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Effects of Chlorhexidine on Taste Perception :A Systematic Review

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Abstract:

Aim:To evaluate the effects of chlorhexidine on taste perception

Methods and material:The studies included in this review are all randomized controlled trials that are directly related to testing the effects of chlorhexidine on taste perception.

Seven (PubMed, Cochrane, Medline, lilacs, science direct, Scopus, grey literature) databases and additional sources were searched for articles published in the English language.

Six articles were identified that met the inclusion and exclusion criteria. The experiments and the results in these articles were then analyzed.

Result: Five out of six articles support the fact that chlorhexidine does change the taste perception and four out of the six articles show that there is a decrease in the taste perception of saltiness and bitterness.

Conclusion:This systematic review confirms that chlorhexidine does indeed have an effect on taste perception.

Keywords: chlorhexidine, taste perception, taste alteration, change in taste.

INTRODUCTION

Chlorhexidine is a germicidal mouthwash that reduces the number of bacteria(oral flora) in the mouth.[1] [2] It is the most widely used anti-plaque agent.[3] It is a major component of many commercially available mouthwashes like Rexidine, Hexidine, Smilehex, Chlorhex, Hexidale, Hex, Everfresh, Gargwell, Periogard and Eludril.[4] It is commonly prescribed for patients with dental problems such as plaque, gingival inflammation, gingival bleeding, malodour (halitosis), as a powerful adjuvant to mechanical oral hygiene measures (brushing and flossing), especially in those cases in whom it cannot be performed correctly, after periodontal and maxillofacial surgeries etc.

Owing to its high frequency of usage and its popularity, naturally there arises a concern regarding its adverse effects. The adverse effects of chlorhexidine should not outweigh the benefits provided by it. Chlorhexidine is a bis-biguanide antiseptic mouthwash, using which produces a profound and prolonged alteration of the saltiness of all salty compounds. It also decreases the bitter taste of bitter compounds (a subset of bitter compounds) , but has little to no effect on sweet and sour tastes. Chlorhexidine solution is the only known chemical blocker of salty taste in human beings.

Chlorhexidine is reported to have many temporary adverse effects such as decreased taste perception, tooth staining, burning sensation in mouth (sore mouth), tongue irritation among other things.[5]

Proposed mechanism of decreased taste perception: chlorhexidine gluconate is a bis-biguanide, strongly cationic antiseptic. The strong cationic charge helps it to bind to the several anionic proteins, anionic bacterial walls and oral mucosa and produce its anti-bacterial effect. This is also one of the main reasons for its long substantivity time. But this strong cationic charge may be responsible for its alteration of taste perception. When used at concentration used to treat periodontal diseases or at low concentrations for longer duration of time, it is said to have the tendency to cause a decrease in the salt and bitter taste perception i.e. hypogeusia of saltiness and bitterness sensation. Taste sensations are identified when the food that we eat gets dissolved and become tastants, these tastants enter the taste pores on the surface of the tongue and stimulate the taste receptors. It is proposed that chlorhexidine due to its strong cationic charge binds to these taste pores and taste buds effectively blocking the pathway required for the perception of saltiness. As for the decreased perception of bitter taste, it may be due to “adapting” of the taste buds to bitter taste after treatment with bitter amphiphilic chlorhexidine that leads to decreased perception of other bitter amphiphilic compounds.[6]

In this systematic review we have included six studies that are aimed at evaluating the effects of chlorhexidine on taste perception. All six articles contain randomized controlled clinical trials on volunteers and were tested using certified and proven methods of evaluation as shown in the inclusion characteristics table later on.

The aim of the systematic review is to evaluate the effects of chlorhexidine on the alteration of taste perception.

Objectives

The objective of this systematic review is to evaluate the effects of chlorhexidine on taste perception by analyzing the six final articles and studying in detail their results to showcase a conclusive result on the subject.

