NEW INSIGHTS IN INTRA-ORAL HALITOSIS MANAGEMENT

Ph.D. Thesis Booklet

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1. INTRODUCTION

1.1. Overview of the topic

1.1.1. What is the topic?

We investigate the diagnosis options and chlorine dioxide (ClO_2) mouthwash therapy for intra-oral halitosis.

1.1.2. What is the problem to solve?

In the field of intra-oral halitosis, there are no evidence-based diagnostic and treatment protocols; we would like to facilitate the filling of these gaps.

1.1.3. What is the importance of the topic?

The investigation into the topic of halitosis holds paramount importance in the realms of both public health and individual well-being. Historically associated with the privileged classes, oral hygiene and dental care have undergone transformative changes in terms of perceptions and accessibility. However, despite advancements, the significance of a comprehensive understanding of halitosis persists, as it is not merely a manifestation of poor oral hygiene but a multifaceted symptom with potential repercussions on mental health and broader systemic well-being.

Halitosis, commonly linked to oral hygiene, can be indicative of underlying health issues when left undiagnosed or untreated. The gravity of the matter becomes apparent when considering its potential to lead to severe psychological consequences, including isolation and, in extreme cases, thoughts of suicide. This underscores the evolving nature of the societal impact of halitosis, which extends beyond the

confines of traditional oral health concerns. The recognition that halitosis may originate from sources beyond the oral cavity emphasizes the need for a holistic healthcare approach that addresses oral health in conjunction with broader health concerns.

The prevalence of halitosis, estimated to range from 20-71%, further emphasizes its complexity as a symptom. This reflects the diverse origins of halitosis, necessitating a nuanced approach to diagnosis and treatment.

The diagnostic landscape of halitosis is equally intricate, with the organoleptic test (OLT) standing as the gold standard despite its subjectivity and potential health risks. Various direct and indirect diagnostic methods have been developed to address these limitations. Measurement of Volatile Sulfur Compounds (VSCs) using instruments like the Halimeter and OralChroma provides an objective approach, although challenges in standardization and cost persist. These advancements in diagnostic tools contribute to a more nuanced understanding of halitosis, facilitating accurate identification of its diverse origins.

Therapeutically, halitosis presents a challenge due to the lack of a definitive treatment protocol. However, using chlorine dioxide (ClO_2) mouthwashes is a promising avenue. ClO_2's selective oxidizing properties and antimicrobial effects on VSC precursors position it as a potential solution, particularly for intra-oral halitosis. Further research and development in this area could revolutionize therapeutic strategies for halitosis, addressing not only the symptoms but also the underlying causes.

The exploration of halitosis is crucial for enhancing diagnostic accuracy and developing effective therapeutic strategies.

1.1.4. What would be the impact of our research results?

We would facilitate our field of interest to get closer to the evidence-based guidelines in diagnosing and treating intra-oral halitosis. This can cause a significant improvement in patient care and quality of life in halitotic patients, and we can avoid the most severe consequences.

1.1.5. Future plans

I want to continue my research. We conducted a protocol for a trial, which will be a pilot randomized controlled trial about the efficacy of hyperpure chlorine dioxide (ClO_2) in halitosis. After receiving ethical approval, we started enrolling the patients in January 2024. Therefore, we established a halitosis working group, and with continuous improvement, we would like to help these patients improve their well-being and quality of life. By the end of the trial, the following steps regarding our field of interest will be more apparent to us and the public.

2. OBJECTIVES

2.1. Study I. - Investigating the diagnostic value of the device-supported measurement in intra-oral halitosis (IOH)

We aimed to find and recommend the best method for the device-supported measurement of oral malodor. We seek to answer the following clinical questions: Are halitometers suitable for measuring IOH as OMs?

We hypothesized that the halitometers are as appropriate as the organoleptic method to measure the level of halitosis.

2.2. Study II. - Investigating the efficacy of ClO_2 in IOH

In Study II, we wanted to understand: Are mouthwashes containing ClO_2 effective in patients with IOH?

