The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/23708

Please be advised that this information was generated on 2019-09-05 and may be subject to change.
A Meta-analysis of Clinical Studies on the Caries-inhibiting Effect of Chlorhexidine Treatment

H.M. van Rijkom*, G.J. Truin, and M.A. van 't Hof¹

Department of Cariology and Endodontology and ¹Department of Medical Statistics, TRIKON: Institute for Dental Clinical Research, Faculty of Medical Science, University of Nijmegen, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands; *to whom correspondence should be addressed

Abstract. A meta-analysis was performed on published data on the caries-inhibiting effect of chlorhexidine treatment. The results of the various studies are difficult to evaluate because of various treatment procedures, dissimilar features of participants, and different presentations of study results. A meta-analysis provides a more structured approach than the traditional review, due to systematic analysis and numerical processing of the available information. The objectives of this meta-analysis were: (1) to assess a more accurate estimate of the caries-inhibiting effect of chlorhexidine treatment than provided by individual studies, and (2) to explore factors potentially modifying the effect of chlorhexidine treatment in caries prevention, i.e., the application method, application frequency, target population, the fluoride regime, and caries criteria. Caries reduction was expressed by the prevented fraction, indicating the percentage reduction of caries incidence in the chlorhexidine group. For all prevented fractions, 95% confidence intervals were calculated. The overall caries-inhibiting effect of the chlorhexidine treatment studies was 46% (95% CI = 35% - 57%). Multiple-regression analysis showed no significant influence on the prevented fractions for the variables “application method”, “application frequency”, “caries risk”, “fluoride regime”, “caries diagnosis”, and “tooth surface”.

Key words: dental caries, chlorhexidine, meta-analysis.

Introduction

The bis-biguanide chlorhexidine is an antimicrobial agent with special affinity for oral structures and has a long history as a substance for inhibiting plaque formation. Moreover, chlorhexidine selectively suppresses the growth of some types of micro-organisms—in particular, mutans streptococci—which are associated with the development of caries lesions (Rölla and Melsen, 1975; Brown et al., 1986; Marsh, 1993). During the last 20 years, clinical studies have been published on the caries-inhibiting effect of chlorhexidine. Recently, the outcomes of studies on the effectiveness of chlorhexidine in caries prevention have been reviewed (Kidd, 1991; Emilson, 1994). The results of the various studies on the effectiveness of chlorhexidine, however, are difficult to evaluate because of various treatment procedures, dissimilar features of participants, and different presentations of study results. A meta-analysis provides a more structured approach than the traditional review, due to systematic analysis and numerical processing of the available information. The structure of a meta-analysis depends upon its purpose, whether a simple on-the-average summary or an interaction analysis (Light and Pillemer, 1984). For instance, policymakers are interested in average program performance. They investigate the overall effect of a treatment. On the other hand, the objectives of researchers go beyond main effects, focusing on factors that possibly affect study outcomes, like program and setting characteristics, participant characteristics, research design, and analysis techniques, which can contribute to refinement of future research. This meta-analysis includes both aspects. The objectives of this study were: (1) to assess an estimate of the caries-inhibiting effect of chlorhexidine treatment more accurate than that provided by individual studies, and (2) to explore factors potentially modifying the effect of chlorhexidine in caries prevention, i.e., the application method, application frequency, target population, the fluoride regime, tooth surfaces involved, and caries diagnosis.
Materials and methods

Selection and selection criteria
A list was compiled of studies that reported on the effect of chlorhexidine treatment in caries prevention. For this purpose a literature search was conducted on the key words “chlorhexidine” and “(dental) caries” in the MEDLINE database. A first selection on articles published between 1975 and 1994 in English, French, or German resulted in 24 papers, which were all evaluated independently by two examiners. To provide for a systematic analysis of the past research, studies were selected on comparability for dental and methodological reasons. After an initial screening of the selected papers, these additional criteria were formulated: (1) chlorhexidine applied to permanent teeth from 11- to 15-year-old children; (2) studies performed in a clinical trial with randomly assigned treatment groups, including generally treated experimental groups as well as treatment focused on subjects in the experimental group with Streptococcus mutans > 2.5 x 10^5/mL saliva; (3) the availability of caries incidence data on surface level; (4) a treatment duration of at least one year; and (5) evaluation at the end of the treatment period.