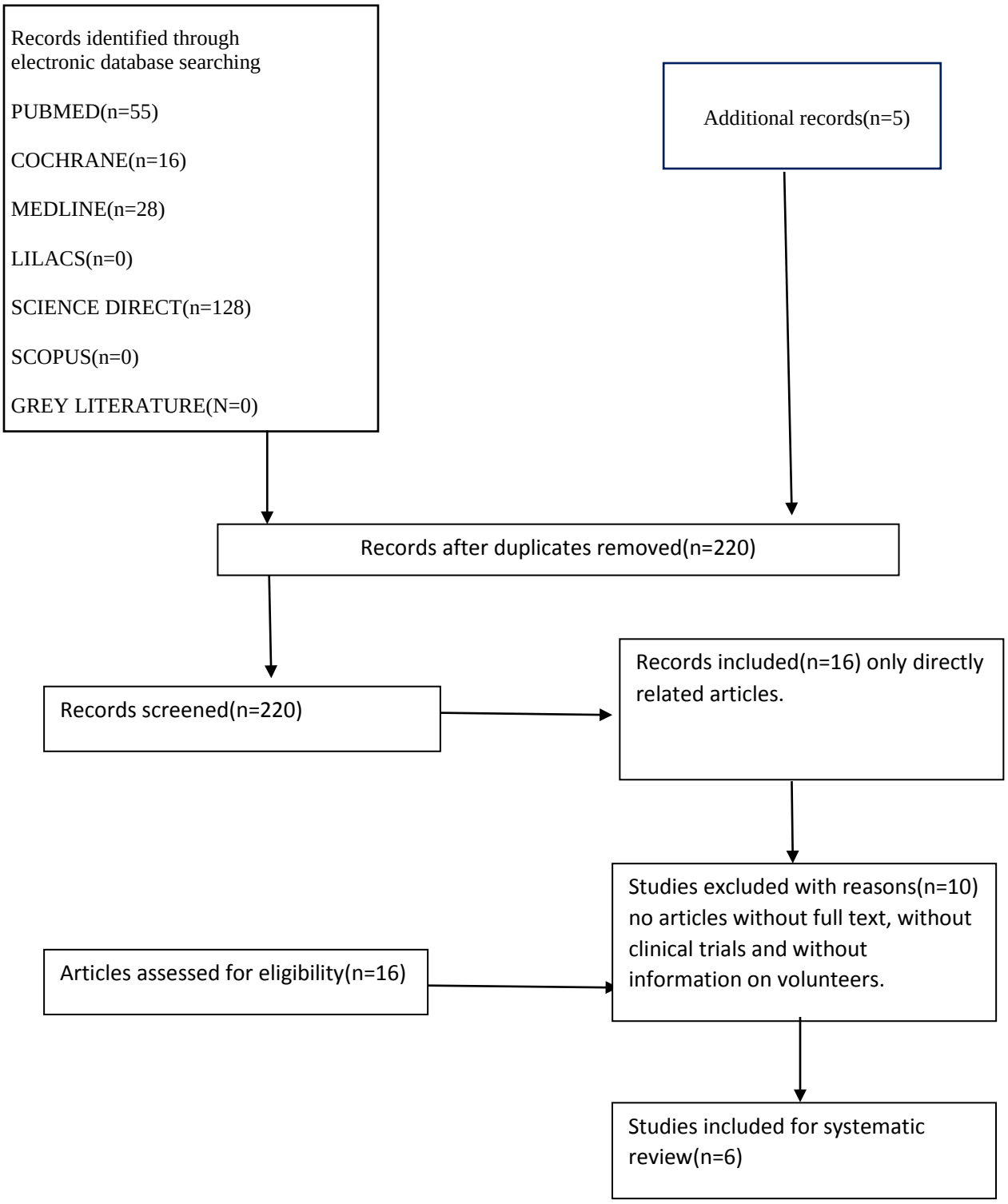
MATERIALS AND METHODS

Only randomized controlled trials were included in this study and the articles were narrowed down using certain inclusion and exclusion criteria.

Search Strategy And Eligibility Criteria

Seven search engines (PubMed, Cochrane, Medline, lilacs, science direct, Scopus, grey literature) were searched using the keywords "chlorhexidine, taste perception, taste alteration" and 220 related articles were obtained after deletion of duplicates. All 220 articles were read thoroughly and out of the 220 articles, 6 articles were finally selected on the basis of the inclusion and exclusion criteria described below:

FIGURE 1: SEARCH AND SELECTION: EFFECTS OF CHLORHEXIDINE ON TASTE PERCEPTION



INCLUSION CRITERIA:

1. Directly related articles.
2. Articles in English.
3. Articles containing randomized controlled trials.
4. Studies taken from 1980 – 2019.
5. Experiments on healthy volunteers.

