Clinical Significance Versus Statistical Significance with Regards Gingival Scores in Herbal and Chlorhexidine Mouthwash Clinical Trials- A Systematic Review

Deepika Dagar[1], Pradnya Kakodkar[2], Sahana Hegde Shetiya[3]

[1]Public Health Dentist, [2]Dy Director, Dr D Y Patil Vidyapeeth, Pune, [3]Prof and HOD, Dr D Y Patil Vidyapeeth,Pune, Department of Public Health Dentistry

Abstract

Purpose: Does clinical significance match with the statistical significance with respect to gingival score when herbal mouthwash is used in comparison to the chlorhexidine mouthwash?

Material and Method: A systematic search of literature was conducted on two databases (PubMed and Google Scholar) for the studies published from 1st January 2006 to 31st December 2018. Cross-references were checked. Hand searching was done in the library. Studies were included if they were done among healthy, non hospitalized humans and compared chlorhexidine with herbal mouthwash for the gingivitis score.Clinical significancewas ascertained based on Loe and Sillness (1967) Gingival index interpretation.

Results:A total of 22 unique clinical trials were identified and 24estimates which used Gingival index as outcome assessor. 18 estimates showed matching between clinical significance and statistical significance in the chlorhexidine group while in herbal group it was found only in 15 estimates. As per Thirthalli J, Rajkumar RP criteria none of the studies showed clinical significance.

Conclusion: Statistical significance does not always mean clinical significance. Researchers should modify their study design to focus on clinical significance along with statistical significance.

Keywords: *Clinical significance, statistical significance, herbal mouthwash, chlorhexidine .*

Introduction

Gingivitis is a worldwide phenomenon reaching to high epidemic proportions.[1] Microbial plaque plays an important role in development of gingivitis.[2] It can be controlled by using mechanical plaque control measures like toothbrush, dental floss, interdental brush etc. In addition, chemical control such as mouthwashes can also be used. Mouthwashes have the ability to reach those areas where mechanical plaque control cannot reach.Many agents such as bis-biguanides, essential oils, quaternary ammonium compounds, antibioticsand antiseptics have been used as mouth washes. Chlorhexidine (bis-biguanide) is well known and well studied chemical agent to control gingivitis.It is commonly used in two concentrations 0.2% and 0.12%, which can be with or without alcohol, and literature shows that there is no difference in their efficacy with regards the two different concentrations.[3] There are some side effects such as staining of teeth and loss of taste sensation which restricts its use for long duration. To overcome this side effect many other alternative mouthwashes are been researched for. Herbal products havebeen used since ancient times, and in last 2 decades it has become mainstream for research because of its natural ingredients and less expensive prescriptions.[4] Herbal mouthwashes available over the counter indicates they are in demand by the people.

Corresponding Author:
Dr Pradnya V Kakodkar
Deputy Director Research, Dr D Y Patil Vidyapeeth, Pune. Email:pradnya.kakodkar@gmail.com
Mobile: 9881409089

In a clinical trial, when two interventions are compared and statistical significance is obtained for the outcome variable, the null hypothesis is rejected and thus it is concluded that one treatment procedure is better than the other.[1] However, a statistically significant reduction in symptom ratings may or may not represent a clinically meaningful treatment response or the magnitude of the difference.[5,6] The p value of <0.05 tells us that there is difference between the groups but does not necessarily tell us how much clinically significant difference.

Statistical significant deals with the numbers, while according to LeFort, results will be called clinically significant if the newer modality is better enough to make a real difference in the people's life, effect of the treatment will last for a longer time, it is cost effective and it is easy to implement.[7]

The aim of this study was to compile all the clinical studies conducted, comparing herbal mouthwash against Chlorhexidine and to evaluate if statistical significance matches with the clinical significance with regards gingival scores.

One of the reasons to undertake this study was that the authors, researchers and readers should be able to appreciate the difference between statistically significant clinically relevant data and statistically significant clinically insignificant data.

