PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of conventional treatment with composite resin and atraumatic restorative treatment in posterior primary teeth: study protocol for a randomized controlled trial
AUTHORS	Ladewig, Nathalia; Saihara, Cintia; Yoshioka, Laysa; Olegário, Isabel; Floriano, Isabela; Tedesco, Tamara; Mendes, Fausto; Braga, Mariana; Raggio, Daniela

VERSION 1 - REVIEW

REVIEWER	Elham Kateeb Al-Quds University, Jerusalem, Palestine
REVIEW RETURNED	15-Jan-2017

GENERAL COMMENTS	The protocol is well written and well designed. My only three comments are: 1. I would prefer if they used cross-over design where they can compare both type of restorations at the same child to minimize variability. They can do it at different point of time so they can record patient's self-reported acceptability. 2. I would like if the authors applied CONSORT criteria to their protocol in addition to SPIRIT 3. I would like if the authors clarify more about how did they adjust for the dependent observations, two or more restorations in the same child mouth, in sample size calculation and in final analysis.

REVIEWER	Dr Sapna Konde A.E.C.S Maruti Dental College, Bengaluru India
REVIEW RETURNED	22-Jan-2017

GENERAL COMMENTS	Many thanks for giving me an opportunity to review this study protocol, which is a well designed study in my opinion. The study is adequately powered with a good sample size. In addition, they have 20% sample loss which has also been factored in. The primary outcome of longevity of both restorative treatments after follow-up at 2 years is the salient feature of this study. I would be keen to know how many patients the team have already recruited and if there was a plan to do an interim analysis. Inter and intra observer variability would be taken into consideration, which is reassuring. Secondary outcomes which includes the cost-efficacy of both types of restorative treatment and self-reported discomfort will be an interesting report to read. In summary, in my opinion this study will add more information to the

	inadequate data that is currently available with regards to the long term follow-up and these results may add information to the field of community dentistry. My only criticism would be the grammer and the spell check that would require before the final submission.

REVIEWER	Gustavo Molina Universidad Nacional de Córdoba, Argentina
REVIEW RETURNED	19-Feb-2017

GENERAL COMMENTS	My only suggestion would be, in the ART protocol, to specify the time for finger pressure (using a hand mixed GIC, at least 1 minute) and the type of matrix system that will be used for the restoration of occlusal-proximal cavities.

REVIEWER	Gerd Göstemeyer Department of Operative and Preventive Dentistry Charité University - Berlin Germany
REVIEW RETURNED	17-Mar-2017

GENERAL COMMENTS	This is a study protocol for a randomized clinical trial on a relevant research question. The study design seems appropriate. There are only minor suggestions for revision of the protocol: Abstract line 53: "no evidence" should be rephrased to "linited evidence" line 57: "efficacy" should be rephrased to "restoration longevity" Introduction a hypothesis should be formulated at the end of the introduction Methods/Design please describe the included lesion types more clearly (e.g. by ICDAS code, radiographical appearance, lesion depth) Figures/Table Please provide figure legends/descriptions. A link in the text to Figure 2 is missing. Figure 2: "Profissional" should be "Professional", "Equipament" should be "Equipement"

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dear Dr. Elham Kateeb,

I really appreciate all considerations made in relation to the submitted article as well as all the time dedicated to do so. All comments were helpful to improve the understanding of our protocol and to enhance its design. Please find below all answers to your questions. The updated article is attached.

1. "I would prefer if they used crossover design where they can compare both type of restorations at the same child to minimize variability. They can do it at different point of time so they can record

patient's self-reported acceptability."

Thank you for you suggestion. This is a really tricky question. However, we cannot perform a cross-over study because the same tooth would have to receive both treatments. In order to directly compare both treatments at the same child we would have to use the split-mouth design. However, we would have to consider only two cavities of the same type (occlusal or occlusal-proximal) per child which should be located in contralateral sides of the mouth. So, in case of three occlusal and two occlusal-proximal cavities in a participant, only a pair of occlusal cavity would be in the study, the other three cavities would be discarded. Thus, reaching a significative sample would be far more difficult, even unfeasible. Moreover, according to the design proposed by the protocol, we can simulate more accurately what usually occurs in clinical practice, since professionals often choose only one type of treatment per child, increasing our external validity.

We want to test the acceptability of each treatment rather than the child's preference for one of them. This is important information to the pediatric dentistry commmunity, since if only one treatment is well accepted by children, we will have an important factor to be considered besides the longevity when choosing a definitive restorative treatment for children.

It is a goal for us to design a study which the primary outcome is patient-centered in order to obtain some other answers such as those proposed by the reviewer. For now, as a secondary outcome, some limitations are inherent.

2. "I would like if the authors applied CONSORT criteria to their protocol in addition to SPIRIT."

We chose SPIRIT because it is a checklist designed specifically for study protocols, which is available at CONSORT website. As CONSORT also covers results, discussion and conclusion, we were not able to use it because we do not have these data yet. But for our final analysis and paper, we will consider this protocol for sure.

