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Evaluation of Slow-release Mucoadhesive Paste of" MUCODENTOL "in Oral Vestibule on Prophylaxis of Symptoms and Signs of COVID-19 Disease: A triple-blind, randomized clinical trials

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Research Article

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Abstract

Background

To evaluate the efficacy of a slow-release mucoadhesive paste containing 3% Carvacrol (Mucodentol) applied to the oral vestibule in preventing the onset and severity of COVID-19 symptoms among high-risk healthcare personnel.

Methods

A triple-blind, randomized, placebo-controlled field trial was conducted on 1,624 asymptomatic healthcare workers in COVID-19 center hospitals. Participants were randomly assigned to use either Mucodentol or an identical placebo paste three times daily for four weeks. The primary outcome was the total symptom severity score, assessed weekly via telephone interviews. Data were analyzed using an intention-to-treat approach with Generalized Estimating Equations (GEE) to model the effect of the intervention over time, adjusting for key confounding variables.

Results

Analysis with the GEE model, after adjusting for covariates, revealed a statistically significant group-by-time interaction for the total symptom severity score ($p < 0.001$), indicating a time-dependent treatment effect. Mucodentol demonstrated significant benefits for a range of specific symptoms, including dry cough, shortness of breath, fatigue, myalgia, and ageusia (loss of taste). The intervention's effect on individual symptoms varied dynamically over the study period, with some showing increasing benefits over time.

Conclusions

The analysis revealed that Mucodentol provided a significant and progressively evolving benefit in reducing overall symptom severity over the course of the study ($p < 0.001$), after adjusting for key confounding variables.

Trial registration

IRCT20130428013151N2 '(20200506), https//en.irct.ir/trial/49356.

Introduction

The COVID-19 disease, which was first reported in Wuhan, China in late December 2019, rapidly spread across China and many other countries around the world, claiming many victims. Unfortunately, the spread of this disease in Iran has, according to reported statistics from the Ministry of Health and Medical Education, resulted in 45,000 infected individuals and at least 2,900 deaths to date (1).

Given that most treatments for this disease have not been specifically effective, a key recommendation from the World Health Organization and other health organizations has been the strict implementation of health protocols to prevent infection. Based on studies concerning the disease's mechanisms and the initial colonization of the virus in the mouth and throat of individuals, it seems that the use of some readily available products with minimal potential side effects—products possessing antimicrobial and antiviral properties that work by reducing the local microbial load—could play a valuable role in preventing and even alleviating symptoms in the early stages of the disease in individuals exposed to COVID-19 (2).

The pharmaceutical product Mucodentol, which is formulated as an adhesive mucosal paste based on a 3% Carvacrol composition, has proven highly effective in controlling oral and pharyngeal infections. Its mechanism relies on a sustained-release formula that delivers an appropriate drug concentration to the site of infection, thereby enhancing the therapeutic effect and reducing local side effects.

Just as handwashing can reduce the microbial load on the hands and prevent its transfer to the nose and mouth and subsequently to the respiratory tract it is anticipated that the antiviral properties of this herbal drug can reduce the viral load in the mouth and throat. Furthermore, its antibacterial and antifungal properties may help reduce secondary infections.

In line with this, the present study will investigate the use of Mucodentol for disease prevention and personal protection of healthcare personnel working in COVID-19-related medical centers. Based on existing evidence from preliminary studies conducted by the researchers and previous laboratory studies, it appears that the use of this drug may be effective in reducing and eliminating the microbial load in the mouth and throat of exposed individuals, and to a considerable extent, in controlling and alleviating symptoms caused by the disease.

On February 12, 2020, the World Health Organization, recommended phenolic compounds as disinfectants against the coronavirus, listing hypochlorite (bleach), alcohol, hydrogen peroxide, quaternary ammonium compounds, and phenolic compounds as effective substances (1). Carvacrol is one such powerful phenolic compound that has been known for years and is used as an antibacterial, antiviral, and antifungal agent, a use further supported by a 2003 WHO document which announced that various compounds, including 2% phenol, can destroy coronaviruses in less than 5 minutes (2). Extracted as a monoterpene derivative of “Cymene”, carvacrol has been used as a food additive for many years due to its bacteria growth-inhibiting properties, and it also acts as a potential activator of ion channel receptors TRPV3 and TRPA1, leading to its use in the food industry as a volatile oil component, a flavouring agent, and an antimicrobial substance.

In the 2013 article "Antiviral Efficacy and Mechanisms of Action of Oregano Essential Oil and Its Primary Component Carvacrol Against Murine Norovirus," American researchers demonstrated the antiviral effects of carvacrol against human norovirus and MNV (6). In Lorestan province, the drug Mucodentol, with carvacrol as its major component, has been produced in recent years by Kharaman Pharmaceutical Company. This product is a sustained-release adhesive mucosal paste that has been used clinically as

an oral disinfectant and anti-inflammatory agent based on the active ingredient of mountain savory, whose major constituent is carvacrol. It should be noted that this drug has official approval from the Ministry of Health for throat disinfection, which has been appended to the documentation. Given that the number of healthcare workers in Iran is significantly higher than the global average, this study aims to use topical Mucodentol to prevent the onset of clinical symptoms and the need for hospitalization related to COVID-19 in asymptomatic personnel working in hospitals providing care to COVID-19 patients in Lorestan province.

