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Evaluation of different mouthwashes for the treatment of halitosis

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Abstract

Background: Halitosis, defined as an offensive or unpleasant odor, is a very common problem affecting up to 50% of the population.

Aim: This study aims to assess the efficacy of different mouthwashes in the treatment of halitosis.

Methodology: A PubMed search through June 2018 using the following Medical Subject Headings terms “halitosis/therapy” and “mouthwashes” was performed. Studies with findings of the use of mouthwashes for the treatment of halitosis were assessed. From 75 studies of mouthwashes with full-text availability, 62 were excluded for several reasons: Studies with no placebo group (35) and no usable data (27). The data were analyzed using statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For continuous outcomes, the estimates of the effects of an intervention were expressed as mean differences (MD) or standardized MD (SMD) using the inverse variance method with 95% confidence intervals.

Results: A total of 13 studies on the treatment of halitosis with mouthwashes were included in this meta-analysis. The greatest reductions in organoleptic score were achieved with the zinc acetate and chlorhexidine diacetate mouthwash (MD: −1.10); of volatile sulfur compounds with 0.12% chlorhexidine gluconate mouthwash (SMD: −6.19); of the hydrogen sulfide levels with the zinc acetate and chlorhexidine diacetate mouthwash (SMD: −1.31); of the methyl mercaptan levels with the chlorine dioxide mouthwash (SMD: −1.06); and of the dimethyl sulfide levels also with the ClO_2 mouthwash (SMD: −1.22).

Conclusions: Mouthwashes are an acceptable alternative for the treatment of halitosis, especially those that contain chlorhexidine as the main active principle.

Introduction

Halitosis is defined as an offensive or unpleasant odor that emanates from hollow cavities in the mouth, nose, sinuses, or pharynx. 80% of the cases of halitosis may be attributed to oral sources and the remaining 20% to extraoral sources.[1]

The prevalence of halitosis in the general population is very variable, ranging between 2.4% and 78% although, according to the American Dental Association, about 50% of American adults suffer from oral malodor.[2]

Oral sources comprise the metabolism of different Gram-negative anaerobic bacteria species that generate volatile sulfurous compounds. Extraoral sources include infections of the upper respiratory tract and disorders of the gastrointestinal tract. Halitosis has a great negative impact on the quality of life of patients who suffer from it, hampering the interpersonal relationships.[3]

The success of the treatment of halitosis is based on the reduction in the levels of these volatile sulfurous compounds by mechanical (brushing, flossing, and tongue scraping) and/or chemicals (toothpastes and mouthwashes) procedures. Therefore, these treatments have as main goals the decrease in the number of bacteria producing these compounds and the elimination of food and cell debris from oral mucosal surfaces. Various mouthwashes have been marketed with antibacterial and flavoring agents that neutralize or mask the bad smell, improving self-esteem, and the interpersonal relationships of the patients.[4]

The aim of this study was to assess different mouthwashes proposed for the treatment of halitosis.

Methodology

A PubMed search of studies on halitosis treatment was carried out. Search strategies included the combination of the following terms from the Medical Subject Headings: "Halitosis/therapy" and "mouthwashes." A total of 160 articles published between 1967 and 2018 were found. The inclusion criteria were as follows: (a) Studies with full-text availability (*n* = 99) and (b) studies that exclusively used mouthrinses for the treatment of halitosis (*n* = 75). The exclusion criteria were as follows: (a) Studies that did not include a placebo group among its different therapeutic options (*n* = 35) and (b) studies without usable data (*n* = 27). After applying the inclusion and exclusion criteria, 13 studies were included in this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For continuous variables, the inverse of variance for the mean difference (MD) or the standardized MDs (SMD) when different scales were applied to measure the same variable were used, both with 95% confidence intervals (95% confident interval [CI]). Heterogeneity was determined according to *P* values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effects model was applied. The statistical significance level was set at $P < 0.05$.