3. "I would like if the authors clarify more about how did they adjust for the dependent observations, two or more restorations in the same child mouth, in sample size calculation and in final analysis."

The child will be set as the unit of randomization, which means that all eligible teeth of a child included in our research will be treated according to the same treatment independently of the number of cavities. In other words, the intervention will be applied at the level “child”, while the outcomes will be measured at the “tooth” level, which characterizes our clinical trial as a cluster RCT, since we add the patient effect to be considered in the sample calculation.

Usual sample size estimation assumes independence of observations. When people are members of the same cluster (e.g., classroom, GP surgery), they are more related than we would expect to be at random. This is the intra-cluster correlation coefficient (ICC).

The ICC needs to be incorporated into the sample size calculations. The formula is as follows: Design effect = 1 + (m – 1) X ICC. Design effect (DE) is the size the sample needs to be inflated by. M is the number of people in the cluster.

Assuming the ICC as 0.05 – which is quite high – and the worst scenario of eight teeth included per child, considering the maximum of 8 primary molars with dentin carious lesions, our design effect was calculated.

DE = 1 + (8-1) x ICC = 1 + (1 – 8) x 0.05 = 0.4, we needed to increase our sample size in 40%.

As it can be found in our paragraph about sample size calculation: “The child will be set as the unit of randomization, which means that all eligible teeth of a child included in our research will be treated according to the same treatment independently of the number of cavities. For sample size calculation, data on the longevity of 2 years of occlusal and occlusal-proximal composite resin restorations [15] were extracted from the literature as 86% and 60%, respectively. A minimum difference of 10% between treatment longevities was set as the superiority limit. Taking the significance level as 5%, a power of 80% and the addition of 40% owing to study design (cluster per children), the minimum number of teeth per group was calculated using a two-tailed test.”

As the Reviewer pointed out in his comments, cluster RCTs require special statistical considerations not only when designing the trial, but also later when analyzing the data. As our first outcome is the restoration survival, we need to obtain the hazard ratio in our analysis, which involves not only the chances of failures but also the time in each evaluation. This ratio can be calculated using the Cox regression. However, when observational or experimental unit is aggregated into the same individual - as in a cluster RCT – there are correlations between these units, which make the Cox regression model limited. In these cases, a fragility model is indicated.

The fragility model is able to provide a convenient way to deal with correlated observations or unobserved heterogeneity. A fragility is an unobserved and supposed random effect, shared by observational or experimental units within a group (an individual, a school, a research center, etc.). In the simplest form, the random effect (fragility) of the group has a multiplicative effect on the risk function for all individuals in the same group. Thus, individuals from groups with large values for the random effect (fragility) tend to experience the event before individuals belonging to groups with small values in the random effect.

That’s why we chose the Cox regression with shared frailty to compare the longevity of the restorations.

Moreover, multilevel Poisson regression will be used to compare both groups and the other independent variables to the self-reported discomfort, since it is an ordinal variable. The analysis will be adjusted for the cluster effect by considering the child as our cluster level, justifying the need to perform a multilevel analysis.

“To compare the longevity of the restorations, both Kaplan–Meier survival analysis and Cox regression with shared frailty will be applied. The association between restoration longevity and caries experience or the type of cavity will also be evaluated using Cox’s Regression with shared frailty. To determine the data normality, the Kolmogorov–Smirnov test will be used. In relation to the secondary outcomes, the comparison between groups in relation to the time spent in each procedure as well as the average cost of a restoration will be done through the use of linear regression adjusted to the cluster effect. Multilevel Poisson regression will be used to compare both groups and the other independent variables to the self-reported discomfort. The significance level will be adjusted to 5%.”

Reviewer 2
Dear Dr. Sapna Konde,

Thank you so much for your considerations as well as for all the time dedicated to do so. All comments were really encouraging and help us to think further about our analysis. Please find below all answers to your questions. The updated article is in attachment.

"Many thanks for giving me an opportunity to review this study protocol, which is a well designed study in my opinion. The study is adequately powered with a good sample size. In addition, they have 20% sample loss, which has also been factored in. The primary outcome of longevity of both

restorative treatments after follow-up at 2 years is the salient feature of this study. I would be keen to know how many patients the team has already recruited and if there was a plan to do an interim analysis. Inter and intra observer variability would be taken into consideration, which is reassuring."

Until now, we included 169 participants, presenting 346 cavities. From these, 158 are occlusal and 188 are occlusal-proximal cavities.

We are planning to perform an interim analysis when at least 60% of our participants have been treated. We pretend to finish the inclusion by June of 2017.

Secondary outcomes which include the cost-efficacy of both types of restorative treatment and self-reported discomfort will be an interesting report to read. In summary, in my opinion this study will add more information to the inadequate data that is currently available with regards to the long term follow-up and these results may add information to the field of community dentistry. My only criticism would be the grammar and the spell check that would require before the final submission.

Thank you for your comment. In relation to the grammar and spell check, we have already submitted our article to English revision by a professional team of the Edanz – Expert English Editing.