Materials and methods

In this field trial, the study population consists of all physicians, nurses, nursing assistants, service personnel, administrative staff, and personnel from the pharmacy, operating room, radiology, and laboratory departments in hospitals providing services to COVID-19 patients in the cities of Khorramabad, Al-Shatar, Nurabad, and Dorud, and Qom during the first quarter of the March-June 2020. Eligible participants must have been free of all seven specified symptoms fever, dry cough, shortness of breath, sudden loss of taste or smell, sore throat, myalgia, and arthralgia in the two weeks prior, and must also meet all the study's inclusion criteria.

Sampling method:

Sampling will be conducted using a quota method; whereby each city's quota from the total sample size is determined proportionally to the number of hospital personnel in that city, and within each hospital, convenience sampling will be used. The allocation of samples to the two groups will be performed using stratified randomization. Strata will be created based on the city of employment (Khorramabad, Al-Shatar, Qom, Nurabad, or Dorud), personnel gender (male, female), and personnel age group (under 40 years, 40 years or older) (totaling 16 strata). Within each stratum, permuted block randomization will be used to assign personnel to the two groups, and the block size will be four. This study is triple-blinded; meaning the personnel, the outcome assessor—who is not a member of the research team—and the data analyst are all unaware of the type of intervention. The two drug compositions in question are identical in appearance and color, with no differences between them, and are labeled only with codes A and B. Finally, after data analysis, unblinding will be performed by an individual who is not a member of the research team.

Based on a similar study by Reusken et al.(20):

Approximately 4% of Dutch hospital personnel had a confirmed COVID-19 infection. Therefore, if in this study we aim to reduce this percentage to one-third, i.e., to approximately 1.33%, we will have:

$$n=(Z_{1-\alpha/2}+Z_{1-\beta})^2(p_1q_1+p_2q_2)/(p_1-p_2)^2=(1.96+1.28)^2(0.04\times0.96+0.013\times0.987)/(0.04-0.013)^2\approx738$$

$\alpha = 0.05$

1-β = 0.90

P1 = 0.040

(The expected proportion of confirmed infection based on PCR in the placebo group)
P2 = 0.013

(The expected proportion of confirmed infection based on PCR in the drug group)

Subsequently, considering a potential 10% dropout rate, the final sample size was determined to be 812 individuals per group.

The study participants were selected based on specific inclusion and exclusion criteria. Eligible individuals were required to have no hypersensitivity to similar drugs, no history of prior hospitalization for COVID-19, and no confirmed COVID-19 diagnosis via PCR test. Furthermore, participants needed to have no history of abnormal chest X-rays or lung CT scans during the pandemic period, possess the ability to communicate for telephone interviews, and be under 60 years of age. Conversely, exclusion criteria encompassed unwillingness to cooperate, inability to be reached for telephone interviews, irregular use of the study drug, hypersensitivity to the drug, pregnancy and breastfeeding status, and death of the patient after enrollment in the study.

Procedure

Following the approval of the proposal by the Research Council of the Medical School and the University Ethics Committee, data will be collected from 1624 volunteer, asymptomatic personnel working in various departments of COVID-19 center hospitals, all of whom must meet the study's inclusion criteria. Written informed consent will be obtained from all volunteers, who must also be verbally communicative and available for telephone interviews.

After random allocation of volunteers into two groups, the following interventions will be administered:

Dentol Group:Will be provided with Mucodentol ointment and instructed to use it three times daily and before sleep, applying two drops into the buccal vestibule, with no need for reapplication until the next morning.

Placebo Group: Will be provided with a placebo ointment and instructed to use it identically, applying two drops into the buccal vestibule as above.

Participants will be instructed to shake the tube gently before each use to mix the contents, which ensures a consistent formulation and minimizes any potential stinging sensation, as the unmixed drug has a strong flavor that can be unpleasant. The 3% Mucodentol adhesive mucosal paste, manufactured by Kharaman Pharmaceutical Company in 5-gram tubes, will be consumed at a rate of two tubes per participant per week, totaling eight tubes over the four-week study period. The placebo ointment is identical in size and appearance.

All participants will receive standard personal protection advice against COVID-19 per the Ministry of Health protocol, including frequent handwashing, mask use, appropriate PPE for healthcare workers, gloves, etc.

To ensure researcher safety, symptom data will be collected via weekly telephone interviews at the end of weeks one through four. Participants who discontinue the use of Mucodentol or placebo will be withdrawn from the study. If clinical symptoms of COVID-19 develop, volunteers will be examined by an infectious disease specialist. History and physical examination will be conducted per the Ministry of Health protocol, with further diagnosis via CXR, lung CT, and Sao2 measurement as needed. It is important to note that if a volunteer is hospitalized for COVID-19-related reasons or has a positive PCR test, the administration of the drug/placebo and the weekly symptom monitoring will be discontinued.