We hypothesized that mouthwashes containing ClO_2 are more effective than placebos and as effective as other mouthwashes in reducing oral malodor.

3. METHODS

Both meta-analyses were registered at the International Prospective Register of Systematic Reviews (PROSPERO), using the registration numbers CRD42022320024 (Study I.) and CRD42021281195 (Study II.).

The Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA 2020) led to the processing of the meta-analyses.

3.1. Literature search and eligibility criteria

In both cases, the literature search was done in five databases (MEDLINE, CENTRAL, Embase, Scopus and Web of Science). Study I. included studies where organoleptic measurement in intraoral halitosis was correlated to halitosis measuring devices. Case reports, non-English conference papers, in vitro or animal research and non-English publications were rejected. We didn't include children in our population. In Study II., we searched for randomized controlled trials, where the effect of ClO2 mouthwashes was contrasted to other mouthwashes and measured with an organoleptic scale (OLS) or with devices that measure the VSC. We did not include patients with systemic diseases or children as a population, nor in vitro or animal trials. We also did not include experiments where mouthwash contained ClO2 and zinc together in the same mouthwash.

3.2. Study selection and data collection

After automatic and manual duplicate elimination, two researchers independently checked eligible titles and abstracts, later full texts. In the event of a dispute, a third investigator was brought in. We also scanned

the grey literature, review papers, and articles that met the eligibility requirements' reference lists. Two investigators who worked independently collected all available data in predefined tables. From Stud I., the following data items were collected: first author, year of publication, study design, demographic data of the population, type of index and reference tests, type of correlations, c.c., exclusion of extraoral halitosis and children, sensitivity, specificity, threshold, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC). In those articles where correlations were available for multiple dates, only one (preferably the baseline) was included in the analyses. The following data from the eligible articles were extracted from Stud II.: population characteristics, interventions, comparator, measurement methods, and the changes in the outcomes (OLT and VSC).

3.3. Quality assessment

Two investigators worked independently with the quality assessment tool for diagnostic accuracy studies (QUADAS-2) and QUADAS-C for Study I. and the revised tool for assessing the risk of bias (RoB 2) for Study II. To assess the quality of the evidence for Studies I and II., we used the GRADEpro tool to perform the evidence profile according to the GRADE Handbook.

3.4. Data synthesis and analysis

Since we predicted significant between-study heterogeneity, the Hartung-Knapp adjustment was used to do random-effects meta-analyses on the various datasets. Variance measure I^2 and Tau-squared (τ^2) statistics were applied to estimate the degree of heterogeneity among the studies. With the Q profile approach, the constrained maximum-likelihood estimator was used to estimate the confidence interval (CI)

variance in Study I. Study II. analyzed the data by mean difference (MD) and standardized mean difference (SMD) meta-analyses with a 95% confidence level.

Forest plots were applied to represent the results graphically. Where appropriate, we also provided the results' prediction ranges or the projected range of their influence on subsequent investigations. Outlier and influence analyses were carried out. All statistical analyses were performed using the R statistics software and its meta-package

4. RESULTS

4.1. Correlation between the halitometers and OLS (Study I.)

The qualitative analysis could involve 14,635 participants.

The pooled Spearman's c.c. for the sulfide monitor devices was 0.65; 95% CIs: [0.53 – 0.74]; I^2= 95%, p<0.01, and the pooled Pearson c.c. for the sulfide monitor devices was 0.57; 95% CIs: [0.35 – 0.73]; I^2= 93%, p<0.01.

The pooled Spearman's c.c. for portable gas chromatographs was 0.69; 95% CIs: [0.63 – 0.74]; I^2= 12%, p<0.01, and the pooled Pearson c.c. for portable gas chromatographs was 0.59; 95% CIs: [0.37 – 0.75]; I^2= 90%, p<0.01.

The pooled Spearman's c.c. for the gas chromatographs was 0.76; 95% CIs: [0.67 – 0.83]; I^2= 0%, p<0.01, and the pooled Pearson c.c. for gas chromatographs was 0.57; 95% CIs: [0.32 – 0.47]; I^2= 84%, p<0.01.