EXCLUSION CRITERIA:

1. Articles without full texts.
2. Studies with other interventions.
3. Articles without information on volunteers.
4. Pilot studies.

RESULT

The studies are tabulated in the following figure and tables.

FIGURE 1: shows flow diagram showing the number of studies identified, screened, assessed for eligibility, excluded and included in the systematic review.

TABLE 1:Shows information on the final included articles such as the author name, the number of volunteers, the condition of the volunteers, their gender and age. The duration of the experiment from the pre-experimental procedure period till the final results were obtained is also mentioned. The experiments were conducted either as a single group experiment or multiple group experiment consisting of controlled group in them. The information on the conditions for each group are described here.

TABLE 1: CHARACTERISTICS OF THE INTERVENTIONS IN THE INCLUDED STUDIES

S. No.	AUTHOR NAME	YEAR	SAMPLE SIZE	VOLUNTEER CHARECTERISTICS	DURATION	INTERVENTIONS (CASES/ CONTROLLED)
I.	Gabriela Otero dos SANTOS *et al* [7]	2017	35	18 men and 17 women; mean age: 22.5 ± 3.2 years.	May to June 2015 (3 experiments lasting 4 days each)	**Group A (CHXAL)**: an alcohol-containing 0.12% chlorhexidine solution. **Group B (CHX)**: an alcohol-free 0.12% chlorhexidine solution. **Group C (PLA)**: placebo.
II.	Niklaus P. Lang *et al* [8]	1988	24	24 healthy and non-smoking clinical instructors, dental assistants and dental students.	42 days	**Group A**: rinsed with a 0.2% chlorhexidine solution, **Group B**: (Control) 0.001 molar solution of quinine hydrochloride as a placebo rinse, **Group C**: (Second control group) rinsed with distilled water.
III.	JILL. A. HELMS *et al* [9]	1995	15	7 Males and 8 Females; Age: 22-36.	4 to 5 weeks.	Single group experiment: 0.12% of chlorhexidine gluconate.
IV.	Ana Rita Duarte Guimaraes *et al*[10]	2006	164	Children; Age: 11-15 years.	14 days	**Group 1**: (G1 − 0.05% NaF + 0.12% CHX) **Group 2**: (G2- 0.05% NaF)
V.	Janneane F Gent *et al* [11]	2002	18	Controlled group (water rinse): 9 (5 females and 4 males) aged 22-50 years; Chlorhexidine group: 9 (7 female and 2 male) aged 21-40 years.	Not specified	**Group 1**: test group (chlorhexidine rinse). **Group 2**: control group (water rinse).
VI.	Paul A.S. Breslin *et al* [12]	2001	29	EXP 1: 5 women, 8 men; mean age 27 ± 3.4 years and EXP 2: 11 women, 5 men; mean age 26 ± 4.3.	Not specified	**EXP 1**: Chlorhexidine digluconate (CHX) 0.12% and varying concentration of quinine hydrochloride were given to the volunteers and were asked to rate the bitterness using Labeled Magnitude Scale. **EXP 2**: Chlorhexidine digluconate (CHX) 0.12% and varying concentration of NaCl, KCl, NH_4Cl, urea, sucrose octa-acetate, QHCl, sucrose, MSG, citric acid, HCl and water were given and asked to rate the corresponding tastes using Labeled Magnitude Scale.