Material and Method

Literature Search :

The electronic search was initially conducted on the MEDLINE via PUBMED database with the following search strategy "Gingivitis (tw)* AND Chlorhexidine (tw)* AND herbal (tw)* AND mouthwash (tw)*", "Gingival inflammation (tw)* AND chlorhexidine (tw)* AND natural product (tw)* AND mouthrinse (tw)*", "Gingival inflammation* OR gingivitis* AND chlorhexidine* AND natural product* OR herbal* AND mouthrinse* OR mouthwash*.In addition, Google Scholar was also searched. We also manually searched the reference lists of eligible studies to ensure identification of relevant published and unpublished studies. We also contacted study authors to provide full text articles. Search was conducted for the article during the period of January 1st 2006 to December 31st 2018

Eligibility criteria: All the studies reporting randomized control trials for herbal and chlorhexidine mouthwashes used for anti-gingivitis regimen; studies conducted in humans; studies considering Loe and Sillness (1967) gingival index as an outcome assessor and papers written in English language only and where there is a possibility to translate the foreign language to English. Case reports,Letter to the editor abstracts and narrative reviews were excluded.

Two reviewers (DD and PK) independently performed the first stage of screening by titles of all the identified studies. Round 2 included screening by the abstracts. Round 3 was full text assessment.

Data extraction

A standardized, pre-piloted form was used to extract data from the included studies for evidence synthesis. One review author (DD) extracted data independently and second author (PK) cross checked the data. Discrepancy if any, was identified and resolved through discussion with a third author (SHS) where necessary. The extracted data included the following: Study ID, author name, year of publication, sample size, intervention group, comparison group, duration of the trial, index used, mean and standard deviation of the gingival baseline and end of trial scores, statistical significance as reported in the article and the clinical significance (calculated by the reviewers).

Clinical significance calculation:

It was ascertained based on Gingival index score interpretation[8]. The interpretation score mentioned is as follows: 0.0- No gingivitis ;0.1-1.0 – Mild gingivitis ; 1.1 – 2.0 Moderate gingivitis ; 2.1 – 3.0 Severe gingivitis.

At the end of the trial, in both the study and control group, if the baseline score moved up from higher interpretation grade to lower, it was considered as clinically significant. For e.g. before intervention the base line score was 1.3 (moderate gingivitis) and post intervention the end score was 0.9(mild gingivitis) , than this intra group comparison was considered as clinically significant. But if the baseline score and the end score remained in the same interpretation grade, it was not termed as clinically significant.

Thirthalli J and RajkumarRP[9] proposed five criteria which were used to assess the clinical significance of the studies. The criteria were as follows: 1.What are the implications of the adverse effects profiles? 2. Are the outcome measures appropriate? 3. Are the effects of a treatment sustained?4. Is the treatment cost effective?5. Do the findings generalize to different context?

Results

A total of 22 articles unique clinical trials and 24 estimates were identified (Prisma Flow chart depicted as Fig 1).

The characteristics of experimental and control group mouthwashes are depicted in Table 1. There was a wide variation noted in the duration of the study period (Table 1) . Four studies (XIX-XXII), were conducted for 30 days, four studies (XV-XVIII) were conducted for 4 weeks,eight studies (VII-XIV) were conducted for 21days, two studies (V,VII) for 15 days, two studies were conducted for 14 days (III, IV) , one study (II) was conducted for 7 days and one study (I) was conducted for 5 days.

Intra group comparison remarks (Table 1): The mean gingival score at baseline and end of trial in both experimental and control group were correctly reported in all the studies. In the herbal mouthwash group, there were seven studies which were statistically significant clinically not significant (I,IV-VIII,XIX), whereas 15 studies were clinical and statistically significant (II,III,IX-XVIII, XX-XXII) . In the Chlorhexidine mouthwash group: six were statistically significant but not clinically significant (I,IV-VII,XIX) and 18 studies showed a clinical and statistical significance (II,III,VIII-XXII).

Table 2 showed results of clinical significance as assessed by Thirthalli J and Rajkumar RP[9] criteria.The studies considered in this review, reported adverse effects in four studies (II, XVI,XXII) with both chlorhexidine and herbal mouthwash.All the studies reported the outcome measurements and statistical significance.None of the studies carried out any follow up after the study was completed and also none of the studies mentioned the cost of the mouthwash in their paper and hence it cannot be commented whether the treatment was cost effective or not.The findings cannot be generalized to different context in any study. Overall, none of the study showed clinical significance.

