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Direct effect of chlorine dioxide, zinc chloride and chlorhexidine solution on the gaseous volatile sulfur compounds

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Abstract

Objective. This study focused on the ability of aqueous anti-volatile-sulfur-compound (VSC) solutions to eliminate gaseous VSCs by direct contact in a sealed space to describe possible mode of action of anti-VSC agents. ***Materials and methods.*** Twenty milliliters of each experimental solution, 0.16% sodium chlorite, 0.25% zinc chloride, 0.1% chlorhexidine and distilled water, was injected into a Teflon bag containing mixed VSCs, hydrogen sulfide, methyl mercaptan and dimethyl sulfide and mixed vigorously for 30 s. The VSC concentration was measured by gas chromatography before, immediately after, 30 min and 60 min after mixing. ***Results.*** The sodium chlorite solution reduced the VSC concentration remarkably. After mixing, nearly all VSCs were eliminated immediately and no VSCs were detected at 30 and 60 min post-mixing. However, in the other solutions, the VSC concentration decreased by ~30% immediately after mixing and there was no further decrease. ***Conclusion.*** The results suggest that sodium chlorite solution has the effect of eliminating gaseous VSCs directly. This must be because it can release chlorine dioxide gas which can react directly with gaseous VSCs. In the case of other solutions that have been proved to be effective to reduce halitosis clinically, it can be proposed that their anti-VSC effect is less likely due to the direct chemical elimination of gaseous VSCs in the mouth.

Key Words: *bad breath, halitosis, mouthrinse, volatile sulfur compounds*

Introduction

Oral malodor is defined as an offensive odor of the breath originating from the oral cavity itself or its neighboring structures. It is well documented that oral malodor originates from oral causes in ~80–90% of cases [1–3] and that volatile sulfur compounds (VSCs) such as hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulfide ($(CH_3)_2S$) are its major malodorous components [4].

Various anti-VSC agents have been introduced and proved to be effective in reducing VSC concentration in the breath [5–18]. Chlorine dioxide, a stable free radical solution, has been reported to show anti-VSC effects that last for 4 h immediately after a single mouth rinsing [5] and also after the clinical use for 7 days [6] when compared with placebo solution. Zinc chloride, a metal ion solution, has also been reported to show anti-VSC effects against hourly cysteine challenges [7,8]. Zinc-containing gum as well as solution showed significant anti-VSC effects [9,10]. Chlorhexidine is an antimicrobial agent proven in its ability to reduce oral malodor [11,13,14,18]. As the underlying mechanism of VSC reduction, antimicrobial action and inhibition of VSC production through oxidation of the thiol group of amino acids and VSC precursors have been suggested [6,7,10,12,17,19–22].

However, the majority of such previous studies are based on the results of clinical use and most salivary putrefaction experiments are focused on the decrease of the final concentration of VSCs in the breath at least 30 min after the application of an anti-VSC agent. So it is hard to see the results of direct interaction between those aqueous anti-VSC chemical agents and gaseous VSCs as they come into contact with each other in a different physical phase, solution and gas, respectively. By analyzing the direct effect of anti-VSC solution on gaseous VSCs, the results will be beneficial in further understanding the

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interaction between the two substances and this will lead to the development of a more effective mixed chemical agent to control oral malodor. In this study, solutions of chlorine dioxide, zinc chloride and chlorhexidine were mixed with gaseous VSCs in a sealed inert bag and the VSC levels were examined and compared.

Materials and methods

Experimental solutions

Four experimental solutions were prepared: (A) 0.16% sodium chlorite (0.1% chlorine dioxide), (B) 0.25% zinc chloride, (C) 0.1% chlorhexidine, and (D) distilled water. Sodium chlorite ($NaClO_2$) in a solution was converted to gaseous chlorine dioxide (ClO_2) via the following equation to produce chlorine dioxide gas dissolved in the solution.

$$5\,NaClO_2 + 4\,H^+ \rightarrow 4\,ClO_2 + 2\,H_2O + NaCl + 4\,Na^+$$

Following the above equation, four molecules of chlorine dioxide are derived from five molecules of sodium chlorite, so 0.16% sodium chlorite is theoretically equal to 0.1% chlorine dioxide. The sodium chlorite solution was prepared by reacting 0.16% sodium chlorite, 1.13% citric acid and distilled water as previously described [6] and the pH was adjusted to 5.65 with sodium hydroxide. The zinc chloride ($ZnCl_2$) solution was prepared at a concentration of 0.25% by dissolving zinc chloride powder in distilled water [23]. It was titrated with hydrochloric acid to increase the solubility. A commercial chlorhexidine product, Hexamedin (Bukwang Pharm., Seoul, Korea), with a concentration of 0.1% was used.