TABLE 2: CHARECTERISTICS OF THE OUTCOMES OF THE STUDY

S. No.	AUTHOR NAME	YEAR	EFFECT MEASURE	REGIMEN DOSE	MEASUREMENT PARAMETER	RESULTS/ OUTCOME
I.	Gabriela Otero dos SANTOS *et al* [7]	2017	Primary outcome-change in taste perception.	15 ml of an alcohol-containing 0.12% chlorhexidine solution, an alcohol-free 0.12% chlorhexidine solution, or placebo.	9-point hedonic scale.	Change in taste perception was seen in 12 with PLA (placebo), 10 with CHX (without alcohol) and 20 with CHXAL (with alcohol). Adverse effects for CHXAL VS CHX (57.1% versus 28.6%; p = 0.013).
II.	Niklaus P. Lang *et al* [8]	1988	Primary outcome-decrease in perception of salt taste.	Group A: unflavoured aqueous solution of 0.2% chlorhexidine digiuconate. Group B: 0.001 M solution of quinine hydrochloride. Group C: Distilled water.	Suprathreshold scaling procedure called magnitude estimation.[13][14][15]	The scaling procedures of the salty taste were significantly ($p<0.01$) different for the short-term (day 1 and 2) and treatment-related (day 13 and 14) observation periods in the test group (A) compared to controlled group (B, C).
III.	JILL A. HELMS *et al* [9]	1995	Primary outcome-decrease in perception of salt taste.	0.12% chlorhexidine gluconate followed by a series of solutions containing increasing concentration of citric acid, sucrose, quinine hydrochloride and sodium chloride.	magnitude matching (Marks et al. 1988; Bartoshuk, 1989).	Mean magnitude estimate scores for NaCl and QHCl were reduced by 52.1% ($p < 0.001$) and 48.6%($p<0.02$), respectively, during the chlorhexidine treatment period compared to before treatment, but scores for sucrose and citric acid did not change ($p > 0.10$).
IV.	Ana Rita Duarte Guimaraes *et al* [10]	2006	Primary outcome-no significant change in taste perception.	Group 1 (0.05% solution of NaF and 0.12% CHX) and Group 2 (0.05% solution of NaF) and both solutions had glycerine, non-cariogenic anise aroma, blue food colouring, preservative and vehicle also.	Labeled Magnitude Scale [16]	No significant change in the perception of taste were observed but that may be due to presence of anise flavouring used in the solution ($p=0.062$).
V.	Janneane F Gent *et al* [11]	2002	Primary outcome-non-significant decrease in perception of sourness and sweetness, significant decrease in perception of saltiness and bitterness.	1.34 mM chlorhexidine gluconate (test group) and water (control group). Ten stimuli: [water, 0.1 M NaCl, 0.1 M KCl, 0.1 mM quinine-HCl (QHCl), 0.1 M monosodium glutamate (MSG), 3 mM citric acid, 0.3 M sucrose and mixtures of NaCl, QHCl and citric acid with sucrose.	The taste confusion matrix (TCM) method	the mean percent correct identification for all 10 stimuli was 54.2 ± 5.3% for the chlorhexidine rinse group, which was significantly less than the 81.9 ± 4.0% for the water control group [$P < 0.001$]. There was a significant A versus B stimulus type × treatment interaction [$P < 0.007$].
IV	Paul A.S. Breslin *et al* [12]	2001	Primary outcome-decrease in the perception of saltiness and bitterness.	0.12% chlorhexidine and varying concentration of quinine hydrochloride, NaCl, KCl, NH_4Cl, urea, sucrose octa-acetate, QHCl, sucrose, MSG, citric acid, HCl and water.	Labeled Magnitude Scale [16]	There was mild to strong decrease in perception of bitterness. CHX decreased the salty taste of NaCl, KCl and NH_4Cl, but did not affect the tastes of sucrose, MSG, citric acid, HCl and the taste of water.

TABLE 3: CHARECTERISTICS OF BIAS IN THE STUDIES TAKEN FOR REVIEW

	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS
Gabriela Otero dos SANTOS *et al* [7]	+	+	–	+	?	+	–
Niklaus P. Lang *et al* [8]	–	?	?	?	?	–	–
JILL A. HELMS *et al* [9]	–		–	–	?	–	–
Ana Rita Duarte Guimaraes *et al* [10]	+	+	–	+	?	?	–
Janneane F Gent *et al* [11]	–	–	–	+	?	–	–
Paul A.S. Breslin *et al* [12]	–	–	–	+	?	–	

+: indicates low risk of bias -: indicates high risk of bias ? : indicates unknown

TABLE 2: shows the results show that there is a change in the taste perception according to Gabriela Otero dos SANTOS et al[7] while according to Ana Rita Duarte Guimaraes et al[10] there is no significant change in the taste perception in her study but Niklaus P. Lang et al[8] , JILL A. HELMS et al[9] show evidence that there is a decrease in salt perception and Janneane F Gent et al[11] and Paul A.S. Breslin et al[12] show a decrease in the perception of both saltiness and bitterness.