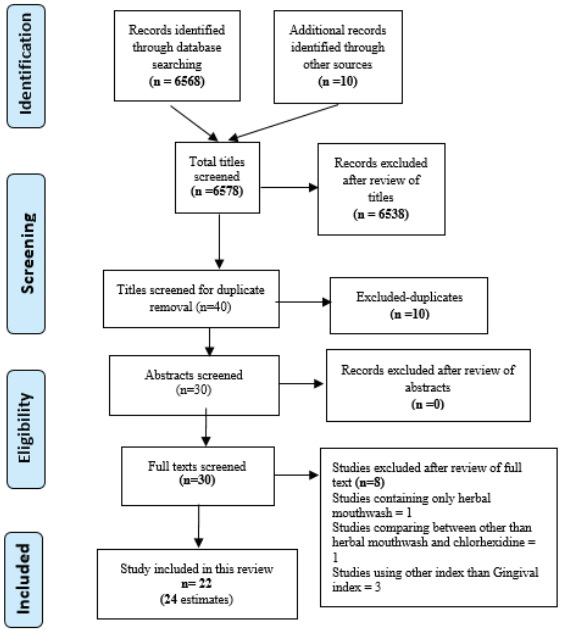

Fig 1: PRISMA flow-chart

Table 1: Data extraction sheet.

Study id	Intervention	Comparison	Duration of trial	Herbal baseline	CHX baseline	Herbal End score	CHX End score	Herbal		CHX	
				Mean	Mean	Mean	Mean	Statistical significane	Clinical significane	Statistical significane	Clinical significane
I	Hiora mouthwash	0.2% CHX	5 days	0.57	0.56	0.83	0.77	S	NS	S	NS
II	1% Lippia sidoides	0.12% CHX	7 days	1.57	1.63	0.7	0.6	S	S	S	S
IIIa	2% Neem	0.2% CHX	14 days	2.5	2.67	1.11	1.22	S	S	S	S
IIIb	0.5% Green tea	0.2% CHX	14 days	2.44	2.67	1.11	1.22	S	S	S	S
IV	Hiora mouthwash	0.2% CHX	14 days	0.15	0.19	0.03	0.04	S	NS	S	NS
V	M. Koenigii	0.2% CHX	15 days	1.94	1.92	1.24	1.27	S	NS	S	NS
VIa	2% Neem	0.2% CHX	15 days	0.49	0.48	0.34	0.22	S	NS	S	NS
VIb	2% Neem	0.2% CHX	15days	0.55	0.61	0.36	0.39	S	NS	S	NS
VII	0.19% *A. Indica*	0.2% CHX	21 days	1.7	1.9	1.2	1.1	S	NS	S	NS
VIII	Hiora mouthwash	0.12% CHX	21 days	1.9	1.92	1.1	0.15	S	NS	S	S
IX	0.25% lemongrass oil	0.2% CHX	21 days	2.19	2.23	1.59	1.67	S	S	S	S
X	Triphala and Ela decotion	0.2% CHX	21 days	1.78	1.89	0.53	1.29	S	S	S	S
XI	Arimedadi oil	0.2% CHX	21 days	1.81	1.82	0.66	0.66	S	S	S	S
XII	0.1% turmeric	CHX	21 days	1.7	1.8	0.66	0.7	S	S	S	S
XIII	Turmeric	CHX	21 days	1.81	1.77	0.71	0.73	S	S	S	S
XIV	0.6% Triphala	0.12% CHX	21 days	1.24	1.23	0.9	0.94	S	S	S	S
XV	Herboral mouthwash	0.2% CHX	4 weeks	1.96	2	0.6	0.28	S	S	S	S
XVI	4% Ocimum sanctum	0.12% CHX	4 weeks	2.23	2.36	1.35	1.44	S	S	S	S
XVII	Sefdent	0.2% CHX	4 weeks	1.18	1.15	1.02	0.87	S	S	S	S
XVIII	Green tea	CHX	4 weeks	2.01	2.06	1.23	1.2	S	S	S	S
XIX	Aloe vera	0.12% CHX	30 days	1.99	1.97	1.15	1.11	S	NS	S	NS
XX	Cinnamon	CHX	30 days	2.7	2.9	1.1	0.7	S	S	S	S
XXI	Aloe vera	CHX	30 days	2.23	2.36	1.35	1.44	S	S	S	S
XXII	Herbal	CHX	30 days	3.6	3.2	2.01	1.6	S	S	S	S