The data collection tool is a researcher-developed checklist, created by reviewing relevant literature and integrating existing tools from national protocols, WHO, and CDC. To confirm its content validity qualitatively, it was reviewed by four faculty members of the Lorestan University of Medical Sciences. The tool includes demographic details (age, gender, residence, department, household size), occupational characteristics (work department, shift status, weekly work hours), type of underlying disease/risk factors, the presence of clinical symptoms (including sore throat, fever/chills, dry cough, shortness of breath, myalgia, arthralgia, and sudden loss of smell/taste), as well as the need for hospitalization, results of lung CT scans, chest X-rays, and PCR tests.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle, with missing data handled using the Last Value Carried Forward method. Descriptive statistics, including frequency distributions, means (± standard deviations), medians (interquartile ranges), and graphical summaries, were used to characterize the data.

Univariate analyses comparing baseline characteristics employed Chi-square, Fisher's exact, independent t-tests, or Mann-Whitney U tests, as appropriate. All baseline variables with a univariate p-value < 0.25 (including hospital, gender, job category, and history of underlying diseases/tobacco use) were considered for multivariate modeling. To mitigate multicollinearity, department of service, hypertension history, and asthma history were excluded from the final models. The primary analysis used marginal models with Generalized Estimating Equations (GEE), an identity link, and an exchangeable correlation structure to evaluate the effect of Mucodentol on the clinical symptom severity score over time. Secondary outcomes were analyzed using logistic, Firth logistic, and multinomial regression models. All analyses were performed at a 0.05 significance level using SPSS (v21/22) and SAS (v9.2).

The study faced several limitations, including the inability to perform baseline PCR testing for all volunteers due to access constraints, high costs, and the limited sensitivity of available test kits, alongside challenges related to irregular participant adherence to the drug or placebo regimen and

occasional inability to conduct telephone interviews. Furthermore, diagnostic criteria were necessarily based on the evolving guidelines from the Ministry of Health and WHO, which were frequently updated with new information such as the recognition of anosmia as a symptom during the pandemic. Ethically, informed written consent was secured from all volunteers for their participation and interviews, with firm assurances given that their personal identifiers would remain confidential and not be used within the study.

Results

Comparison of baseline variables revealed significant differences ($p < 0.05$) between the Mucodentol and placebo groups in the distribution of hospital of service, department of service, job category, history of underlying disease, and history of asthma. No other baseline characteristics showed statistically significant differences.

Symptom Severity Analysis

All analyses were performed using a marginal model with GEE estimation, adjusting for hospital of service, job category, gender, history of underlying disease, and tobacco use (Table 1).

Table 1
Baseline Characteristics of Participants in the Placebo and Mucodentol Groups

Variable	Category	Placebo Group (n, %)	Mucodentol Group (n, %)	p-value
Hospital of Employment	Shohad-Ashayer	214 (34.2%)	369 (41.8%)	0.011
	Qom	297 (47.5%)	379 (42.9%)	
	Other hospitals	114 (18.2%)	135 (15.3%)	
Gender	Male	256 (41.0%)	330 (37.4%)	0.164
	Female	369 (59.0%)	553 (62.6%)	
Age	< 40 years	469 (75.0%)	649 (73.5%)	0.512
	≥ 40 years	156 (25.0%)	234 (26.5%)	
Department of Employment	Emergency	213 (34.1%)	247 (28.0%)	< 0.001
	ICU	88 (14.1%)	161 (18.2%)	
	Inpatient Ward	152 (24.3%)	323 (36.6%)	
	Operating Room	161 (25.8%)	104 (11.8%)	
	Administrative	11 (1.8%)	48 (5.4%)	
Job Category	Nurse	377 (60.3%)	623 (70.6%)	< 0.001
	Administrative Staff	114 (18.2%)	136 (15.4%)	
	Service Staff	109 (17.4%)	118 (13.4%)	
	Physician	25 (4.0%)	6 (0.7%)	
Underlying Disease History	Yes	47 (7.5%)	93 (10.5%)	0.048
	No	578 (92.5%)	790 (89.5%)	
Smoking Status	Yes	8 (1.3%)	22 (2.5%)	0.133
	No	617 (98.7%)	861 (97.5%)	
Diabetes History	Yes	3 (0.5%)	9 (1.0%)	0.379
	No	622 (99.5%)	874 (99.0%)	
Hypertension History	Yes	25 (4.0%)	52 (5.9%)	0.122
	No	600 (96.0%)	831 (94.1%)	
IHD History	Yes	4 (0.6%)	6 (0.7%)	< 0.999
	No	621 (99.4%)	877 (99.3%)	

Variable	Category	Placebo Group (n, %)	Mucodentol Group (n, %)	p-value
COPD History	Yes	1 (0.2%)	2 (0.2%)	< 0.999
	No	624 (99.8%)	881 (99.8%)	
Asthma History	Yes	1 (0.2%)	14 (1.6%)	0.006
	No	624 (99.8%)	869 (98.4%)	
History of Addiction	Yes	1 (0.2%)	2 (0.2%)	< 0.999
	No	624 (99.8%)	881 (99.8%)	