In Table 1, the excluded studies are listed according to main reason for rejection. It is likely that three publications (Zickert et al., 1982, 1983, 1987) reported on only one study sample. Only Zickert et al. (1982) was selected, since this paper best fit the criteria. From this paper, the “all tooth surfaces” results were excluded, because sealants were applied only in the experimental group. After the application of these criteria, only eight publications remained for analysis (Table 2).

Evaluation criteria
The caries-inhibiting effect of chlorhexidine was expressed by the prevented fraction, calculated as the difference in number of new decayed and filled surfaces (DFS or DS) between the control group and the chlorhexidine group, divided by the number of new decayed and filled surfaces in the control group. Likewise, in the meta-analytical evaluation of the effectiveness of sealants to experimental circumstances than the absolute reduction. In all other studies, it was scored clinically as well as radiographically.

In the meta-analytical evaluation of the effectiveness of sealants (Llodra et al., 1993), the caries-inhibiting effect was also recorded by the prevented fraction, which was merely described as reduction. For all prevented fractions, 95% confidence intervals were calculated. In one study (Axelsson et al., 1987), standard deviations (or standard errors) were not published, and in two studies, standard deviations were unavailable for one of the risk groups (Gisselsson et al., 1988; Luoma et al., 1978). In this particular meta-analysis, missing standard deviations could be estimated by regression analysis.

Covariables
From the papers, several variables could be derived for the study of possible influences on the caries-inhibiting effect of chlorhexidine (Table 2):

- “Application methods” consisted of topical gel application, rinsing, incorporation into toothpaste, and a combination of rinsing and toothpaste.
- “Application frequencies” were divided into intervals of (a) 90 to 180 days, (b) every 30 days, or (c) more frequently.
- “Caries risk” was recorded either as ‘nonselected’ or as ‘selected subjects with high caries risk’, depending on the description in the relevant paper. (The latter was determined according to Streptococcus mutans levels or caries activity.)
- The “fluoride regime” reflects the fluoride prophylaxis setting of each study, involving all participants of the individual studies in the control as well as the experimental groups. This variable was quantified and included in the analysis as an effect modifier. For analysis purposes, a distinction was made among: (1) those who used only fluoride toothpaste, (2) those who did additional rinsing with fluoride or had a fluoride application, and (3) those who had more frequent fluoride rinsing or fluoride rinsing in combination with fluoride application. In none of the papers was the use of fluoride tablets reported. Either the drinking water contained a negligible fluoride concentration or data were not available.

- Two “caries diagnostic” levels were distinguished: (1) dentinal caries, and (2) caries including enamel lesions. In one study (Axelsson et al., 1987), caries was scored radiographically, and in all other studies, it was scored clinically as well as radiographically.
- The factor “tooth surface” included “all tooth surfaces” or “approximal tooth surfaces”.

It was assumed that the results of the selected studies, expressed as prevented fraction, were influenced neither by the
Table 2. Studies and variables included in the meta-analysis (in chronological order)