Results

Table 1 shows the descriptive characteristics of the 13 clinical trials that evaluated 10 different mouthwashes for the treatment of halitosis.[5-17] The 10 mouthwashes and their main active ingredients were (1) 0.9% zinc chloride and essential oil – thymol, eucalyptol, and methyl salicylate (zinc lactate [Zn]+eo); (2) 0.12% chlorhexidine gluconate (0.12 chlorhexidine digluconate [CLX]); (3) 0.05% chlorhexidine, 0.05% cetylpyridinium chloride, and 0.14% zinc lactate (CLX+Cetylpyridinium chloride [CPC]+Zn); (4) 0.20% chlorhexidine gluconate (0.2 CLX); (5) 0.12% chlorhexidine gluconate and 0.05% cetylpyridinium chloride (CLX+CPC); (6) 0.12% chlorhexidine gluconate and 0.05% sodium fluoride (CLX+NaF); (7) 0.12% chlorhexidine gluconate and 5% alcohol (CLX+alc); (8) ClO_2, trisodium phosphate, citric acid, sodium bicarbonate, and sodium chlorite (ClO_2); (9) 0.03%

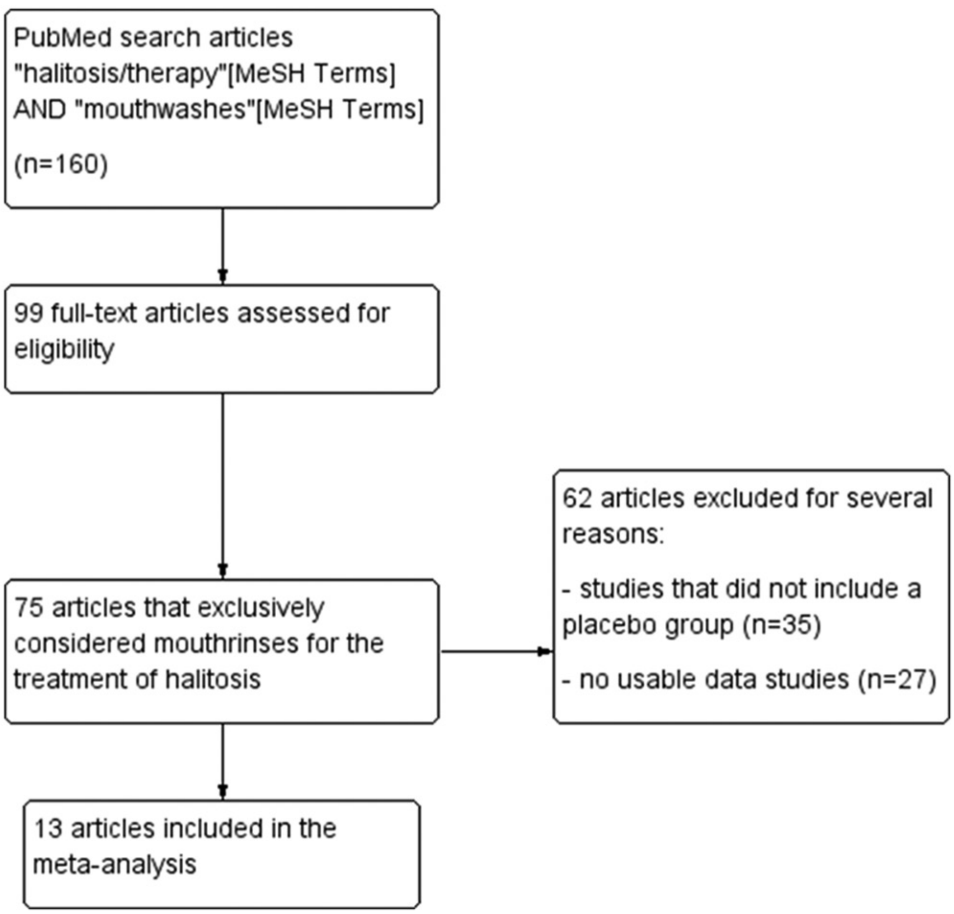

Figure 1: Study flow diagram

Table 1: Main descriptive characteristics of the selected clinical trials

Study (year)	Country	Participants*	Mouthrinses (n)	Placebo (n)	Regimen
Rosenberg *et al*. (1992)[5]	Israel	60 dental students	Zn+eo (22) 0.12 CLX (19)	AS (19) AS (19)	To rinse for two consecutive 30 s periods during 2 days
Roldan *et al*. (2003)[6]	Spain	40 subjects	CLX+CPC+Zn (20)	AS (20)	To gargle with 15 ml of the mouthwash twice per day for 1 min
Winkel *et al*. (2003)[7]	The Netherlands	40 subjects (21 M, 19 F, 21–84 yrs)	CLX+CPC+Zn (20)	AS (20)	To gargle with 15 ml of the mouthwash for 1 min twice daily during 14 days.
Carvalho *et al*. (2004)[8]	Brazil	12 dental students (19–23 yrs)	Zn+eo (12) 0.12 CLX (12) 0.20 CLX (12) CLX+CPC (12)	AS (12) AS (12) AS (12) AS (12)	To rinse for 1 min twice daily during the 4-day period.
Roldan *et al*. (2004)[9]	Spain	10 dental students (25–40 yrs)	0.12 CLX (10) CLX+CPC+Zn (10) CLX+CPC (10) CLX+NaF (10) CLX+alc (10)	AS (10) AS (10) AS (10) AS (10) AS (10)	To rinse twice per day for 1 min
Conceição *et al*. (2008)[10]	Brazil	50 individuals	CLX+CPC (25)	AS (25)	To gargle 5 ml of the mouth rinse for 20 s every 12 h (morning and night).