Preparation of standard VSC gas

Standard VSC gas was prepared from mixed standard gases (Rigas Co., Daejeon, Korea) composed of hydrogen sulfide, dimethyl sulfide, and methyl mercaptan at 10 ppm concentration of each gas to form a final concentration of 30 ppm. The mixed standard gas was diluted with nitrogen gas to 3 ppm (1 ppm as each VSC) to a total volume of 500 mL and manually inserted into a 1 L Teflon bag (Tedlar Bags, Supelco Inc., Bellefonte, PA) by flowing 30 ppm mixed standard gas for 3 s and nitrogen gas for 27 s at a constant flow rate of 1 L/min.

Effect of the experimental solutions on gaseous VSCs

Twenty milliliters of experimental solution was injected into a Teflon bag containing the mixed standard VSCs through a valve attached to the bag and then the Teflon bag containing the experimental solution and the mixed VSCs was shaken vigorously for 30 s. After shaking, the bag was rocked gently on a rocker during the experiment. Ten milliliters of the mixed gas sample was collected by a gas tight syringe (Hamilton, Reno, NV) from the bag through the injection septa for gas chromatography analysis. The concentrations of mixed VSCs were measured by gas chromatography four times: before (baseline), immediately after, 30 min and 60 min after the injection of an experimental solution and vigorous shaking. Each chromatography measurement was repeated three times.

Measurement of VSC concentration

The gas chromatography equipment (6890N, Agilent technologies, Santa Clara, CA) was supplied with a flame photometric detector to detect sulfur compounds. It used a 60/80-mesh glass column (Chromosil 330, Supelco Inc., Bellefonte, PA). A 10 ml volume mixed standard VSC sample collected from the Teflon bag using a gas tight syringe was directly injected into the gas chromatography apparatus. Nitrogen gas was used as a carrier gas at a continuous flow rate of 20 ml/min. The temperatures of the injector and detector were held constant at 100°C and 250°C, respectively. After an injection, the oven temperature was held at 40°C for 2 min and then increased by 8°C/min to 100°C for better resolution of the peaks. It was subsequently maintained at 100°C for 5 min in a washing-out step. The gas chromatography result was integrated by ChemStation software (3365 ChemStation revision A09, Agilent Technologies). The recorded peak area was calculated via a ChemStation regression analysis to a parts-per-billion (ppb) concentration [24–26].

Statistical analysis

The sample size was calculated as described previously [27] to estimate an appropriate number of repetition of experiments for 0.05 statistical significance and 0.95 statistical power. The difference of total VSC concentration changes from baseline to immediate measures between experimental solutions (expected differences) and the standard deviations (SD) of total VSC concentration changes from baseline to immediate measures (expected SDs) were calculated after the experiment was repeated three times. Because three repetitions turned out to be statistically enough to prove the differences between 0.16% sodium chlorite and other experimental solutions while the number of repetition required to prove differences between other solutions was impractical, further analysis was done with the results of three repetitions. Significance of VSC concentration changes were analyzed by repeated measures ANOVA (RMANOVA).

Results

Effect of the four experimental solutions on VSCs

The 0.16% sodium chlorite solution induced a remarkable decrease in the concentration of VSCs. After mixing, nearly all VSCs were immediately eliminated and no VSC was detected at 30 and 60 min post-mixing. In the cases of 0.25% zinc chloride solution, distilled water and 0.1% chlorhexidine solution, the VSCs concentration decreased to ~70% of the baseline value immediately after mixing. However, there was no additional decrease at 30 min or 60 min post-mixing (Table I and Figure 1). Repeated measures ANOVA revealed that interaction of time and sort of solutions was significant as well as time effect on VSC concentration ($p < 0.001$), but it was also revealed that such significant interaction was affirmed only between 0.16% sodium chlorite and others (Table I).