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Chlorhexidine Application Methods</th>
<th>Application Frequencies</th>
<th>Risk Group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Tooth Surfaces</th>
<th>Fluoride Regime&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Caries Diagn.</th>
<th>Follow-up (Years)</th>
<th>Age Group (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Spets-Happonen et al., 1991</td>
<td>0.05% CHX rinse 1/day at school +1/day at home</td>
<td>2/day, 5 days, every 21 days</td>
<td>high</td>
<td>all</td>
<td>2</td>
<td>1</td>
<td>2.75</td>
<td>11</td>
</tr>
<tr>
<td>2.1 Lindquist et al., 1989</td>
<td>1% CHX gel professionally applied</td>
<td>2 consec. days, every 90 days</td>
<td>high</td>
<td>all</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>2.2 Lindquist et al., 1989</td>
<td>1% CHX gel professionally applied</td>
<td>2 consec. days, every 90 days</td>
<td>high</td>
<td>approx.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>3.1 Gisselsson et al., 1988</td>
<td>1% CHX gel professionally applied</td>
<td>2 consec. days, every 90 days</td>
<td>incl. floss., every 90 days</td>
<td>nonselect.</td>
<td>approx.</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.2 Gisselsson et al., 1988</td>
<td>1% CHX gel professionally applied</td>
<td>2 consec. days, every 90 days</td>
<td>incl. floss., every 90 days</td>
<td>high</td>
<td>approx.</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4  Axelsson et al., 1987</td>
<td>0.2% CHX rinse supervised+ 1% CHX gel professionally applied</td>
<td>every 180 days</td>
<td>high</td>
<td>approx.</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>5  Lundström and Krause, 1987</td>
<td>1% CHX gel professionally applied</td>
<td>2 days, every 30 days</td>
<td>high (+ orth.)</td>
<td>all</td>
<td>3</td>
<td>2</td>
<td>1.8</td>
<td>11-15</td>
</tr>
<tr>
<td>6  Zickert et al., 1982</td>
<td>1% CHX gel 1 day professionally applied + consec. days at home</td>
<td>14 consec. days, every 120 days</td>
<td>high</td>
<td>approx.</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>13-14</td>
</tr>
<tr>
<td>7  Dolles and Gjermo, 1980</td>
<td>2% CHX toothpaste at home</td>
<td>2/day, every day</td>
<td>nonselect.</td>
<td>all</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>8.1 Luoma et al., 1998</td>
<td>0.05% CHX rinse supervised + CHX toothpaste supervised</td>
<td>every schoolday</td>
<td>high</td>
<td>all</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>11-15</td>
</tr>
<tr>
<td>8.2 Luoma et al., 1998</td>
<td>0.05% CHX rinse supervised + CHX toothpaste supervised</td>
<td>every schoolday</td>
<td>high</td>
<td>approx.</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>11-15</td>
</tr>
</tbody>
</table>

<sup>a</sup> High = selected high-risk subjects.

<sup>b</sup> 1 = fluoride toothpaste; 2 = additional fluoride rinsing or application; 3 = additional, more frequent fluoride rinsing or additional fluoride rinsing plus application.

<sup>c</sup> 1 = dentinal caries; 2 = including enamel lesions.

<sup>d</sup> Subjects in control group and experimental group all received individual prevention.

age of the children, ranging from 11 to 15 years, nor by the caries index (DS, DFS, or DMFS) used. "Follow-up years", indicating the total length of the study as well as the treatment duration, was excluded as a parameter, because the prevented fraction was assumed to be independent of the duration of the study. In all studies, the subjects received restorative treatment at the start of the trial, if required. Additional oral hygiene instruction was given to the children in all studies, except in the Dolles and Gjermo (1980) study. Professional mechanical tooth cleaning was used in the Dolles and Gjermo (1980) study, as it was in the studies by Axelsson et al. (1987) and Zickert et al. (1982). Therefore, oral hygiene was also not seen as a relevant covariable in this meta-analysis.

**Statistical analysis**

Confidence intervals of 95% for the prevented fractions were calculated on the basis of the binomial distribution. Study results have been combined to yield an overall treatment effect with a statistical power greater than that of the compiled individual studies. We calculated the overall confidence interval by weighting the individual data for the reciprocal error variance. Multiple regression (weighted according to the reciprocal error) was used to detect factors influencing the caries-inhibiting effect of chlorhexidine (i.e., effect modifiers).

**Results**

Table 3 shows the prevented fractions and 95% confidence intervals of the individual chlorhexidine studies.

Multiple-regression analysis showed no significant influence on the prevented fractions for the variables "application method", "application frequency", "caries risk", "fluoride regime", "caries diagnosis", and "tooth surface", indicating homogeneity of the studies. Three parameters were highly correlated: Multicollinearity was found among the variables "application method", "application frequency", and "caries diagnosis", complicating the interpretation of the effect of each of these three variables separately.

The Fig. depicts the prevented fractions plus the 95% confidence intervals of the individual studies and the
average caries-inhibiting effect of the combined studies (grey area). The overall caries-inhibiting effect of the chlorhexidine treatment studies was 46% (95% CI = 35% - 57%). Due to the observed homogeneity of the published results, the overall effect of chlorhexidine treatment could be calculated by pooling the results.