Shinada *et al*. (2010)[11]	Japan	30 volunteers (19–38 yrs)	ClO2 (15)	AS (15)	To rinse with 10 ml of the mouthwash for 30 s twice per day for 7 days.
Jacinto *et al*. (2011)[12]	Mexico	78 subjects (57 F, 21 M)	Zn+eo (20) CLX+CPC (19) TCS+c (21)	AS (18) AS (18) AS (18)	To rinse 20 ml of the mouthwash for 30 s or 60 s, according to manufacturer's instructions.
Ademovski *et al*. (2013)[13]	Sweden	21 subjects (11 M, 10 F, 21–66 yrs)	Zn+CLX (21)	AS (21)	To rinse with 10 ml of the mouthwash during 1 min twice daily during 14 days.
Ademovski *et al*. (2016)[14]	Sweden	24 subjects (17 F, 7 M, 31–68 yrs)	Zn+eo (24) CLX+CPC+Zn (24) ClO2 (24) Zn+CLX (24)	AS (24) AS (24) AS (24) AS (24)	To rinse with 10 ml of the mouth rinse for 1 min twice daily.
Mendes *et al*. (2016)[15]	Portugal	11 dental students (8 F, 3 M, 20–23 yrs)	CLX+CPC+Zn (10) TCS+c (11)	AS (10) AS (10)	To rinse with the mouthwash for 1 min.
Seemann *et al*. (2016)[16]	Germany	34 dental students	Zn+CLX (18)	AS (16)	To rinse with 10 ml of the mouth rinse for 30 s
Ademovski *et al*. (2017)[17]	Sweden	43 subjects (24 F, 19 M, 22–77 yrs)	Zn+CLX (22)	AS (21)	To rinse with 10 ml of the mouthwash for 1 min twice daily.

*M: Males; F: Females; yrs: Years; ml: milliliter; Zn+eo: 0.9% zinc chloride and essential oil (thymol, eucalyptol, and methyl salicylate); 0.12 CLX: 0.12% chlorhexidine gluconate; AS: Aqueous solution; CLX+CPC+Zn: 0.05% chlorhexidine, 0.05% cetylpyridinium chloride, and 0.14% Zn; 0.2 CLX: 0.20% chlorhexidine gluconate; CLX+CPC: 0.12% chlorhexidine gluconate and 0.05% cetylpyridinium chloride; CLX+NaF: 0.12% chlorhexidine gluconate and 0.05% sodium fluoride; CLX+alc: 0.12% chlorhexidine gluconate and 5% alcohol; ClO_2: Chlorine dioxide, trisodium phosphate, citric acid, sodium bicarbonate, and sodium chlorite; TCS+c: 0.03% TCS and 0.2% copolymer; Zn+CLX: 0.3% zinc acetate and 0.025% chlorhexidine diacetate, CPC: Cetylpyridinium chloride, CLX: Chlorhexidine digluconate, Zn: Zinc lactate, TCS: Triclosan

triclosan (TCS) and 0.2% copolymer (TCS+c); and (10) 0.3% zinc acetate and 0.025% chlorhexidine diacetate (Zn+CLX).