Several symptoms demonstrated significant group-by-time interactions, indicating Mucodentol's effect varied dynamically over the study period. For fever ($p = 0.022$), the treatment effect decreased over time, showing its largest intergroup difference at Time 1 (1.021 vs 1.091) and smallest at Time 4 (1.021 vs 1.043). Conversely, for dry cough ($p = 0.001$), the therapeutic effect increased over time, with the largest differences observed at Time 3 (1.110 vs 1.162) and Time 4 (1.098 vs 1.137). The effect on sore throat ($p < 0.001$) varied temporally, being most pronounced at Time 1 (1.219 vs 1.149) and Time 2 (1.308 vs 1.205), while the effect on chills ($p < 0.001$) decreased over time, with its maximal difference at Time 1 (1.040 vs 1.110). A pattern of increasing benefit was seen for both arthralgia ($p = 0.006$), peaking at Time 3 (1.024 vs 1.062), and myalgia ($p < 0.001$), with the largest differences at Time 3 (1.055 vs 1.155) and Time 4 (1.049 vs 1.125). The effect on diaphoresis ($p = 0.003$) also varied, reaching its maximum at Time 3 (1.036 vs 1.101). For neurological symptoms, the impact on anosmia ($p = 0.030$) and ageusia ($p = 0.004$) showed temporal variation, with the largest effects both observed at Time 2 (1.036 vs 1.122 and 1.056 vs 1.146, respectively), as did dizziness ($p < 0.001$), which showed its greatest difference at Time 2 (1.095 vs 1.183) (Fig. 1).

For several symptoms where no significant interaction with time was observed, Mucodentol nonetheless demonstrated a significant and consistent overall benefit, as shown by a significant main effect; this was evident for shortness of breath ($p = 0.004$), with lower adjusted severity scores in the Mucodentol group (1.049) compared to the placebo group (1.089), for fatigue ($p < 0.001$), which also showed a clear advantage for the treatment group (1.136 vs. 1.196), and for diarrhea ($p < 0.001$), where the Mucodentol group again had a lower mean severity score (1.058 vs. 1.096).

For symptoms including hemoptysis, nausea, vomiting, and anorexia, no significant main effects of the drug or interactions with time were found, although the severity of all these symptoms demonstrated significant temporal variations across the study period ($p < 0.001$ for the time effect)(Fig. 2). Meanwhile, headache showed a non-significant trend toward benefit with Mucodentol ($p = 0.058$), with lower adjusted scores in the treatment group (1.133) versus the placebo group (1.158). Importantly, a significant group-by-time interaction was observed for the total symptom score ($p < 0.001$), indicating that the effect of Mucodentol on the overall clinical presentation varied over time, with the largest

difference between groups seen at Time 3 (18.908 vs. 19.797) and the smallest at Time 2 (19.814 vs. 20.417) (Fig. 3).

Discussion

This large, triple-blind, randomized field trial demonstrated that the slow-release mucoadhesive paste *Mucodentol*, containing 3% carvacrol, significantly reduced the overall severity of COVID-19-related symptoms among healthcare workers at high risk of exposure. After adjustment for key confounders using a Generalized Estimating Equation (GEE) model, a significant time-dependent interaction ($p < 0.001$) was found, indicating that *Mucodentol* progressively lessened the clinical severity of COVID-19 symptoms over the four-week intervention period. Specifically, marked benefits were observed for respiratory and systemic manifestations including dry cough, shortness of breath, fatigue, myalgia, and taste disturbances. These findings suggest a cumulative protective effect potentially linked to the pharmacokinetics of the mucoadhesive formulation, which ensures prolonged mucosal contact and sustained local release of carvacrol.

Our findings are consistent with previous laboratory and clinical research demonstrating the broad-spectrum antiviral, antibacterial, and antifungal effects of carvacrol, the major bioactive phenolic compound in *Satureja khuzistanica* and *Origanum* species. In vitro studies have shown that carvacrol inactivates a range of viruses, including murine norovirus and herpes simplex virus type 1 (HSV-1), primarily through disruption of the viral envelope and capsid proteins (Gilling et al., 2014; Sharifi-Rad et al., 2016). Similarly, Pilau et al. (2011) reported that carvacrol exhibited potent antiviral activity against human rotavirus and respiratory syncytial virus, with selectivity indices comparable to those of standard antiviral drugs. These mechanisms may explain the observed reduction in viral symptom expression among *Mucodentol* users, as SARS-CoV-2, like many enveloped viruses, is sensitive to lipid-soluble phenolic compounds that compromise membrane integrity.

Furthermore, our results align with previous clinical findings demonstrating the local antimicrobial and anti-inflammatory properties of Dentol™, another carvacrol-containing formulation. Shahab et al. (2010) observed that subgingival irrigation with Dentol™ led to a significant decrease in anaerobic bacterial load and inflammatory cytokines such as IL-1β and TNF-α, achieving efficacy comparable or superior to chlorhexidine. The anti-inflammatory properties of carvacrol have also been confirmed by Landa et al. (2009), who showed that carvacrol inhibits COX-2-mediated prostaglandin E_2 biosynthesis at concentrations similar to those of indomethacin, suggesting that it may attenuate mucosal inflammation and oxidative stress associated with viral replication.

