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The influence of intraoral cooling on taste and smell perception

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ABSTRACT

Background: Cryotherapy using ice chips has been successfully used to prevent chemotherapy-induced oral mucositis. Although effective, concerns have been raised that the low temperatures that are obtained in the oral mucosa during cooling may be potentially harmful to taste and smell perception. Thus, this study aimed to investigate whether intraoral cooling permanently affects taste and smell perception.

Subjects and methods: Twenty subjects inserted an ounce of ice chips and moved the ice around in the mouth to cool as large a part of the oral mucosa as possible. Cooling continued for 60 min. At baseline (T0 – minutes), and following 15, 30, 45, and 60 min of cooling, taste and smell perception were registered, using the Numeric Rating Scale. The same procedures were repeated 15 min (T75 – minutes) after completion of cooling. Taste and smell were evaluated using four different solutions and a fragrance, respectively.

Results: A statistically significant difference was seen for taste perception with Sodium chloride, Sucrose, and Quinine at all the follow-up time points tested as compared to baseline ($p < .05$). Citric acid and smell perception proved to be significantly different from baseline following 30 min of cooling. When the same assessments were carried out 15 min following completion of cooling, i.e. T75, all taste and smell perceptions had recovered to some extent. For taste perception, however, a statistically significant difference was still seen for all solutions tested as compared to baseline ($p < .01$).

Conclusion: In healthy individuals, intraoral cooling with IC leads to a temporary reduction in taste and smell perception, with a tendency to return to baseline values.

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Background

It is well recognized that chemotherapeutic drugs, e.g. 5-fluororacil (5-FU) or high-dose chemotherapy in preparation for hematopoietic stem cell transplantation instigates a variety of adverse effects [1]. These include, for example, oral mucositis (OM), a debilitating adverse effect which is observed in up to 80% of all patients [2]. Furthermore, although reported to a lesser extent compared to OM, chemosensory alterations following the administration of cytotoxic drugs are common and known to be distressing among advanced cancer patients [3,4].

An estimated 50–70% of all patients subjected to chemotherapy (CMT) report altered gustation (below referred to as taste perception) to some extent, consequently leading to loss of appetite, diminished nutritional status, and impaired quality of life [5]. Adverse olfaction (below referred to as smell perception) on the other hand affects up to 90% of all patients who receive CMT [6,7], and may lead to both intensified and reduced sense of smell [8]. These numbers are significantly higher compared to those reported for the general population, where the point prevalence is 17.3% and 13.5% for taste-, and smell impairment, respectively [9].

Over the past decades, cryotherapy (CT) using ice chips (IC) has been successfully used to prevent OM. Promotion of vasoconstriction resulting in reduced delivery of chemotherapeutic agents to at-risk tissues (e.g. the mucous membrane), continues to be viewed as the most likely protective mechanism [10]. The preservation of the tissue could also be attributed to a decreased metabolic activity in the basal epithelial cell layer resulting in lower exposure to cytotoxic drugs [11,12].

Despite the positive effects of CT for CMT-induced OM [11,13], concerns have been raised that the low temperatures that are obtained in the oral mucosa in conjunction with CT, may itself be potentially harmful to the gustatory, and olfactory cells. Thus, this study aimed to investigate whether intraoral cooling permanently affects taste and smell perception in healthy individuals.

Subjects and methods

Study design and subjects

This prospective experimental trial was carried out between August 2019–October 2019 at the Institute of Odontology,

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The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. All twenty ($n=20$) subjects were recruited from the Sahlgrenska Academy and were considered eligible to participate in the study if they met the following inclusion criteria's: (i) ≥ 18 years, willing and able to provide informed consent, (ii) no medical diagnoses established by a physician, (iii) no mucosal lesions or xerostomia, and (iv) no use of nicotine-containing products such as cigarettes, chewing tobacco or Swedish snuff.

Procedures and data collection

All measurements were performed in the same examination office (ambient temperature 22 ± 2 °C) to maintain standardization in the experimental design. Prior to inclusion, medical history was gathered, weight in kilogram and height in meters were measured, and BMI (kg/m^2) was calculated. Next, each participant underwent an intraoral examination to assure a healthy oral mucosa. All subjects received verbal and written information in Swedish regarding the aim of the study, the procedures and any potential risks associated with the trial. Following written informed consent, each subject was assigned to one cooling session of 60 min.

Prior to the cooling session, subjects were informed to insert an ounce of ice chips (IC) and move the IC around in the mouth to cool as a large part of the oral mucosa as possible. They were also briefed to rinse the melted ice slurry that was obtained for a few seconds before it was swallowed or spat out. Cooling continued for 60 min, and the participants were requested to refrain from eating or drinking for at least 30 min prior to cooling.