The organoleptic score (OLS) in exhaled air with the various mouthwashes (CLX+CPC+Zn, Zn+eo, CLX+CPC, TCS+c, ZN+CLX, and ClO_2) and the placebo solutions used for the treatment of halitosis are presented in Table 2. The 12 interventions in seven studies analyzed[5,6,11-14,17] comprised a total of 256 individuals treated with a mouthwash and 246 with a placebo. In general, the OLS score was lower in the mouthwash groups compared to the placebo groups, although no statistically significant differences (MD = −0.44, 95% CI: −0.88–0.01, $P = 0.06$). The greatest reduction in the OLS was achieved with the Zn+CLX mouthrinse ($P < 0.001$).[14]

Table 3 illustrates the levels of volatile sulfur compounds (VSCs) with the different mouthwashes (CLX + NaF, 0.12 CLX, CLX + CPC + Zn, Zn + eo, 0.2 CLX, CLX + CPC, CLX + alc, TCS

Table 2: OLS of the intervention and the placebo groups for the treatment of halitosis

First author	Mouthwash active agents	Intervention			Placebo			MD	[95% CI]	*P*-value
		ℜ	SD	n	ℜ	SD	n			
Roldan *et al.*, 2003[6]	CLX +CPC+Zn	1.5	1.0	20	2.5	1.1	20	−1.00	[−1.65, −0.35]	<0.01*
Ademovski *et al.*, 2016[14]	CLX+CPC+Zn	1.4	0.9	24	2.3	0.9	24	−0.90	[−1.41, −0.39]	<0.001*
Rosenberg *et al.*, 1992[5]	Zn+eo	1.0	0.5	22	1.3	1.1	19	−0.30	[−0.84, 0.24]	0.27
Jacinto *et al.*, 2011[12]	Zn+eo	4.6	0.13	20	3.7	0.19	18	0.90	[0.80, 1.00]	<0.001*
Ademovski *et al.*, 2016[14]	Zn+eo	1.6	1.1	24	2.3	0.9	24	−0.70	[−1.27, −0.13]	0.02*
Jacinto *et al.*, 2011[12]	CLX+CPC	4.15	0.24	19	3.7	0.19	18	0.45	[0.31, 0.59]	<0.001*
Jacinto *et al.*, 2011[12]	TCS+c	3.23	0.2	21	3.7	0.19	18	−0.47	[−0.59, −0.35]	<0.001*
Ademovski *et al.*, 2013[13]	Zn+CLX	1.6	0.6	21	2.3	1.0	21	−0.70	[−1.20, −0.20]	<0.01*
Ademovski *et al.*, 2016[14]	Zn+CLX	1.2	0.8	24	2.3	0.9	24	−1.10	[−1.58, −0.62]	<0.001*
Ademovski *et al.*, 2017[17]	Zn+CLX	2.0	0.7	22	2.4	0.7	21	−0.40	[−0.82, 0.02]	0.06
Shinada *et al.*, 2010[11]	ClO_2	1.43	0.46	15	1.73	0.56	15	−0.30	[−0.67, 0.07]	0.11
Ademovski *et al.*, 2016[14]	ClO_2	1.3	1.0	24	2.3	0.9	24	−1.00	[−1.54, −0.46]	<0.001*
	Total			256			246	−0.44	[−0.88, 0.01]	

Heterogeneity: Tau^2=0.57; Chi^2=417.62, df=11 (*P*<0.00001); I^2=97%, Test for overall effect: Z=1.91 (*P*=0.06), CLX+CPC+Zn: 0.05% chlorhexidine, 0.05% cetylpyridinium chloride, and 0.14% Zn; Zn+eo: 0.9% zinc chloride and essential oil (thymol, eucalyptol, and methyl salicylate); CLX+CPC: 0.12% chlorhexidine gluconate and 0.05% cetylpyridinium chloride; TCS+c: 0.03% TCS and 0.2% copolymer; Zn+CLX: 0.3% zinc acetate and 0.025% chlorhexidine diacetate; ClO_2: Chlorine dioxide, trisodium phosphate, citric acid, sodium bicarbonate, and sodium chlorite, CI: Confident interval, SD: Standard deviation, CPC: Cetylpyridinium chloride, CLX: Chlorhexidine digluconate, Zn: Zinc lactate, TCS: Triclosan. ℜ: Mean; SD: Standard deviation; n: Number of cases. MD: Mean difference according to inverse variance (IV) method; [95% CI]: 95% confidence interval; *statistically significant, OLS: Organoleptic scores