Another plausible explanation for the progressive benefit observed in our trial is the mucoadhesive delivery system. Mucoadhesive carriers extend the contact time of active ingredients on mucosal surfaces, allowing sustained drug release and localized antiviral protection. Similar findings were reported by Rojsitthisak et al. (2021), who demonstrated enhanced mucosal drug retention and antiviral efficacy using mucoadhesive nanoparticles for intranasal favipiravir delivery. The *Mucodentol* paste likely

provides similar advantages by maintaining a constant protective layer in the oral vestibule, the primary site of SARS-CoV-2 entry and replication.

The oral cavity plays a critical role in the early stages of COVID-19 infection, as ACE2 receptors—the main viral entry points—are abundantly expressed in the oral mucosa, tongue, and salivary glands (Paradowska-Stolarz, 2020). Several studies have reported frequent oral manifestations in COVID-19, such as dysgeusia, xerostomia, and mucosal inflammation (Iranmanesh et al., 2020; Rusu et al., 2020; Aragoneses et al., 2021). By directly reducing viral load and mucosal inflammation in this region, *Mucodentol* may help prevent or mitigate such oral and systemic symptoms.

The findings also support the World Health Organization's (2020) recommendation of phenolic compounds including carvacrol derivatives as effective virucidal agents against coronaviruses. Earlier WHO laboratory data indicated that phenolic disinfectants could inactivate SARS-CoV within minutes, supporting the biochemical plausibility of our results.

Nonetheless, several limitations should be acknowledged. First, due to logistical constraints, baseline PCR screening could not be performed for all participants, potentially introducing undetected asymptomatic infections at enrollment. Second, although adherence was generally high, some participants reported irregular use of the paste or missed follow-up interviews. Finally, the evolving nature of COVID-19 diagnostic criteria during the early pandemic may have influenced symptom classification and temporal comparisons. Despite these challenges, the large sample size, rigorous triple-blind design, and use of GEE modeling strengthen the internal validity and generalizability of the findings.

Conclusion

The results of this study are consistent with prior in vitro and clinical research confirming the antiviral, antibacterial, and anti-inflammatory properties of carvacrol-based formulations such as Dentol™ and Satureja khuzistanica extracts. Compared to conventional oral antiseptics, Mucodentol offers an innovative and safe prophylactic approach, particularly suitable for continuous use in healthcare and high-exposure environments.

Further multicenter clinical trials with molecular confirmation of infection (PCR and antigen testing) and extended follow-up are recommended to evaluate the long-term efficacy, safety, and potential use of Mucodentol as a preventive adjunct in respiratory viral epidemics, including emerging SARS-CoV-2 variants.

Declarations

Conflict of interest:

The authors deny any conflict of interest in any terms or by any means during the study.

Sources of Funding

No funding was secured for this study.

Ethical

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Lorestan University of Medical Sciences (IR.LUMS.REC.1399.013), research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and registered in the Iranian Registry of Clinical Trials (IRCT20090304001739N3). https://irct.behdasht.gov.ir/trial/49065

Consent to participate:

Patient consent was obtained prior to the surgery.

Contributors' Statement Page:

Dr. Sepideh Vahabi and Dr. Ali Salehnia conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Zahra Abbasi: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Ghasem Azimi: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Author Contribution

Dr. Sepideh Vahabi and Dr. Ali Salehnia conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.Dr. Zahra Abbasi: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr. Ghasem Azimi: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

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N/A

Data Availability

The dataset generated and/or analyzed during the current study is not publicly available due to ethical restrictions and institutional regulations governing patient confidentiality. De-identified data may be made available from the corresponding author upon reasonable request and subject to approval by the institutional ethics committee. The statistical analysis workflow and SPSS procedures are described in the Methods section to ensure reproducibility of the reported results.