Effect of different concentrations of sodium chlorite and different baseline values of VSCs

Because 0.16% sodium chlorite solution eliminated VSCs immediately, the solution was diluted to 0.016% to observe the eliminating ability according to concentration. With 0.016% sodium chlorite, the concentration of the VSCs decreased to 45% of the baseline immediately after mixing and to nearly zero after 30 min (Table II and Figure 2). This indicates that 0.16% sodium chlorite would be more useful than 0.016% sodium chlorite for the immediate elimination of VSCs. On the other hand, two different concentrations, 3 ppm and 7 ppm, decreased at the same ratio when the 0.016% concentration of sodium chlorite solution was used. Moreover, even in the case of more excessive VSCs, 7 ppm, which hardly can be measured in the mouth, all VSCs were eliminated in an hour (Table II and Figure 2).

Discussion

Anti-VSC agents are known to work in two ways to reduce oral malodor, through antimicrobial action and inhibition of VSC production. Various chemical agents such as chlorhexidine, chlorine dioxide, zinc chloride, cetylpyridinium chloride, essential oils and triclosan have all been reported to reduce oral malodor by their antimicrobial action [6,7,19,28–32], which results in a reduction of the amount of bacteria that produces malodorous materials. On the other hand, it is assumed that chlorine dioxide, a stable free radical, and zinc chloride, a metal ion, can reduce VSC production through their sulfur affinity to react with and oxidize the thiol group of amino acids and VSC precursors [6,7,10,17,19,21]. It is obvious that the contact between two chemicals should precede their interaction. In order to oxidize the thiol group of amino acids and VSC precursors, chemical agents should be able to actually reach the thiol groups. While it is verisimilar within a single medium such as plaque or saliva, it is not so likely between media in different phases, such as a chemical solution and gaseous VSCs in the breath.

Table I. Change of VSC concentrations before, immediately, 30 min and 60 min after injection of four experimental solutions into the Teflon bag followed by vigorous shaking.

	Hydrogen sulfide					Methyl mercaptan				
	Baseline	Immediate	30 min	60 min	Time	Baseline	Immediate	30 min	60 min	Time
0.16% Sodium chlorite (A)	1024 ± 78	143 ± 129	0	0		968 ± 58	0	0	0	
0.25% Zinc chloride (B)	1000 ± 159	685 ± 34	737 ± 113	753 ± 98		976 ± 105	688 ± 56	725 ± 35	748 ± 47	
0.1% Chlorhexidine (C)	996 ± 26	672 ± 79	630 ± 91	592 ± 113	***	966 ± 10	683 ± 46	687 ± 49	683 ± 72	***
Distilled water (D)	958 ± 80	565 ± 118	792 ± 54	718 ± 25		964 ± 27	656 ± 29	756 ± 15	712 ± 66	
Time × Solution	*** (A,B)***, (A,C)***, (A,D)***					*** (A,B)***, (A,C)***, (A,D)***				

	Dimethyl sulfide					Total VSCs				
0.16% Sodium chlorite (A)	1009 ± 159	0	0	0		3001 ± 271	143 ± 129	0	0	
0.25% Zinc chloride (B)	1095 ± 98	721 ± 102	743 ± 56	750 ± 59		3071 ± 358	2094 ± 173	2205 ± 153	2250 ± 156	
0.1% Chlorhexidine (C)	949 ± 17	646 ± 34	638 ± 49	643 ± 60	***	2910 ± 52	2001 ± 151	1954 ± 181	1919 ± 241	***
Distilled water (D)	1025 ± 51	690 ± 43	723 ± 48	692 ± 106		2946 ± 85	1910 ± 118	2272 ± 19	2122 ± 146	
Time × Solution	*** (A,B)***, (A,C)***, (A,D)***					*** (A,B)***, (A,C)***, (A,D)***				

Mean ± SD (ppb).
Time, time effect of VSC concentration changes; Time × Solution, interactions of time and sort of solutions; () , pairs significant by Bonferroni post-hoc test.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by repeated measures ANOVA.