+ c, and ZN + CLX) and the placebo solutions for the treatment of halitosis. The 22 interventions in 10 studies[5-10,12,13,15,16] counted a total of 660 individuals, of which 336 were treated with a mouthwash and 324 were treated with a placebo.

Two mouthwashes, CLX + NaF (P = 0.97) and CLX + alc (P = 0.80) did not obtain a significant reduction in VSC levels with respect to placebo.[9] In contrast, two of the three studies[5,8] performed with the 0.12 CLX mouthwash; three of the four[6,7,15] with CLX + CPC + Zn, one of the four[8] with CLX + CPC, and another one of the two[13] with ZN + CLX, did find statistically significant differences in terms of the reduction of VSC levels. In all the studies performed with the mouthwashes Zn + eo,[5,8,12] 0.2 CLX,[8] and TCS + c,[8,12,15] these mouthrinses were significantly more effective than placebo in reducing VSC levels.

The levels of hydrogen sulfide (H_2S), methyl mercaptan (MM), and dimethyl sulfide (DMS) with the mouthwashes (ZN+CLX and ClO_2) and the placebo solutions used in the treatment of halitosis are shown in Table 4. 12 interventions in three studies[11,13,14] that included a total of 168 individuals, 84 treated with a mouthwash and other 84 with placebo solutions, assessed these volatile compounds.

In the evaluation of H_2S levels [Table 4a], H_2S levels were lower in the subjects treated with the mouthwash compared with placebo with a highly significant statistical relationship (SMD = −1.00, 95% CI: −1.32−−0.67, P < 0.001).

In the MM levels analysis [Table 4b], the levels of MM were lesser in the subjects treated with mouthwash than in the subjects treated with placebo with a highly significant statistical association (SMD = −0.78, 95% CI: −1.09 to −0.46, P < 0.001).

Regarding the levels of DMS [Table 4c], the ZN+CLX mouthwash seemed to have no significant effect on the levels of DMS;[13,14] meanwhile, the ClO_2 mouthwash did achieve a significant reduction in the levels of DMS compared to placebo.[11,14]

Discussion

In the present meta-analysis on the different therapeutic options for the treatment of halitosis, data from 13 studies have been included.

Of the 12 interventions in the seven studies that considered the OLS in exhaled air with the different mouthwashes and placebo solutions, nine of them in six studies[5,6,11,13,14,17] found lower levels of OLS in exhaled air in patients taking different mouthwashes (CLX + CPC + Zn, Zn + eo, TCS + c, Zn + CLX, and ClO_2) in comparison with patients who used placebo solutions with statistically significant differences (P < 0.05). Patients with halitosis had high prevalence of the bacteria *Fusobacterium nucleatum*, *Prevotella intermedia,* and *Porphyromonas gingivalis* in samples taken from the lingual surface, saliva, and subgingival fluid. A significant positive correlation was also found between the total basal counts of *P. gingivalis* in saliva samples and the OLS and the concentrations of VSC. After 2 weeks of treatment, there was a reduction in total anaerobic bacteria counts in all samples with a direct correlation between the reduction in total counts in saliva samples and the reduction in OLS score in the group of patients treated with mouthwashes.[6] Only Jacinto *et al.*[12] found significantly higher levels of OLS in patients

Table 3: Total VSC levels of the intervention and the placebo groups for the treatment of halitosis