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Figures

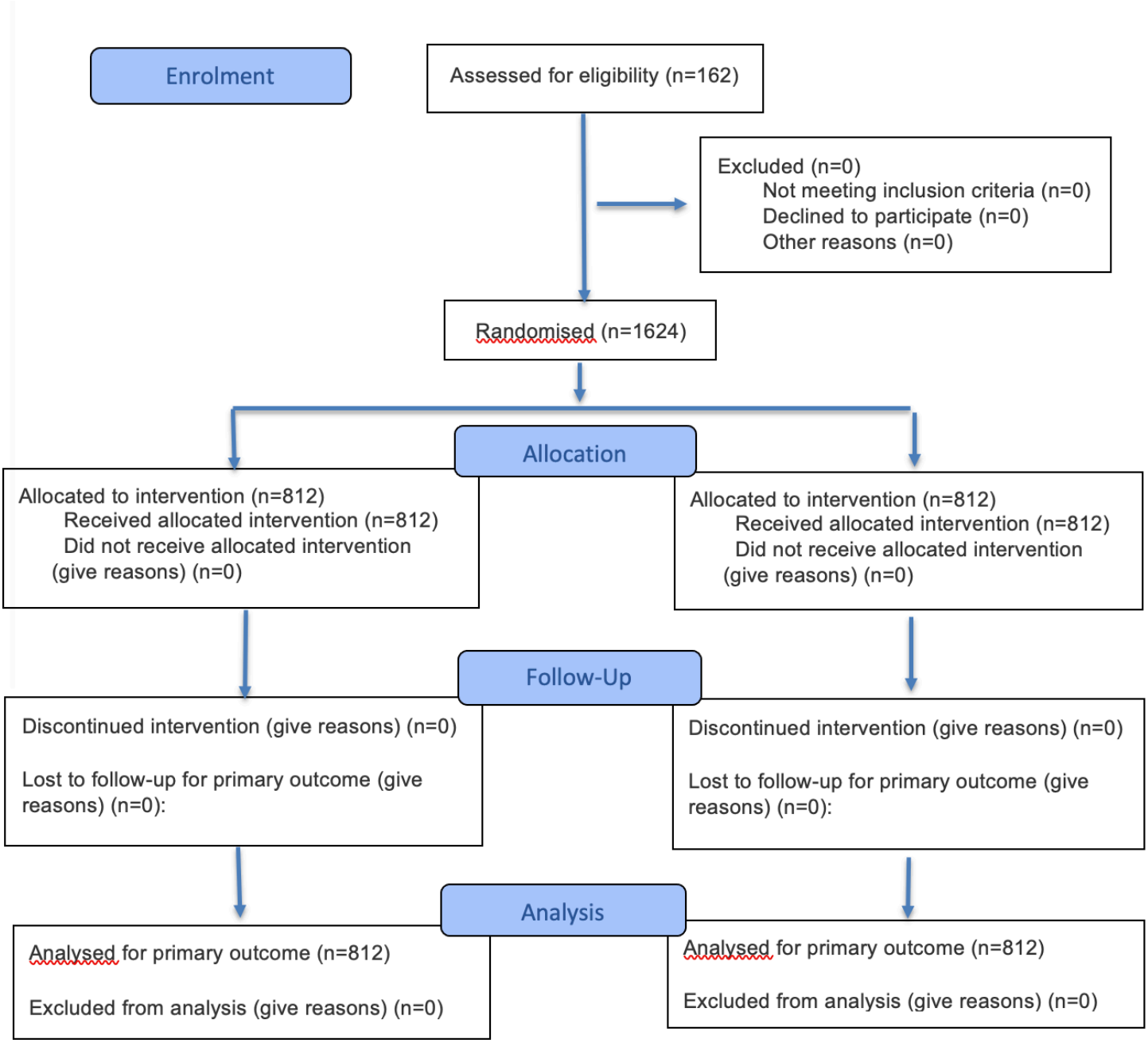


Figure 1

Comparison between the placebo and Mucodentol groups, including fever, dry cough, throat, breath, fatigue and headache.

