical controlled (including randomised control trials and non- randomised control trials) and laboratory trials (including: in-vitro; in-vivo on animal tissues);
- Head-to-head comparison of high-viscosity glass-ionomers (HVGIC) versus amalgam;
- Longest follow-up period reported per trial;
- Relevance to tooth restorations in posterior teeth of the permanent dentition;
- Computable data reported:
  - o Continuous data per intervention group: N = Number of evaluated units;  $\bar{x}$  = Mean value of measured outcome; SD = Standard deviation or SE = Standard error.
  - o Dichotomous data per intervention group: N = Number of evaluated units; n = Number of failed interventions.

#### 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;
- Low-viscosity chemically cured, metal-reinforced, resin-modified or light-cured glass-ionomers as test intervention;
- Reports and/or results of earlier follow-up periods than reported elsewhere;
- Clinical trials investigating tunnel or sandwich restorations;
- Clinical trials investigating restorations placed in primary and/or anterior teeth;
- Dichotomous datasets with zero number of failed interventions ( $n = 0$ ) in both test and control groups.

#### 3.2.3. Types of trial participants in clinical trials

Trial participants will include all patients of any age, gender or place of origin with restorable cavities in permanent posterior teeth.

#### 3.2.4. Types of measured outcome

In clinical trials: The measured outcome will be the number of teeth with restoration failures ( $n$  = Number of failures) from the total number of evaluated teeth ( $N$ ) 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.

In laboratory trials: Any type of investigated comparative outcome expressed as the statistical mean ( $X$ ) of outcomes with standard deviation (SD) or standard error (SE) from the total number of evaluated units ( $N$ ).

### *3.3. Trial selection process*

Titles and abstracts of identified citations from data sources will be scanned by two reviewers 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:

- Article first author; year of publication and full article reference;
- Per test- and control group:
  - o Product name of material used;
  - o Number of subjects/units at beginning of trial (BSL);
  - o Number of evaluated units at end of follow-up period ( $N$ );
  - o Number of failures ( $n$ ) for dichotomous data;
  - o Statistical mean ( $X$ ) of outcomes with standard deviation (SD) or standard error (SE)\* for continuous data;
  - o Length of trial (follow-up period);
- Verbatim conclusions and recommendations for clinical practice.

\* Any SE will be converted into SD.

### *3.5. Data analysis*

#### 3.5.1. 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 Odds ratio (OR) 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 Standardised Mean difference (SMD) [19] with 95% Confidence intervals (CI) and p-values will be computed.

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

#### 3.5.2. Analysis of direction of results

In order to test the null-hypotheses ( $H_0$ ) that the results from laboratory trials and clinical controlled trials indicate similar effect directions, fixed meta-analysis will be conducted for clinical and laboratory data, separately. All extracted

datasets will be pooled using fixed-effects model meta-analysis with RevMan 4.2 statistical software. A pooled Odds ratio (OR) and a pooled Standardised Mean difference (SMD) with 95% CI and p – values for dichotomous and continuous data, respectively, will be computed. Statistical significance is set at alpha 5%.

Three types of effect direction are considered:

- (i) Statistically significant differences ( $p < 0.05$ ) between HVGIC and amalgam (in favor of amalgam);
- (ii) Statistically significant differences ( $p < 0.05$ ) between HVGIC and amalgam (in favor of HVGIC);
- (iii) Lack of statistically significant differences ( $p > 0.05$ ) between HVGIC and amalgam.

Rejection of the null-hypothesis will be conditioned on the observation that the pooled effect estimates of both, clinical and laboratory trials will have different effect direction (i) – (iii).

Because the objective of this study is to investigate whether results from, both, clinical and laboratory trials generally point in the same effect direction and not to establish the actual clinical meaning of the pooled effect estimates, aspects of in-between-dataset heterogeneity will not be considered.

### 3.5.3. Analysis of magnitude of results

In order to test the null-hypotheses (H02) that the results from laboratory trials and clinical controlled trials have similar effect magnitude the following analysis steps will be undertaken:

- (i) Conversion of Odds ratios (OR) with 95% Confidence intervals (CI) from clinical dichotomous data into SMD with 95% CI using the method by Hasselblad and Hedges [19,20]:
  - a. Natural log transformation of OR values and Upper/Lower confidence interval limits;
  - b. Division of ln-values by 1.81
- (ii) Statistical comparison of SMD point estimates from clinical and laboratory trials;
- (iii) Statistical comparison of SMD conservative point estimates, defined as Upper or Lower 95% Confidence levels closest to zero value, from clinical and laboratory trials.

The data from both, clinical and laboratory trials are considered to be independent from each other and the variances of both data types expected to be unequal. In addition, past systematic reviews of clinical trials in dentistry have shown only a limited number of head-to-head comparisons for posterior HVGIC and amalgam restorations in the permanent dentition [21] and thus a limited number of datasets ( $< 30$ ) is expected to be available for analysis. Therefore, the Mann-Whitney U test will be chosen as appropriate tool for statistical comparison within the context of this study. For computation the statistical software Biostat 2009 will be used.

Statistical significance is set at alpha 5%. Rejection of the null-hypothesis will be conditioned on the observation that the difference between the SMD point estimates from clinical and laboratory trials, is statistically significant ( $p < 0.05$ ) for both statistical comparisons.

### *3.6. Assessment of publication bias risk*

The  $I^2$  point-estimate with 95% CI of all extracted datasets will be computed for clinical and laboratory data, separately. Thresholds for  $I^2$  point estimates (in %) and its upper confidence values will be used in order to interpret the  $I^2$  test results [22]:

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

High statistical in-between-datasets heterogeneity as per thresholds will be taken under consideration when assessing publication bias risk by graphical and statistical methods.