First author	Mouthwash active agents	Intervention			Placebo			SMD	[95% CI]	*P*-value
		ℜ	SD	n	ℜ	SD	n			
Roldan *et al*., 2004[9]	CLX+NaF	234.1	83.1	10	236.2	159.2	10	−0.02	[−0.89, 0.86]	0.97
Rosenberg *et al*., 1992[5]	0.12CLX	0.7	0.1	19	1.7	0.2	19	−6.19	[−7.79, −4.59]	<0.001*
Carvalho *et al*., 2004[8]	0.12CLX	45.0	56.0	12	222.0	140.0	12	−1.60	[−2.54, −0.66]	<0.001*
Roldan *et al*., 2004[9]	0.12CLX	223.6	77.6	10	236.2	159.2	10	−0.10	[−0.97, 0.78]	0.83
Roldan *et al*., 2003[6]	CLX+CPC+Zn	172.0	104.0	20	360.0	254.0	20	−0.95	[−1.61, −0.29]	<0.01*
Winkel *et al*., 2003[7]	CLX+CPC+Zn	172.0	104.0	20	360.0	254.0	20	−0.95	[−1.61, −0.29]	<0.01*
Roldan *et al*., 2004[9]	CLX+CPC+Zn	168.7	61.8	10	236.2	159.2	10	−0.54	[−1.43, 0.36]	0.24
Mendes *et al*., 2016[15]	CLX+CPC+Zn	147.0	73.5	10	262.0	115.1	10	−1.14	[−2.10, −0.18]	0.02*
Rosenberg *et al*., 1992[5]	Zn+eo	1.4	0.1	22	1.7	0.2	19	−1.91	[−2.66, −1.15]	<0.001*
Carvalho *et al*., 2004[8]	Zn+eo	80.0	80.0	12	222.0	140.0	12	−1.20	[−2.08, −0.32]	<0.01*
Jacinto *et al*., 2011[12]	Zn+eo	240.68	33.99	20	200.16	35.31	18	1.15	[0.45, 1.84]	<0.01*
Carvalho *et al*., 2004[8]	0.2 CLX	32.0	13.0	12	222.0	140.0	12	−1.85	[−2.83, −0.86]	<0.001*
Carvalho *et al*., 2004[8]	CLX+CPC	98.0	61.0	12	222.0	140.0	12	−1.11	[−1.98, −0.24]	0.01*
Roldan *et al*., 2004[9]	CLX+CPC	155.2	35.3	10	236.2	159.2	10	−0.67	[−1.58, 0.23]	0.15
Conceiçao *et al*., 2008[10]	CLX+CPC	141.56	40.16	25	119.64	110.08	25	0.26	[−0.30, 0.82]	0.36
Jacinto *et al*., 2011[12]	CLX+CPC	215.34	48.9	19	200.16	35.31	18	0.35	[−0.30, 1.00]	0.30
Roldan *et al*., 2004[9]	CLX+alc	221.9	50.4	10	236.2	159.2	10	−0.12	[−0.99, 0.76]	0.80
Carvalho *et al*., 2004[8]	TCS+c	81.0	86.0	12	222.0	140.0	12	−1.17	[−2.05, −0.29]	<0.01*
Jacinto *et al*., 2011[12]	TCS+c	167.85	46.97	21	200.16	35.31	18	−0.75	[−1.41, −0.10]	0.02*
Mendes *et al*., 2016[15]	TCS+c	134.0	49.3	11	262.0	115.1	10	−1.41	[−2.39, −0.43]	<0.01*
Ademovski *et al*., 2013[13]	Zn+CLX	122.0	55.3	21	221.7	166.6	21	−0.79	[−1.42, −0.16]	0.01*
Seemann *et al*., 2016[16]	Zn+CLX	208.6	100.0	18	300.8	346.13	16	−0.36	[−1.04, 0.32]	0.30
	Total			336			324	−0.79	[−1.80, 0.22]	

Heterogeneity: $Tau^2=0.54$; $Chi^2=227.62$, df=21 ($P<0.00001$); $I^2=91\%$, Test for overall effect: Z=1.53 ($P=0.13$), CLX+NaF: 0.12% chlorhexidine gluconate and 0.05% sodium fluoride; 0.12 CLX: 0.12% chlorhexidine gluconate; CLX+CPC+Zn: 0.05% chlorhexidine, 0.05% cetylpyridinium chloride, and 0.14% Zn; Zn+eo: 0.9% zinc chloride and essential oil (thymol, eucalyptol, and methyl salicylate); 0.2 CLX: 0.20% chlorhexidine gluconate; CLX+CPC: 0.12% chlorhexidine gluconate and 0.05% cetylpyridinium chloride; CLX+alc: 0.12% chlorhexidine gluconate and 5% alcohol; TCS+c: 0.03% TCS and 0.2% copolymer; Zn+CLX: 0.3% zinc acetate and 0.025% chlorhexidine diacetate. ℜ: Mean; SD: Standard deviation; n: Number of cases. SMD: Standardized mean difference according to inverse variance (IV) method; [95% CI]: 95% confidence interval; *statistically significant. VSCL: Volatile sulfur compounds