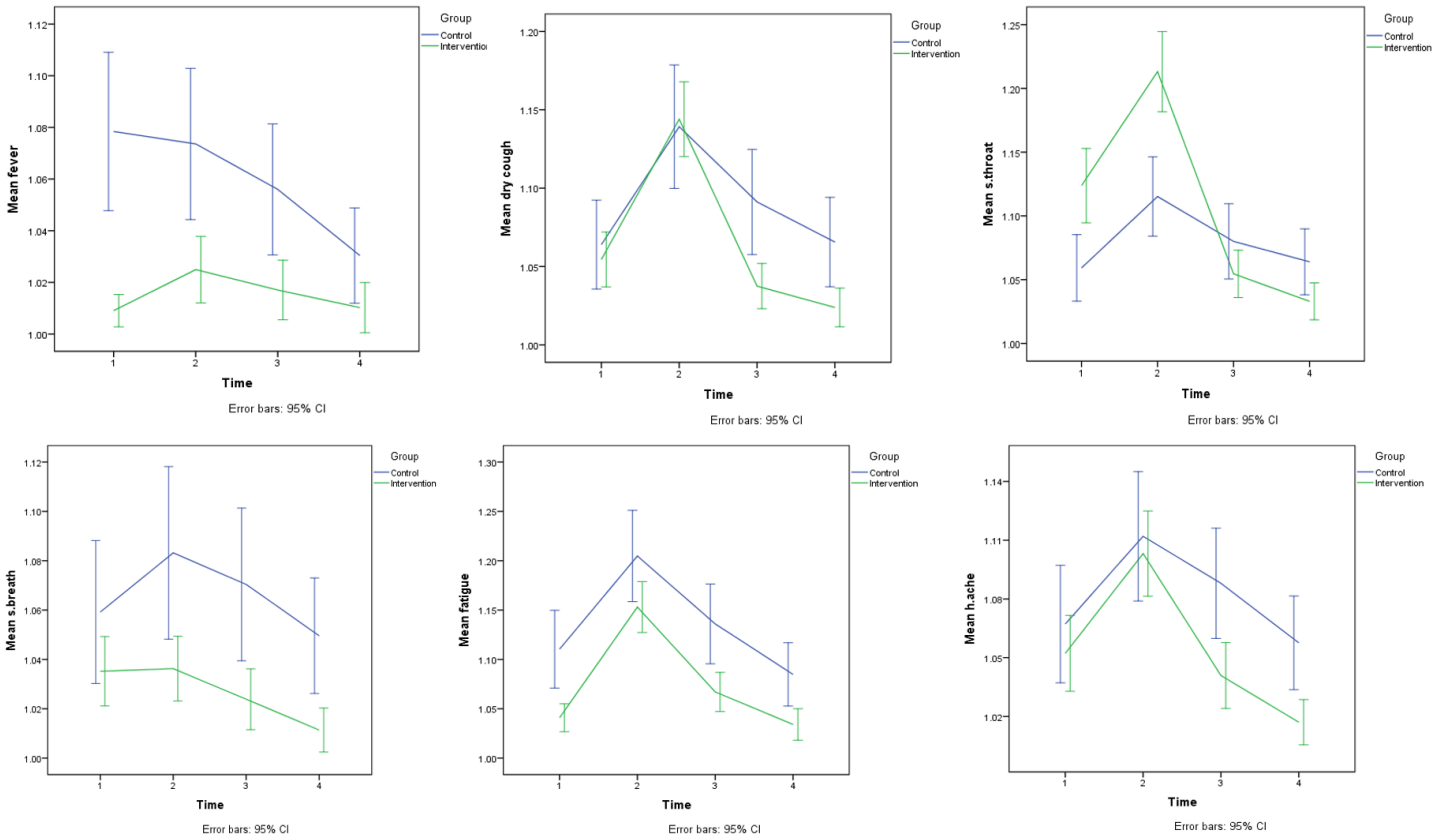


Figure 2

Comparison between the placebo and Mucodentol groups, including shake, arthralgia, myalgia, hemoptysis, Sweating, and nausea.