Table 2:Thirthalli Jand Rajkumar RP criteria for clinical significance

Study Id	What are the implications of the adverse effects profiles?	Are the outcome measures appropriate?	Are the effects of a treatment sustained?	Is the treatment cost effective?	Do the findings generalize to different context?	Overall interpretation (Clinical significance)
I	🔴	🟢	🔴	🔴	🔴	NS
II	🟢	🟢	🔴	🔴	🔴	NS
III	🔴	🟢	🔴	🔴	🔴	NS
IV	🔴	🟢	🔴	🔴	🔴	NS
V	🔴	🟢	🔴	🔴	🔴	NS
VI	🔴	🟢	🔴	🔴	🔴	NS
VII	🔴	🟢	🔴	🔴	🔴	NS
VIII	🔴	🟢	🔴	🔴	🔴	NS
IX	🔴	🟢	🔴	🔴	🔴	NS
X	🔴	🟢	🔴	🔴	🔴	NS
XI	🔴	🟢	🔴	🔴	🔴	NS
XII	🔴	🟢	🔴	🔴	🔴	NS
XIII	🔴	🟢	🔴	🔴	🔴	NS
XIV	🔴	🟢	🔴	🔴	🔴	NS
XV	🔴	🟢	🔴	🔴	🔴	NS
XVI	🟢	🟢	🔴	🔴	🔴	NS
XVII	🔴	🟢	🔴	🔴	🔴	NS
XVIII	🔴	🟢	🔴	🔴	🔴	NS
XIX	🔴	🟢	🔴	🔴	🔴	NS
XX	🔴	🟢	🔴	🔴	🔴	NS
XXI	🔴	🟢	🔴	🔴	🔴	NS
XXII	🟢	🟢	🔴	🔴	🔴	NS

🟢 mentioned 🔴 not mentioned NS-Not significant

Discussion

The aim of this review was to provide a comprehensive appraisal and differentiate between the statistical significance and clinical significance of the gingival score parameter in the clinical studies conducted using chlorhexidine and herbal mouthwashes among human participants. The results of this review showed that it is possible to have statistical significance without having clinical relevance. As per Thirthalli J and Rajkumar RP[9]criteria all the studies considered in the review showed that there was statistical significance but were clinically in significant. This review, concludes that the clinical trials have not been designed keeping in mind the clinical significance but it is oriented towards finding out the statistical significance only between the two groups to report which treatment is better than the other.

One of the reason why statistical significance may be more popular among the researchers, authors and readers is because p value cut-off ($p<0.05$) gives a simple YES/ NO answer to differentiate between two groups , unlike the clinically significant result which need calculation on multiple factors.

Greenstein G[31] in his paper discusses that statistical significance testing as a method to infer that results of periodontal clinical trials are clinically meaningful, have short comings. He suggests that, what determines clinically significant results should be defined before initiating a study and statistical significance testing should be used to validate that findings did not occur by chance.

This paper recommends that the researchers clearly define parameters for clinical significance testing while designing the study and incorporate following important criteria's: Adverse effects, appropriate outcome measure, post intervention follow up, cost effectiveness and generalizabilty.

This review has few limitations. While calculating the clinical significance, only Gingival index was taken, hence we had to exclude other studies which have used other indices. Only those indices with interpretation remarks can be chosen.

Conclusion

Based on the factors used for assessing clinical significance, the present review concludes that statistical significance does not always match clinical significance. Researchers should modify their study design to focus on clinical significance along with statistical significance.

Ethical Clearance: Not required.

Source of Funding: NA.

Conflict of Interest: Nil

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