treated with the mouthwashes (Zn+eo and CLX + CPC) than in patients treated with placebo solutions; although this result could be due to the characteristics of the population studied and the need for longer use of the mouth rinse to achieve a greater effect.

Regarding the VSC levels of the patients treated with the different mouthwashes or the placebo solutions, of the 22 interventions in 10 studies,[5-10,12,13,15,16] 19 of them found lower levels of VSC in patients treated with different mouthwashes (CLX + NaF, 0.12 CLX, CLX + CPC + Zn, Zn + eo, 0.2 CLX, CLX + CPC, CLX + alc, TCS + c, and Zn + CLX) compared to patients treated with the placebo solutions. The active products of these mouthwashes had effects on intraoral halitosis by establishing a chemical binding and the inactivation of the VSC.[13] However, in the opposite direction, three interventions from two studies[10,12] did not observe a reduction in VSC levels in patients treated with some mouthwashes (Zn + eo and CLX + CPC) with respect to those of the treated patients with placebo solutions. This could be justified by a characteristic common to these mouthwashes that contain hydroalcoholic solutions in their formulation. This causes dehydration of the oral mucosa, increasing the desquamation and the accumulation of debris in the tongue (coated tongue), and other oral tissues. In its metabolism, oral proteolytic bacteria degrade this debris and generate VSC.[10]

Jacinto *et al*.[12] designed an assay to determine the effect of mouthwashes (Zn + eo, CLX + CPC, and TCS + c) in the treatment of halitosis in the short term by analyzing sustainability at 24 h in each of the products. Three measurements were made of the OLS and VSC levels after rinsing, finding that the three rinses promoted significant reductions in the measurements at the 1st and the 3rd h after their use; however, none of them achieved the reduction of the levels at 24 h after its application. Some added factors such as social habits and behaviors may

Table 4: (a-c) H2S, MM, and DMS levels of the intervention and the placebo groups for the treatment of halitosis

(a) H_2S levels

First author	Mouthwash active agents	Intervention			Placebo			SMD	[95% CI]	*P*-value
Ademovski *et al*., 2013[13]	Zn+CLX	159.4	235.4	21	599.2	690.7	21	−0.84	[−1.47, −0.20]	0.01*
Ademovski *et al*., 2016[14]	Zn+CLX	67.2	129.3	24	490.8	432.5	24	−1.31	[−1.93, −0.68]	<0.001*
Shinada *et al*., 2010[11]	ClO_2	0.9	0.93	15	4.78	5.9	15	−0.89	[−1.65, −0.14]	0.02*
Ademovski *et al*., 2016[14]	ClO_2	155.3	257.8	24	490.8	432.5	24	−0.93	[−1.52, −0.33]	<0.01*
	Total			84			84	−1.00	[−1.32, −0.67]	

Heterogeneity: Chi^2=1.30, df=3 (*P*=0.73); I^2=0%, Test for overall effect: Z=6.05 (*P*<0.00001)

(b) MM levels

First author	Mouthwash active agents	Intervention			Placebo			SMD	[95% CI]	*P*-value
Ademovski *et al*., 2013[13]	Zn+CLX	50.5	93.9	21	140.1	164.7	21	−0.66	[−1.28, −0.03]	0.04*
Ademovski *et al*., 2016[14]	Zn+CLX	46.0	63.9	24	184.3	247.7	24	−0.75	[−1.34, −0.16]	0.01*
Shinada *et al*., 2010[11]	ClO_2	0.19	0.29	15	1.1	1.14	15	−1.06	[−1.84, −0.29]	<0.01*
Ademovski *et al*., 2016[14]	ClO_2	44.1	78.1	24	184.3	247.7	24	−0.75	[−1.34, −0.16]	0.01*
	Total			84			84	−0.78	[−1.09, −0.46]	