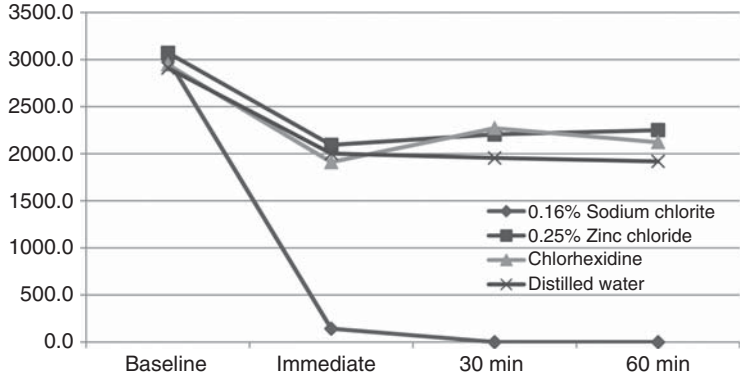

Figure 1. The mean of the total VSC concentrations before, immediately, 30 min and 60 min after the injections of four experimental solutions into a Teflon bag filled with 3 ppm VSCs followed by vigorous shaking.

This study was focused on the direct chemical reaction between anti-VSC agents and gaseous VSCs, not on the inhibition of VSC production in plaque or saliva, because a chemical solution that can react with and eliminate gaseous VSCs directly would be helpful to control oral malodor more immediately and efficiently in the mouth. In order to assess this issue, we used aqueous anti-VSC agents in contact with gaseous VSCs in a sealed inert bag. The results provided clear information on the ability of each agent to eliminate gaseous VSCs directly, excluding the possibility of their effect on the bacterial activity.

In the results, sodium chlorite solution had a remarkable effect on the elimination of VSCs, whereas the effect of zinc chloride and chlorhexidine solution did not differ from the effect of distilled water. This must be because aqueous sodium chlorite solution releases chlorine dioxide gas at an acidic pH; some chlorine dioxide exists in the air as a gas while some remains dissolved in the solution [33]. The gaseous chlorine dioxide released from the sodium chlorite solution could react with the gaseous VSCs immediately, while VSCs must be dissolved in a solution in order to react with zinc ions. This may also explain why the zinc chloride solution showed results similar to those of chlorhexidine solution and distilled water.

The findings suggest that the fast and immediate effect of the chlorine dioxide solution on VSCs is very promising as a chemical agent for oral malodor management. When it is used in a form of spray or mouthrinse, a portion of the chlorine dioxide in a gaseous phase will reduce oral malodor immediately by eliminating pre-existing gaseous VSCs in the mouth and then the remaining sodium chlorite solution will act more persistently by its antimicrobial action and inhibition of bacterial production of VSCs, as previously described [6,19,34].

On the other hand, the result that a zinc chloride solution as well as chlorhexidine or distilled water could not reduce VSC gases as much as sodium chlorite

Table II. Change of VSC concentrations before, immediately, 30 min and 60 min after injection of sodium chlorite into the Teflon bag followed by vigorous shaking with variations of initial VSC concentration or sodium chlorite concentration.

	Hydrogen sulfide				Methyl mercaptan			
	Baseline	Immediate	30 min	60 min	Baseline	Immediate	30 min	60 min
0.16% Sodium chlorite with 3 ppm VSCs	1024 ± 78	143 ± 129	0	0	968 ± 58	0	0	0
0.016% Sodium chlorite with 3 ppm VSCs	1061 ± 50	508 ± 157	0	0	986 ± 43	547 ± 99	31 ± 54	0
0.016% Sodium chlorite with 7 ppm VSCs	2381 ± 50	1250 ± 147	75 ± 65	0	2204 ± 73	1059 ± 52	123 ± 75	0
	Dimethyl sulfide				Total VSCs			
0.16% Sodium chlorite with 3 ppm VSCs	1009 ± 159	0	0	0	3001 ± 271	143 ± 129	0	0
0.016% Sodium chlorite with 3 ppm VSCs	989 ± 41	303 ± 133	0	0	3036 ± 133	1359 ± 380	31 ± 54	0
0.016% Sodium chlorite with 7 ppm VSCs	2107 ± 29	250 ± 97	0	0	6692 ± 151	2560 ± 113	198 ± 84	0

Mean ± SD (ppb).