IC were produced in a commercial ice maker (Porkka KF145 Flake Ice Machine, Oulu, Finland) designed for the hospital environment and stored in styrofoam containers at room temperature during the cooling procedures. IC temperature was −0.5 °C upon exposure.

At baseline (T0 – minutes), and following 15, 30, 45, and 60 min of cooling, taste and smell perception were evaluated using the Numeric Rating Scale (NRS) graded from 0 to 10 (Normosmic-mild 0–3, moderate 4–6 and severe 7–10 olfactory loss [14]. Both procedures were repeated 15 min (T75) after the cooling session was completed. The taste was evaluated using four different solutions: Sodium chloride [15 mg/mL]; Sucrose [70 mg/mL]; Citric acid [3 mg/mL]; and Quinine [1 mg/mL] [13]. The solutions were prepared with distilled water and each of the following solutes, NaCl, Sucrose, Citric Acid, Quinine, respectively (Sigma-Aldrich, Stockholm, Sweden) Table 1. The concentrations used in this study were based on experiments from previous studies [15]. A total of 10 mL of each solution was poured into disposable plastic cups and the subjects were instructed to swirl around the solution in the oral cavity for a maximum of three seconds before it was spat out. The same test sequence, i.e. Sodium chloride – Sucrose – Citric Acid – Quinine, was used throughout the study. For smell testing, the fragrance, (Vanille Yves Rocher, eau de toilette [5–15 mg/mL], La Gacilly, France; referred to as Perfume) was applied on a scent strip. To standardize and maintain the same intensity of the perfume a new scent strip was used for each of the follow-up timepoints. Following each assessment ice- water and commercially available coffee beans (Nescafé, Lyx medium roast) were used, to recover the smell perception.

Table 1. Summary of the solutions used for taste and smell perception and their concentrations, respectively.

Taste	Solute	Solution [mg/mL]
Salt	NaCl	15
Sweet	Sucrose	70
Sour	Citric acid	3
Bitter	Quinine	1

Statistical analysis

The sample size was calculated using data from a previous pilot test on five ($n=5$) healthy volunteers where taste perception was assessed for sweet taste following 60 min of cooling with IC. A mean difference ($\bar{x}$ = 2; SD = 1) in units on the NRS-scale was observed as compared to the baseline. Based on these numbers, *a priori* analysis, using α-significance level of 0.05 and power of 80%, gave a sample size of at least 4 participants (G*power version 3.1.9.4 (University of Düsseldorf, Düsseldorf, Germany).

Normality assumption was controlled using the Shapiro–Wilk test and Gaussian distribution was confirmed for the tested variables. All analyses were done with repeated measures ANOVA (within-subject ANOVA) followed by Bonferroni correction for multiple comparisons. A p-value of ≤.05 was considered statistically significant. The calculations were performed using the IBM® SPSS® Statistics software package (IBM SPSS Statistics version 25, IBM, Armonk, NY).

Ethical consideration

The procedures in this study involving human participants were performed in accordance with the ethical principles established in the Declaration of Helsinki (Fortaleza, October 2013). The study protocol was further reviewed and approved by the regional Ethics Review Board in Gothenburg (Ref. no. 2019 – 0178). All participants received information concerning the study and were informed about the rights to withdraw consent to participate at any given time without reprisal. Informed written consent was obtained from all the participants.

Results

In total, twenty ($n=20$) subjects with a mean age of 25 ± 2 years were enrolled in this experimental trial. Among the included, twelve ($n=12$; 60%) were females and the remaining eight ($n=8$; 40%) were males. All participants were healthy and did not report any medical conditions established by a physician. None of the subjects had mucosal lesions or xerostomia. Each subject completed the assigned cooling session of 60 min and no deviations from the study protocol occurred. At baseline (T0), when taste perception was assessed with each of the following solutions: Sodium chloride, Sucrose, Citric Acid, and Quinine, all participants scored 10 on the numeric rating scale (NRS). Concomitant registration with the NRS – scale for smell perception also showed 10. Following 15 min (T15) of cooling a mean decrease of 1-2 units was seen for Sodium chloride, Sucrose and Quinine, but less than one unit was observed for Citric Acid and smell perception with the perfume, i.e. NRS – score 9 ± 1, respectively (Figure 1; Table 2). Taste perception, regardless of the tested solution, further decreased at each of the follow-up time points. Following 30 min (T30) of cooling the mean NRS – score was 7 ± 2, subsequently decreasing to 6 ± 2 and 5 ± 2 after 45 (T45), and 60 min (T60) of cooling, respectively (Figure 1; Table 2). The same pattern was observed for smell perception, i.e. NRS – score decreased with cooling time. The corresponding NRS – scores for smell perception at the same follow-up time points were as follows: T15: 9 ± 1; T30: 8 ± 2; T45: 8 ± 2; T60: 8 ± 2 (Figure 1; Table 2).