Heterogeneity: Chi^2=0.69, df=3 (*P*=0.87); I^2=0%, Test for overall effect: Z=4.84 (*P*<0.00001)

(c) DMS levels

First author	Mouthwash active agents	Intervention			Placebo			SMD	[95% CI]	*P*-value
Ademovski *et al*., 2013[13]	Zn+CLX	71.9	180.3	21	185.0	600.9	21	−0.25	[−0.86, 0.36]	0.42
Ademovski *et al*., 2016[14]	Zn+CLX	23.5	27.8	24	37.4	33.5	24	−0.44	[−1.02, 0.13]	0.13
Shinada *et al*., 2010[11]	ClO_2	0.07	0.11	15	0.28	0.29	15	−0.93	[−1.69, −0.17]	0.02*
Ademovski *et al*., 2016[14]	ClO_2	7.4	7.5	24	37.4	33.5	24	−1.22	[−1.84, −0.60]	<0.001*
	Total			84			84	−0.69	[−1.13, −0.25]	

Heterogeneity: Tau^2=0.10; Chi^2=5.86, df=3 (*P*=0.12); I^2=49%, Test for overall effect: Z=3.05 (*P*=0.002), Zn+CLX: 0.3% zinc acetate and 0.025% chlorhexidine diacetate; ClO_2: Chlorine dioxide, trisodium phosphate, citric acid, sodium bicarbonate, and sodium chlorite. $\mathfrak{R}$: Mean; SD: Standard deviation; n: Number of cases. SMD: Standardized mean difference according to inverse variance (IV) method; [95% CI]: 95% confidence interval; *statistically significant, DMS: Dimethyl sulfide, H_2S: Hydrogen sulfide, CPC: Cetylpyridinium chloride, CLX: Chlorhexidine digluconate, Zn: Zinc lactate, TCS: Triclosan, CI: Confident interval

increase the risk of halitosis. This is the case of the consumption of tobacco and/or alcohol, which increase the risk of gastritis and peptic ulcers, disorders that promote the development of halitosis.[12]

Twelve interventions in three studies[11,13,14] also evaluated the levels of H_2S, MM, and DMS levels after the use of mouthwashes (ZN + CLX and ClO_2) and placebo solutions for the treatment of halitosis. In all cases and with the two mouthwashes, lower levels of H_2S, MM, and DMS were found in the patients treated with mouthrinses regarding the levels of patients treated with placebo in the case of H_2S or MM and statistically significant differences were observed. Even at 12 h after mouthwash, a significant reduction was observed with the use of mouthwashes compared with placebo.[14] In addition, the unique use of the active mouthwash without the need to accompany it with tongue scraping was able to achieve an effective reduction of intraoral halitosis.[13] However, in the case of DMS levels, the Zn + CLX mouthwash was not significantly effective in reducing DMS levels according to two studies.[13,14] In contrast, with ClO_2 mouthwash, a significant reduction in DMS levels was observed.[14] The DMS is considered as the main contributor to extraoral halitosis. ClO_2 appears to have greater action against halitosis than chlorhexidine diacetate + zinc acetate.[14]

Overall, the effectiveness of these mouthwashes is very conditioned with their daily administration schedule and the time of use of them. Better results were observed that the longer the use of these mouthwashes is prolonged.[12] Other factors that influence halitosis are the concentration and composition of the oral microbiota, as well as the dietary habits of patients that may contribute to the generation of malodorous compounds responsible for halitosis.[15]

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of the studies included and the presence of different bias. The differences among studies could be conditioned by the methods used to collect data, the different devices and procedures to measure halitosis, the type of analysis used, and the particular features of the study populations.

Conclusions

The greatest reductions achieved by the mouthwashes were with the mouthwash Zn+CLX for the OLS levels (MD: −1.10); with the mouthwash 0.12 CLX for the VSC levels (SMD: −6.19); with the mouthwash Zn+CLX for the levels of H_2S (SMD: −1.31); and with the ClO_2 mouthwash for both MM (SMD: −1.06) and DMS levels (SMD: −1.22).

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