**Discussion**

To provide a consistent evaluation of the studies on the caries-inhibiting effect of chlorhexidine treatment, we had to exclude 16 of the 24 publications selected. From the remaining 8 papers, containing 11 study results, 3 more study results would have been lost if missing standard deviations could not be estimated. Regrettably, two-thirds of the published data on the caries-inhibiting effect of chlorhexidine treatment had to be left unused. The exclusion of this relatively large number of studies should be considered an advantage of the meta-analytical approach, because it reveals incoherent studies and avoids conclusions from inconsistent findings, which can be regarded as a precondition for the accumulation of knowledge and advances in research.

Although meta-analysis contributes an objective approach of study results, subjective selection of papers remains a potential biasing factor. Publication bias is a second important confounding factor. Unpublished non-significant study results may lead to overreporting of significant outcomes, implying an overestimation of the total effect. In this meta-analysis, the publication bias is hard to estimate, considering the small number of publications involved.

The overall caries reduction from the chlorhexidine treatment studies was 46% (95% CI = 35% - 57%), which can be considered a substantial effect. It was assumed that the variables "application method", "application frequency", "caries risk", "fluoride regime", "caries diagnosis", and "tooth surface" could potentially influence the effect of caries reduction. However, the effects of these variables on caries reduction were not significant. The selected studies on chlorhexidine were homogeneous, indicating constancy of treatment effects across the studies. The small number of selected studies limited the power of the meta-analysis, although the number of children involved was large (total n = 612). When the number of studies involved in the analysis is small, one should be careful with the interpretation of non-significant results.

Kidd (1991) reviewed the effect of chlorhexidine treatment, stating that chlorhexidine appears to be of benefit in caries control in high-risk groups. In the present meta-analysis, however, the caries-inhibiting effect was not restricted to high-risk subjects. These contradictory results were due to a different selection of papers. The review by Emilson (1994) as well as this meta-analysis studied the caries-inhibiting effect of chlorhexidine treatment according to "caries risk" recorded both in nonselected subjects and in high-risk subjects. The results, however, were not in accordance, due to different interpretations and inclusions of unselected and high-risk subjects, caused by various definitions of caries risk in the selected papers.

When the factor "fluoride regime" was considered, this meta-analysis demonstrated that stronger fluoride regimes did not show significant effect modification due to chlorhexidine. Besides the fluoride regimen, the chlorhexidine

![Figure. The overall caries-inhibiting effect of chlorhexidine treatment (grey area), achieved by pooling the 95% confidence intervals of the individual studies.](image-url)
treatment studies included, with one exception, a more extensive fluoride program than the use of fluoride toothpaste only; moreover, the effect of chlorhexidine has not been studied without a fluoride regime.

Despite the described dissimilarity of the studies, the present meta-analysis showed an obvious consistency of the 95% confidence intervals of the study results. The remarkably wide confidence intervals of several studies indicate a variability of results. The bitter after-taste of chlorhexidine could have contributed to variations in home-applied chlorhexidine use. However, only one study was exclusively performed at home (Dolles and Gjermo, 1980). In five studies, the treatment was applied professionally or was supervised, and in two studies, it was applied both under supervision (or professionally) and at home (Zickert et al., 1982; Spets-Häpponen et al., 1991). The confidence intervals of the chlorhexidine studies exceed the confidence intervals of the caries-inhibiting effect of fluoride treatment (gels, solutions, and dentifrices) (Marthaler, 1971) and fluoride varnish (Duraphat) (Helfenstein and Steiner, 1994).

It could be concluded that the average caries-inhibiting effect from the chlorhexidine treatment studies was 46% (95% CI = 35% - 57%), although publications bias might have led to an overestimation of the overall result. The covariables “application method”, “application frequency”, “caries risk”, “fluoride regime”, “caries diagnosis”, and “tooth surface” did not significantly influence the effect of caries reduction. This should be interpreted carefully, however, because it might be due to the small number of studies involved in the meta-analysis. Future research on the caries-preventive effect of chlorhexidine treatment should emphasize studies complying with the criteria for clinical trials, focusing on the influence of the chlorhexidine application method and the application frequency—in particular, the performance in high-risk participants—and should include the perspective of the cost/benefit relationship.

Acknowledgments

We acknowledge Amy Klipp for editing the manuscript. This study was supported by a grant from the ‘Praeventiefonds’, The Hague, The Netherlands (No. 28-2553).

References