TABLE 3: shows the experiments conducted by Gabriela Otero dos SANTOS et al and Ana Rita Duarte Guimaraes et al show a relatively low risk of bias as opposed to JILL A. HELMS et al whose experiment has a significantly higher risk of bias. There were many unknown factors in the experiment conducted by Niklaus P. Lang et al making it more difficult to conclude the results. The rest had comparatively moderate risk of bias. It is important to take these values into consideration as the reliability of the result depends on there being a low risk of bias in the said experiments.

DISCUSSION

Gabriela Otero dos Santos et al [7] in 2017 conducted a randomized, double-blind, three-way crossover trial. The experiment was done to evaluate the formation of biofilm along with any adverse effects. 35 dental students participated in the study and were put in 3 groups: Group A an alcohol-containing 0.12% CHX solution (CHXAL), Group B an alcohol-free 0.12% CHX solution (CHX) and Group C (PLA), placebo. The subjects were asked to rinse every 12 hours for 1 min (15 ml). Results showed that, at 24 hours, both CHXAL and CHX, showed significantly lower amount of biofilm compared with placebo ($p < 0.01$). At 48 hours, the CHXAL had less amount of biofilm compared to the CHX (34.4% versus 45.1%; $p < 0.01$). At 96 hours, there was no significant difference between both the CHX solutions in removing the biofilm. The adverse events most frequently reported were burning sensation in the mouth, bitter taste after rinsing, and taste disturbance. 12 individuals reported the presence of these events while using the PLA solution, 10 subjects reported adverse events with the CHX solution, and 20 subjects reported adverse events after using the CHXAL solution. The adverse effects were more for CHXAL compared to CHX (57.1% versus 28.6%; $p = 0.013$).

Lang NP et al [8] 's experiment conducted in 1988 was done on 24 volunteers who had low mean plaque indices (PII) and gingival indices (GI) (silness and loe) [6][7] initially, he divided them into 3 groups of 8 each. They rinsed with 20ml of: Group A (unflavoured 0.2% of chlorhexidine digluconate solution), Group B 0.001 M of QHCl solution and group C (distilled water). Group A was the test group while group B and C were the controlled groups. Taste sensations were tested with a suprathreshold scaling procedure called magnitude estimation as described by Bartoshuk et al [13][14][15] on days -3 and -2 and at days 1, 2, 13 and 14 of the experiment. Taste sensitivity was checked using a method called as magnitude estimation, it is a suprathreshold scaling procedure which was done for four taste qualities which are sweet, salty, sour and bitter. six increasing concentrations of each of sucrose solution,

sodium chloride solution, citric acid solution and quinine hydrochloride were used in this experiment [8]. The results showed that the scaling procedures of the salty taste modality (sodium chloride) were significantly ($p<0.01$) different for the short-term (day 1 and 2) and treatment-related (day 13 and 14) observation periods in the test group A when compared with either controlled group (B, C); i.e. there is a significant decrease in the taste perception of saltiness in group A while group B and C showed no significant changes.

Jill A Helms et al [9] in 1995, conducted an experiment in which healthy 15 volunteers participated. This experiment was similar to that of Land NP *et al* [8]. All participants were tested for taste sensation a week before the experiment, on the 4th (last day) of the experiment and 4 days after the experiment. The method of magnitude matching was used to measure the taste intensity (Marks et al. 1988; Bartoshuk, 1989). The volunteers were asked to rinse for 3 min with 0.12% of chlorhexidine gluconate solution twice a day for 4 days during the experiment. Participants were given a series of taste solutions, in random order, consisting of sodium chloride (NaCI; 0.01, 0.032,0.10, 0.32 and h0 M), sucrose (0.01, 0.032, 0.10, 0.32and 1.0 M), citric acid (1.0, 3.2, 10, 32 and 100 mM)and quinine hydrochloride (quinine-HCl; 0.0032,0.01, 0.032, 0.1, 0.32 and 1.0mM)" [9]. The results showed that there was a severe decrease in the perception of salt taste, at mid-range, mean magnitude- estimate scores for NaCl and QHCl were reduced by 52.1% and 48.6%, respectively, during the chlorhexidine treatment period compared to before treatment, but scores for sucrose and citric acid did not change. These results were in agreement with that of *Lang NP et al [8].*