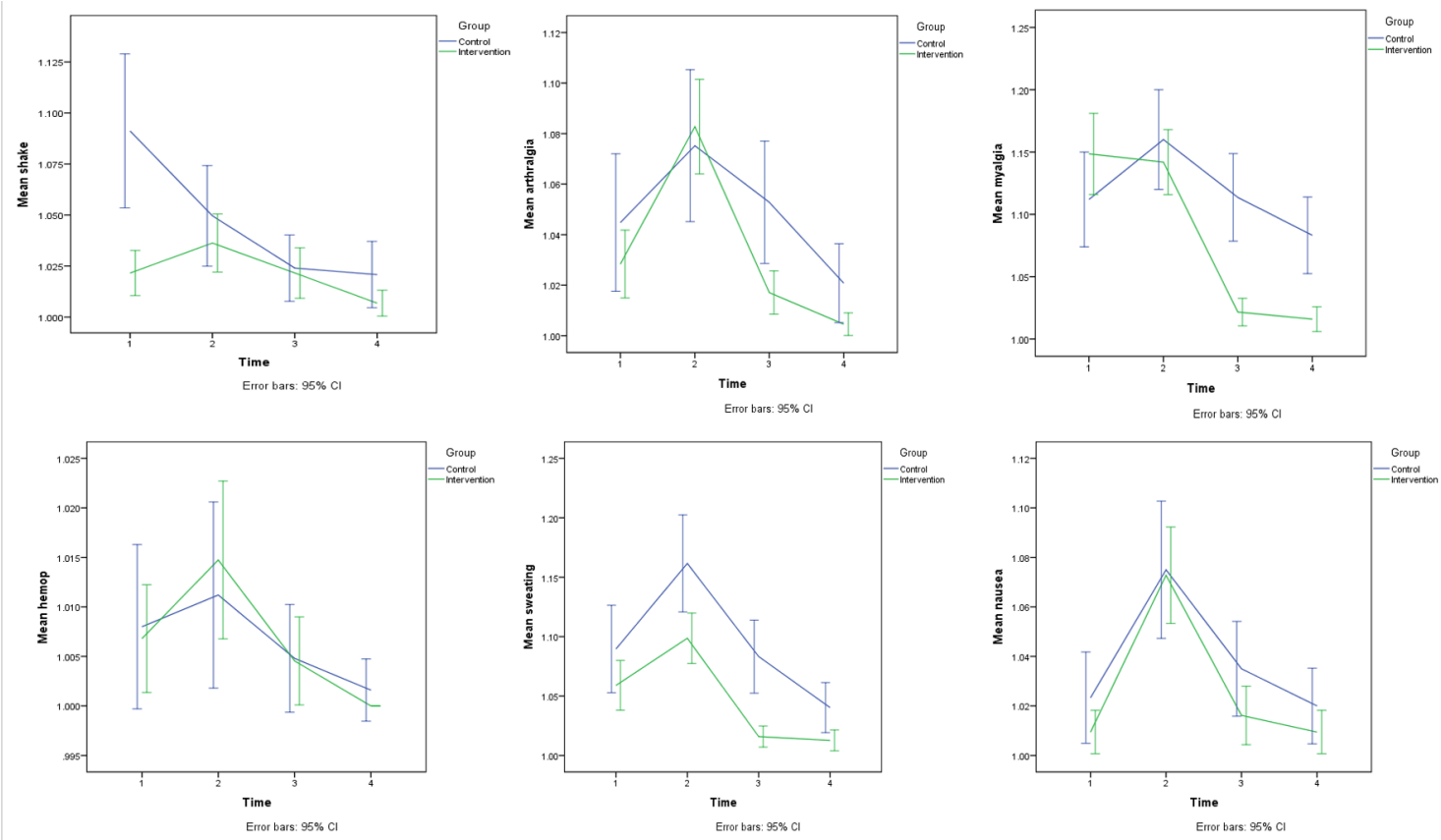


Figure 3

Comparison between the placebo and Mucodentol groups, including dizziness, reduced taste, reduced smell, loss of appetite, and vomiting.

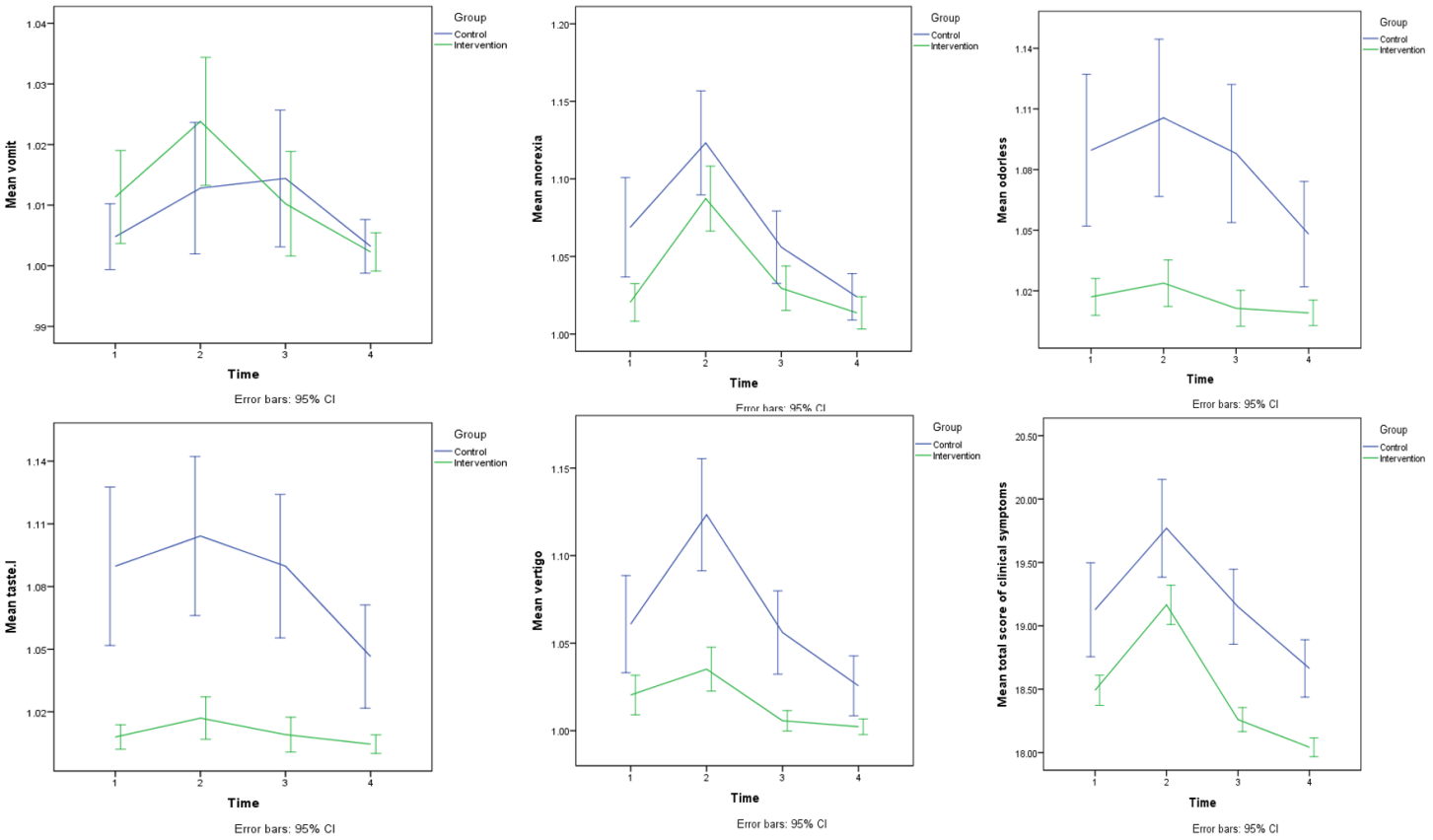


Figure 4

Legend not included with this version.

Supplementary Files

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- Trials1.pdf