In the subgroups of sulfide monitor data where the exclusion of systemic diseases was unknown, the correlation was significantly lower (p<0.05) compared to the subgroup where systemic diseases were excluded. The pooled Spearman's c.c. for sulfide monitors without systemic diseases was 0.72; 95% CIs: [0.56 – 0.83]; I^2= 80%, p<0.01 and without the information on the exclusion or inclusion of systemic diseases the pooled Spearman's c.c. was 0.50; 95% CIs: [0.44 – 0.54]; I^2= 34%, p<0.01.

The pooled Spearman's correlations with the OralChroma for the H_2S was 0.59; 95% CIs: [0.51 – 0.66]; I^2= 93%, p<0.01. The pooled Spearman's c.c. for the CH_3SH was 0.58; 95% CIs: [0.45 – 0.68]; I^2= 97%, p<0.01.

The pooled Spearman's c.c. for the $(CH_3)_2S$ was 0.24; 95% CIs: [0.09 – 0.39]; I^2= 80%, p<0.01. H_2S and CH_3SH correlated significantly (p<0.05) better to OLS than $(CH_3)_2S$.

The pooled Spearman's c.c. between the portable gas chromatographs and sulfide monitors was 0.55; 95% CIs: [0.50 – 0.59]; I^2= 0%, p<0.01.

The pooled Spearman's c.c. for sulfide monitors on the 4-point sale was 0.52; 95% CIs: [0.28 – 0.70]; I^2= 41%, p<0.01.

4.2. Effect of ClO_2 (Study II.)

The quantitative analysis comprised 234 patients in total. There were no patient-reported adverse events mentioned in any of the studies. When compared to the group, the ClO_2 group's organoleptic ratings significantly improved in our forest plots. One-day OLS data were pooled from three articles after 4, 6 and 12 hours. The data from the study indicates that ClO_2 was successful in achieving its intended purpose within a single day (MD: -0.82; 95% CIs): [-1.04 – -0.6]; heterogeneity: I^2= 0%, p= 0.67).

OLS data was collected over a period of one week and was sourced from three different articles. The findings suggest that the group undergoing the experiment achieved a positive result (MD: -0.24; 95% CI: [-0.41 – -0.07]); I^2= 0%, p= 0.52).

OLS data was collected over two weeks and sourced from three articles. The results also favor CLO_2 mouthwashes in halitosis (MD: -0.72; 95% CI: [-1.45 – 0.02]; I^2= 91%, p< 0.01).

Changes in H_2S and CH_3SH on one-day data were collected from three articles. Significant differences were found in H_2S data (SMD: -1.81; 95% CI: [-2.52 – -1.10]; I^2= 73.4%, p= 0.02). The result of CH_3SH one-day data was (SMD: -7.26; 95% CI: [-18.93 – 4.4]; I^2= 98.0%, p< 0.01).

4.3. Certainty of evidence

Due to study designs and considerable variability, the GRADE evidence table displayed extremely low certainty of evidence for the major outcomes in the case of Study I.

The researched outcomes in Study II. received very low to moderate evidence certainty in the certainty rating. Findings needed to be downgraded because of statistical heterogeneity, risk of bias assessment, and imprecision.

5. CONCLUSIONS

5.1. Study I.

We answered our clinical question: no particular halitometer is superior to others or adequate as a stand-alone assessment method in IOH. Despite its limitations, OLS is the recommended diagnostic technique. Our null hypothesis that the halitometers are as appropriate as the organoleptic method to measure the level of halitosis is rejected.

5.2. Study II.

Our findings indicate that mouthwashes containing ClO_2 may play a more significant role in supportive therapy for oral halitosis. The evidence suggests that it is more effective than a placebo in the short term for treating halitosis. Our null hypothesis was partially rejected because we can not prove that mouthwashes containing ClO_2 are as effective as other mouthwashes in reducing oral malodor because of a lack of data. A personalized treatment plan is particularly beneficial for patients with elevated levels of H_2S, as ClO_2 is more effective against this molecule.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

6.1. Publications related to the thesis

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