A statistically significant decrease was seen for Sodium chloride, Sucrose and Quinine at each of the follow-up time-points (T15, T30, T45, and T60) as compared to baseline ($p < .05$). Taste perception with Citric acid and smell perception, however, proved to be significantly different from baseline following 30 min of cooling (T30). For Sodium chloride, the most significant reduction in taste perception was seen at T15, whereas the corresponding reductions were observed at T30 for Sucrose and Citric acid, and at T45 for Quinine.

At T75, i.e. 15 min following completed cooling, both taste and smell perception returned to scores comparable to those observed at T15. However, when T75 was compared to the baseline (T0) for taste perception, a statistically significant difference was seen for all the solutions tested ($p < .01$). In contrast to taste perception, no statistically significant difference was observed for smell perception when T75 was compared to baseline (T0).

Discussion

Despite the numerous options for the management of chemotherapy (CMT)-induced oral mucositis (OM) [16–18], using ice chips (IC) remains the most recommended modality [11,13,19–24]. In fact, it has resulted in the development of a novel intraoral cooling device [12] which has shown promising results in a clinical trial [25]. Nevertheless, the low temperatures which are obtained in the mucosa in conjunction with intraoral cooling may be harmful to the taste and smell perception and caution should be considered. If that would be the case, it would significantly impair the use of cryotherapy (CT) in clinical settings. This was the rationale for conducting this study.

As expected, a reduction in taste and smell perception was observed at each follow-up time point as compared to the baseline. Among the four tested solutions for taste perception, sucrose proved to be affected the most by intraoral cooling. This finding is in parallel with previous studies showing that sweet perception is reduced by lower temperatures [26,27]. One possible explanation for this could be the reduced sensitivity of cation channels, TRPM5, which are essential for the transduction of sweet. These are a group of calcium-dependent channels that constitute the final step in the sweet taste receptor transduction cascade. The TRPM5 activation is strongly temperature dependent. Cooling may cause decreased sensitivity, in turn affecting receptor depolarization and afferent fiber excitation. Both of which

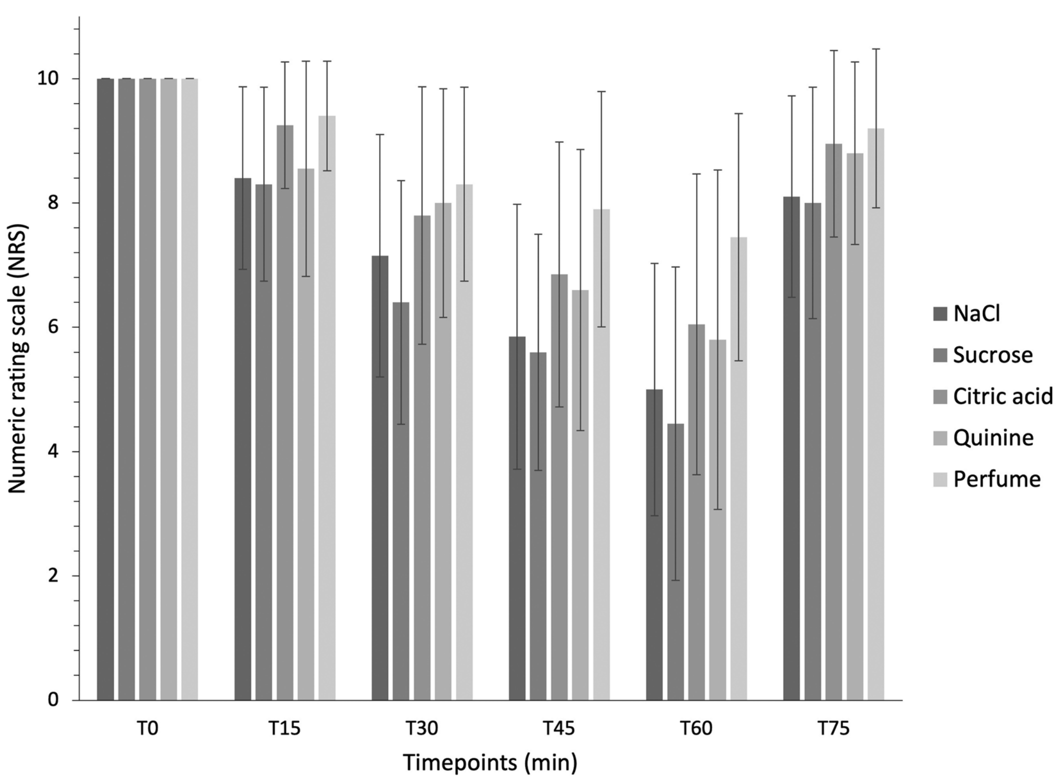

Figure 1. Illustration of taste and smell perception for the different solutions at baseline, and the follow-up timepoints with the numeric rating scale (NRS). All data are presented as mean ± SD.