Graphically a funnel plot will be generated for clinical and laboratory data, separately, 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 [23]. 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 [24]. Both, funnel plot and Egger's regression will not be conducted if the number of extracted datasets is < 10 per data type.

#### **4. REPORTING OF RESULTS**

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

- The pooled effect estimates with 95% CI and p-values for both clinical and laboratory data represented in two separate forest-plots;
- A table of converted Odds ratios and 95% CI into SMD with Upper and Lower Confidence levels for clinical data;
- The median SMD values with 25% and 75% percentile range for effect estimates and conservative effect estimates per clinical and laboratory data;
- A scatter plot presenting all SMD values for both effect estimates and conservative effect estimates per clinical and laboratory data;
- Mann-Whitney U test results for effect estimates and conservative effect estimates comparison.

##### *4.2. Anticipated start date*

01 September 2014

##### *4.3. Anticipates completion date*

01 January 2015

##### *4.4. 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.

##### *4.5. Dissemination plans*

The final report of this systematic review will be submitted to an appropriate peer-reviewed, PubMed/Medline listed journal.

#### **5. FUNDING / SPONSORS**

No funding provided.

#### **6. CONFLICT OF INTEREST**

One of the authors (SM) has been actively involved in the promotion; teaching and research of HVGIC based tooth restorations in the past (from 1998 – 2007).

## REFERENCES

- [1] Ilie N, Hickel R, Valceanu AS, Huth KC. Fracture toughness of dental restorative materials. *Clin Oral Investig* 2012; 16: 489-98.
- [2] Vichi A, Margvelashvili M, Goracci C, Papacchini F, Ferrari M. Bonding and sealing ability of a new self-adhering flowable composite resin in class I restorations. *Clin Oral Investig* 2013; 17: 1497-506.
- [3] Ilie N, Schöner C, Bücher K, Hickel R. An in-vitro assessment of the shear bond strength of bulk-fill resin composites to permanent and deciduous teeth. *J Dent* 2014; 42: 850-5.
- [4] Papagiannoulis L, Kakaboura A, Eliades G. In vivo vs in vitro anticariogenic behavior of glass-ionomer and resin composite restorative materials. *Dent Mater* 2002; 18: 561-9.
- [5] Purk JH, Dusevich V, Glaros A, Spencer P, Eick JD. In vivo versus in vitro microtensile bond strength of axial versus gingival cavity preparation walls in Class II resin-based composite restorations. *J Am Dent Assoc* 2004; 135: 185-93.
- [6] Heintze SD. Systematic reviews: I. The correlation between laboratory tests on marginal quality and bond strength. II. The correlation between marginal quality and clinical outcome. *J Adhes Dent* 2007; 9 Suppl 1: 77-106. Erratum in: *J Adhes Dent* 2007; 9: 546.
- [7] Heintze SD, Cavalleri A. Retention loss of class v restorations after artificial aging. *J Adhes Dent* 2010; 12: 443-9.
- [8] Van Meerbeek B, Peumans M, Poitevin A, Mine A, Van Ende A, Neves A, De Munck J. Relationship between bond-strength tests and clinical outcomes. *Dent Mater* 2010; 26: e100-21.
- [9] Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med* 1989; 8: 431-40.
- [10] Heintze SD, Zimmerli B. Relevance of in vitro tests of adhesive and composite dental materials. A review in 3 parts. Part 3: in vitro tests of adhesive systems. *Schweiz Monatsschr Zahnmed* 2011; 121: 1024-40.
- [11] Ilie N, Hickel R. Mechanical behavior of glass ionomer cements as a function of loading condition and mixing procedure. *Dent Mater J* 2007; 26: 526-33.
- [12] Naasan MA, Watson TF. Conventional glass ionomers as posterior restorations. A status report for the American Journal of Dentistry. *Am J Dent* 1998; 11: 36-45.
- [13] Mickenautsch S, Grossman E. Atraumatic Restorative Treatment (ART): factors affecting success. *J Appl Oral Sci* 2006; 14 Suppl: 34-6.
- [14] Czarnecka B. The use of ART technique in modern dental practice: A personal view. *J Dent* 2006; 34: 620.
- [15] Mickenautsch S, Yengopal V. Direct contra naïve-indirect comparison of clinical failure rates between high-viscosity GIC and conventional amalgam restorations: an empirical study. *PLoS One* 2013; 8: e78397.
- [16] Frencken JE, Van 't Hof MA, Van Amerongen WE, Holmgren CJ. Effectiveness of single-surface ART restorations in the permanent dentition: a meta-analysis. *J Dent Res* 2004; 83: 120-23.
- [17] Yoshida Y, Van Meerbeek B, Nakayama Y, Snauwaert J, Hellemans L, Lambrechts P, Vanherle G, Wakasa K. Evidence of Chemical Bonding at Biomaterial-Hard Tissue Interfaces. *J Dent Res* 2000; 79: 709-71.



- [18] Mickenautsch S, Yengopal V. Absence of carious lesions at margins of glass-ionomer cement and amalgam restorations: An update of systematic review evidence. *BMC Res Notes* 2011; 4: 58.
- [19] da Costa BR, Rutjes AW, Johnston BC, Reichenbach S, Nüesch E, Tonia T, Gemperli A, Guyatt GH, Jüni P. Methods to convert continuous outcomes into odds ratios of treatment response and numbers needed to treat: meta-epidemiological study. *Int J Epidemiol* 2012; 41: 1445-59.
- [20] Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med* 2000; 19: 3127-31.
- [21] Mickenautsch S, Yengopal V. 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 update - III. *J Minim Interv Dent* 2012; 5: 273-331.
- [22] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] – Section 9.5.2. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org) (Accessed: 03.01.2012).
- [23] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-34.
- [24] Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. *BMC Med Res Methodol* 2006; 6: 50.