Ana Rita Duarte Guimaraes et al [10]'s *experiment in 2006* was conducted to evaluate the adverse effects of a mouth rinse, one of whose components was chlorhexidine. It was a double-blind study which was as part of a randomized controlled trial. 170 adolescents of age 11 to 15 years were recruited and randomly divided into 2 group. Group 1 (0.05% solution of NaF and 0.12% CHX) and Group 2 (0.05% solution of NaF). The volunteers were then instructed to rinse for 1 min every day for 14 days using the 10 ml solution containing the above said components along with glycerine, non-cariogenic anise aroma, blue food colouring, preservative and vehicle. This experiment is similar to the one conducted by Paul A.S. Breslin *et al*[12] .The effects on taste perception were evaluated after 14 days using a "Labelled Magnitude Scale"[16].The results showed that there was no significant change in taste perception but this result contradicts the one obtained by Paul A.S. Breslin *et al* but that may be due to the presence of anise flavouring in the solution which may mask the bitter taste disturbance caused by chlorhexidine. Hence the results are not very conclusive

In the experiment conducted by Janneane F Gent et al in 2002, the participants were given a set of 10 stimuli and were asked to identify those stimuli, the results were calculated based on the number of right and wrong responses. The results showed that the mean (± SE) percent of correct identification for all 10 stimuli was 54.2 ± 5.3% for the chlorhexidine rinse group, which was significantly less than the 81.9 ± 4.0% for the water control group ($P < 0.001$).

Two experiments were conducted in this article published by *Paul AS Breslin et al [12]* in 2001. 13 healthy individuals were recruited as volunteers. Chlorhexidine digluconate (CHX) and quinine HCl were the stimuli. The purpose was to intensity match quinine hydrochloride to the 0.12% CHX. After several days of intensity testing, 0.01 M concentration of QHCl was identified to match the concentration of 0.12% of CHX. The decrease in bitterness was assessed as mild to strong. The 2nd experiment was done in a similar way with 16 volunteers. NaCl, KCl, NH_4Cl, urea, sucrose octa-acetate, QHCl, sucrose, MSG, citric acid, HCl and water were used as stimuli. CHX was found to decrease the salty taste of NaCl, KCl and NH_4Cl, but did not affect the tastes of sucrose, MSG, citric acid, HCl and the taste of water.

Majority of the results show that there is a decrease in the perception of salt and bitter taste, this is also seen in other experiments such as those conducted by Ruchi Grover [17] and Gokul G [18], many other invitro tests conducted also resulted in a decreased bitter and salt taste perception.

RECENT ADVANCES

There is a New sustained release dosage form of chlorhexidine for dental use, the ideology behind this is to prevent the side effects such as staining of the tooth and altered taste sensation by slow and low amount of chlorhexidine release over long period of time in particular locations. Sustained release was obtained by embedding chlorhexidine in an ethyl cellulose polymer. It can be coated on partial dentures which may result in prevention of plaque formation. The treatment of periodontal pockets may also be accomplished by inserting this preparation inside the pockets. These new methods may not necessarily eliminate the cause of these adverse effects such as altered taste perception and tooth discolouration but it can help in reducing the effects to an acceptable levels.[19] Some other ways used were adding a strong flavouring agent in the mouthwash to mask the effect of the taste alteration and give a pleasant and refreshing after effect after the mouth rinse.

CONCLUSION

Most of the experiments (5 out of 6) support the statement that long term use of chlorhexidine in any concentration (most commonly used concentrations for mouthwashes are 0.12% and 0.2%) decreases the taste perception. And 4 out of the 5 experiments that show positive result agree that there is a decrease in the taste perception of saltiness and 2 out of the 5 experiments that show positive result show that there is a decrease in the taste perception of bitterness.

The new advances in the development of chlorhexidine mouthwashes with decreased adverse effects or alternative methods to avoid these adverse effects are taking place and it may be preferable to use these new products as it is important to keep the adverse effects to a bare minimum as much as possible.

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