Reviewer 3
Dear Dr. Gustavo Molina,

Thank you so much for your considerations and for all the time dedicated to do so. Your comments were helpful to make our protocol easily to understand and to clarify our steps. Please find below all answers to your questions. The updated article is attached.

"My only suggestion would be, in the ART protocol, to specify the time for finger pressure (using a hand mixed GIC, at least 1 minute) and the type of matrix system that will be used for the restoration of occlusal-proximal cavities."

We will perform the finger pressure for a few seconds according to the protocol cited in our paper (Frencken et al., 1996), which recommends to “Place the finger on top of the mixture, apply slight pressure for a few seconds, and remove the finger.”

“Apply GIC: insert the GIC with a #1 spatula followed by finger pressure using petroleum jelly for a few seconds. For occlusal-proximal cavities, use an adapted matrix strip with a wooden wedge to maintain it in place, providing appropriate contour to the restoration. Protecting the restoration with petroleum jelly is necessary to inhibit syneresis and imbibition;”

We will not use a commercial system of matrix, we’ll just cut 3-4mm of a 0.5mm metal matrix, round the corners, bend it using a cylindrical instrument, such as the handle of a dental mirror, and maintain in place using a wooden wedge.

Reviewer 4

Dear Dr. Gerd Göstemeyer,

I really appreciate all considerations made in relation to the submitted article as well as all the time dedicated to do so. Please find below all answers to your questions. The updated article is attached.

1. "This is a study protocol for a randomized clinical trial on a relevant research question. The study design seems appropriate. There are only minor suggestions for revision of the protocol:

1.1 Abstract
Line 53: 'no evidence' should be rephrased to 'limited evidence'
Line 57: 'efficacy' should be rephrased to 'restoration longevity' "

Thank you for your suggestion. We made the changes as can be seen below.

Introduction: Despite the widespread acceptance of conventional treatment using composite resin in primary teeth, there is limited evidence that this approach is the best option in pediatric clinics. Atraumatic restorative treatment (ART) using high-viscosity glass ionomer cement (GIC) has gradually become more popular because it performs well in clinical studies, is easy to handle and is patient friendly. Therefore, the aim of this randomized clinical trial study is to compare the restoration longevity of conventional treatment using composite resin with that of ART in posterior primary teeth. As secondary outcomes, cost-efficacy and patient self-reported discomfort will also be tested.

1.2 Introduction
"A hypothesis should be formulated at the end of the introduction."

Thank you for your suggestion. We made the changes as can be seen below.

Our hypothesis is that the longevity of restorations using the conventional treatment with resin composite under rubber dam for occlusal and occlusal-proximal cavities in primary molars differs from the longevity of atraumatic restorations using high viscosity glass ionomer. Regarding the secondary outcomes, we expect that ART has a better cost-efficacy and it is the only treatment highly accepted among children in this study.

1.3. Methods/Design
"Please describe the included lesion types more clearly (e.g. by ICDAS code, radiographical appearance, lesion depth)."

The inclusion criteria are: 1) children aged 3–6 years; 2) whose parents consent their participation in the research; 3) with at least one occlusal and/or occlusal-proximal cavity in a primary molar; 4) the carious lesion should be in dentin, clinically classified as a shallow or a medium cavity; 5) the tooth of interest should not be associated with a fistula, abscess, pulp exposure, history of spontaneous dental pain or mobility; and 6) the cavity of interest should allow the access by the operator using hand instruments (ICDAS 5 or 6).

Radiographic examination will be performed if any doubts about the pulp involvement of the tooth of interest persist. As the child will receive complete dental treatment during the study, radiographic examination will also be used if any other treatment need demand it.

1.4. Figures/Table
"Please provide figure legends/descriptions. A link in the text to Figure 2 is missing."

The legends are associated to the figure files:
Figure 1 – Clinical trial’s timeline
Figure 2 – Diagram of total cost calculation

"The direct cost analysis will be based on previous publications [28, 29] adjusted to the Brazilian reality [30]. Both the professional cost and the procedure cost will be considered (Figure 2)."

"Figure 2: "Profissional" should be "Professional", "Equipament" should be "Equipment"."

Thank you for your comments. These alterations were made in the figure in attachment.

If there is any query regarding our manuscript or any related issues, please, do not hesitate to contact us.
On behalf of all authors, I would like to thank you for considering our manuscript for publication.

VERSION 2 – REVIEW

REVIEWER	Gustavo Molina Facultad de Odontología, Universidad Nacional de Córdoba, Argentina. Carrera de Odontología, Facultad de Medicina, Universidad Católica de Córdoba, Argentina.
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	All the suggestions and queries of the reviewers have been responded accurately. The authors show practical skills in such clinical trials, being aware of the difficulties they might have to face in order to carry out the study, minimizing imponderables.

REVIEWER	Gerd Göstemeyer Department of Operative and Preventive Dentistry Charite - Berlin Germany
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	The authors have addressed all the issues raised.