Table 2. Taste and smell perception for the different solutions at baseline, and the follow-up timepoints with the numeric rating scale (NRS).

	T0	T15	T30	T45	T60	T75
NaCl	10 ± 0	8 ± 2	7 ± 2	6 ± 2	5 ± 2	8 ± 2
Sucrose	10 ± 0	8 ± 2	6 ± 2	6 ± 2	5 ± 3	8 ± 2
Citric acid	10 ± 0	9 ± 1	7 ± 2	7 ± 2	6 ± 2	9 ± 2
Quinine	10 ± 0	8 ± 2	8 ± 1	7 ± 2	6 ± 3	9 ± 2
Perfume	10 ± 0	9 ± 1	8 ± 1	8 ± 2	8 ± 2	9 ± 1

All data are presented as mean ± SD.

essential for nerve transmission and taste perception [26,28]. Sweet taste, regardless of the carbohydrate group, has further been shown to be significantly impaired after cooling of the tongue [29]. Impairment of taste perception was also found for Quinine, i.e. bitter taste, which was significantly affected by intraoral cooling. This in turn can be explained by the mechanism of thermal sensitivity of taste transduction and adaptation. Some taste fibers are more sensitive to thermal stimuli, for example, fibers for bitter taste [28]. Studies have shown that the perception of bitter taste is reduced with lower temperatures which is consistent with the results of this study [30].

Across the one-hour cooling session, similar to taste perception for sweet and bitter, salt and sour were significantly affected. These findings agree with one previous study acknowledging that low temperatures can modify taste perception by modulating specific cation channels regulating receptors for salt and sour [31]. However, it remains to be elucidated why the different taste perceptions were unequally affected by intraoral cooling; and whether the outcome would be the same if other concentrations had been studied.

As for smell perception, a statistically significant difference was observed when compared to the baseline. This reduction was however seen later during the course of cooling, as compared to the taste perceptions. One modest but possible explanation for the delay could be the distance between the site of cooling and the nasal mucosa. The distance may postpone the effects of cooling on the molecular mechanisms that are responsible for smell perception. Another explanation for the delay could be the choice-, or the concentration of the perfume used in this study. Other perfumes or stronger scents could be perceived differently. Nevertheless, the specific mechanism of smell perception in conjunction with intraoral cooling needs to be further studied.

At the follow-up timepoint (T75), i.e. 15 min following completed cooling all scores were still significantly different from the ones observed at baseline, although they had recovered markedly. Thus, one can assume that taste perception will return to scores comparable to those at baseline, similar to smell perception. Most likely, taste and smell perceptions are affected temporarily by intraoral cooling in healthy individuals. In this regard, CT with IC may be considered a harmless modality.

This study has some limitations that should be acknowledged. First, even though it seems that taste and smell perceptions are temporarily affected by intraoral cooling with IC, data are collected from young healthy volunteers. Taste and smell perception may be affected by factors other than cooling, e.g. age or gender. In fact, olfaction has been shown to be significantly impaired with increasing age [32]. Furthermore, although not assessed in this study, women tend to maintain their chemical senses to a greater extent as compared to men of the same age [33]. Taste and smell perception may also be perceived different in older patients who possess more comorbidities and consume more drugs, e.g. cancer patients, especially those subjected to CMT. Such a cohort would have been desirable to investigate but as this study aimed to investigate whether intraoral cooling permanently affects taste and smell perception, the influence of CMT had to be excluded. This as CMT is known to harm both taste and smell. Otherwise, it would have been difficult to demonstrate if any changes in perceptions are caused by the CMT *per se*, the intraoral cooling or a combination of both. Second, taste and smell perceptions were subject-reported. It would be more appropriate with objective outcome assessments. This is to overcome the shortcomings of subject-reported outcome measures, which may suffer from poor reliability.

Conclusion

In healthy individuals, intraoral cooling with IC leads to a temporary reduction in taste and smell perception, with a tendency to return to baseline values.

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Author contributions

Study design (VH, SW, JW); conduct of study (VH, SW); collection of data (VH, SW); analysis, interpretation, and management of data (VH, SW, JW); preparation of manuscript (VH, SW, JW); intellectual content review (JW); and approval of final manuscript draft (VH, SW, JW).

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