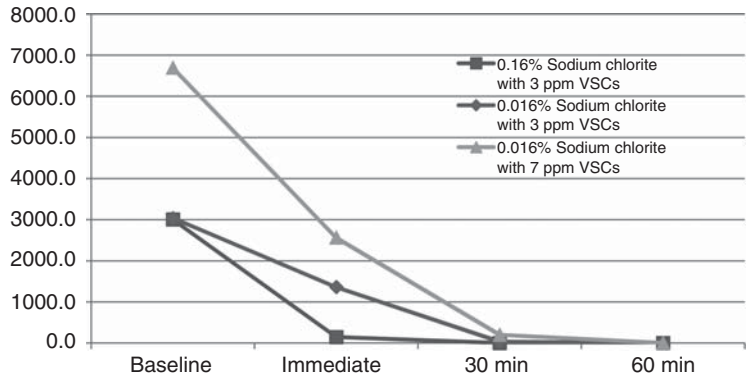

Figure 2. The mean of the total VSC concentrations before, immediately, 30 min and 60 min after an injection of 0.16% and 0.016% sodium chlorite solution into a Teflon bag filled with 3 ppm VSCs and 0.016% sodium chlorite solution into a Teflon bag filled with 7 ppm VSCs followed by vigorous shaking.

solution did may seem to be conflicting with the results of a number of previous studies reporting that zinc chloride solution can eliminate VSC and is effective in reducing oral malodor [7–10,13,14,21,22,35–38]. However, since the results of previous studies were based on the reduction of VSC concentration in the breath after rinsing the mouth and in the headspace of putrefied saliva or the VSC saturated water in the presence of zinc ion, there is no available data regarding the direct effect of a zinc chloride solution on gaseous VSC. Unlike the results of this study, they did not show the ability of the zinc solution to eliminate VSCs in a gaseous phase directly but rather showed the ability of zinc to interfere with the production of VSCs or to eliminate sulfide anions in the same medium such as plaque, saliva, or water where zinc ion existed. Combining the results of this study and previous studies, the effect of zinc chloride solution on reducing oral malodor or VSC concentration presented in previous studies is more likely due to the inhibition of VSC production by antimicrobial effect or oxidation of thiol groups in plaque, saliva or water by chemical effect, not due to the direct elimination of gaseous VSCs.

The concentration of sodium chlorite, 0.16% in this study, was sufficient to eliminate VSCs immediately, although sodium chlorite at 0.016% was also effective in eliminating VSCs after 30 min. Although 0.1% sodium chlorite was used in many previous studies, it has been reported that 0.16% sodium chlorite is equivalent to 0.1% chlorine dioxide and there was no complaint of tongue stimulation or discoloration with the use of 0.1% chlorine dioxide [5,6]. For the preparation of the sodium chlorite solution, the concentration of hydrogen ions and thus pH is important, as these factors determine the conversion rate of sodium chlorite to chlorine dioxide. In this study, citric acid was used because an organic acid releases hydrogen ions slowly, maintaining a constant concentration of chlorine dioxide in the long-term, as described previously [33].

The same ratio of VSC decrease at two different baseline VSC concentrations, 3 ppm and 7 ppm, by 0.016% sodium chlorite solution implies that, if the amount of available gaseous chlorine dioxide is sufficient, oral malodor originating from VSCs will be consistently eliminated regardless of the degree of malodor severity. This holds clinical significance considering the fact that VSC concentration in the breath of oral malordor patients hardly exceeds 7 ppm.

In conclusion, sodium chlorite solution can effectively eliminate mixed VSC gases of hydrogen sulfide, methyl mercaptan, and dimethyl sulfide in a sealed inert bag, while zinc chloride solution, chlorhexidine and distilled water only eliminated ~30% of the mixed VSC gases under identical conditions. These results imply that sodium chlorite solution has the effect of eliminating gaseous VSCs directly while the anti-VSC effect of other solutions is more likely due to the antimicrobial activity and inhibition of bacterial production of VSCs. Considering the recent trend of mixing several substances that have different modes of action for complementary co-action [11,13,14,18,36,39,40], sodium chlorite is a promising candidate as a component of an anti-VSC agent to enhance efficiency in the immediate control of oral malodor.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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