

Electrogustometry and contact endoscopic findings in patients with tonsillar squamous cell carcinoma and radiochemotherapy.

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Abstract

Introduction: Aim is to investigate in parallel changes in electrogustometric thresholds and in morphology of the fungiform papillae as well as in shape and density of the vessels of the tip of the tongue in patients with head and neck malignancy before and after treated with radiochemotherapy. We have also studied whether the observed changes in function and morphology may be reversible. **Materials and Methods:** Eighteen patients with tonsil-cancer treated with radiochemotherapy were prospectively studied. Measurements took place before starting treatment and at the end of each cycle of chemotherapy. Additional measurements were conducted two and four months after the end of the therapy. **Results:** All patients showed alterations in form and vascularization of fungiform Papillae (fPap). After the end of therapy an improvement in the EGM-thresholds without immediate improvement in the shape and vascularization of fungiform papillae was found. Two months after the end of the therapy a minimally significant difference in the EGM-thresholds measured on the tip of the tongue was shown. By the second measurement we have noticed a little improvement of the EGM-threshold, accompanied only by an improvement in the vascularization of fPap. **Conclusions:** The improvement in taste acuity was not directly accompanied by changes in vascularization of papillae and shape. The last parameters seem to recover late in time.

Key Points:

1. The current research is the first to present combined data concerning the alterations in structure and vascularisation of fPap with respect to the variations in EGM-thresholds in HNC patients when they are receiving radiochemotherapy as well as after the treatment.
2. Patients experience a deterioration in taste acuity when they are receiving radiochemotherapy and after the treatment.
3. Taste disorders associated with chemotherapy have a multifactorial aetiology.
4. There is not an improvement in EGM-thresholds concurrently with the morphology and vascularisation of fPap.
5. As a result of the limited number of studies, it is challenging to make suitable recommendations concerning diagnosis, therapy, and the expected development of taste deterioration in oncology environments.

Keywords: Contact endoscopy; radiochemotherapy; electrogustometry; fungiform papillae; vascularisation, taste.

Introduction

When chemotherapeutic (CT) drugs are systemically administered, this can frequently lead to serious acute adverse impacts. For instance, as a result of their cytotoxic effects and suppression of the immune system,

patients may become more susceptible to oral mucositis and bleeding as well as a reduction or impairment of salivary gland function or oral infections [1,2]. Furthermore, as many as 89% of patients with head and neck cancer (HNC) experience taste dysfunction prior to being treated because of the malignancy [1].

After receiving radiation therapy (RT), alterations to taste could persist as a result of hyposalivation and damage to the cellular taste receptors [3]. A patient's taste recovery after receiving treatment can vary between 2 and 6 months subsequent to oncologic therapy, although it may persist for an extended period [4,5].

Hence, this study aimed to evaluate the electrogustometric thresholds and related alterations of form in addition to the vascularisation of the tongue mucosa in patients with tonsillar squamous cell carcinoma and RCT.

Method

To reach this aim, a total of 20 patients with HNC receiving electrogustometry (EGM) treatment along with contact endoscopy were recruited (after obtaining approval from the local ethics committee as well as informed consent from all patients). In particular, EGM-thresholds, vascularisation of the end of the tongue, as well as fPap morphology were measured. Prior to starting the therapy, baseline (initial) measurements were made; subsequently, the second set of measurements were made after the initial CT had been completed, followed by the third measurements a week after the second CT cycle had been completed. Additionally, we scheduled follow-up measurements that would be performed in the 2nd and 4 months post-RCT. Every patient included in the evaluation received concurrent RCT (cisplatin, 5-FU) treatment as a result of the diagnosis of malignancy in the tonsils. The primary tumour was targeted with a dose of radiation varying between 50.4 Gy and 72 Gy. CT was delivered in 2 cycles (each with a duration of 1 week).

EGM was conducted according to previous reports using a single, flat, circular stainless-steel stimulus probe (with a diameter of 5mm) [6]. The device generates low-amplitude stimuli with a fixed time period (0.5, 1, 1.5, and 2 seconds). The output current is controlled by a feedback circuit where the error is < 1%. Measurements of the electric threshold scores were performed at six sites: the vallate papillae on either side of the tongue, innervated by the glossopharyngeal nerve, para-medially on either side of the tongue (both 2cm from the end), at an area innervated by the chorda tympani as well as the soft palate, innervated by the greater petrosal nerve bilaterally.

A non-contact method was firstly used to identify fPap. Subsequently, contact endoscopy was conducted utilising a 30° contact endoscope (magnification × 60 and × 150; Karl Storz, Tuttlingen, Germany). Patients were asked to rinse their mouth with water prior to the contact endoscopy. A contact method was firstly utilised with no staining in order to image the subepithelial vessels. Once the saliva had been carefully suctioned, the epithelia and taste pores were stained with methylene-blue 1% solution. A strip of filter paper covering an area of 1 cm² was situated in a paramedian orientation on the tip of the tongue. Heat at the end of the endoscope was minimised using a cold source of light. CE examinations did not reveal any changes (increases or decreases) in vascularisation.

The fungiform papillae form was categorised into four different types in increasing order of damage: Type 1, (egg-shaped or long ellipse type – with no surface thickness), Type 2 (surface thickness is slightly more than Type 1), Type 3 (surface is thicker with increased irregularity), and Type 4 (surface is notably flat and shows signs of atrophy). It is important to note that papillae with a mushroom form and horned tips were categorised as filiform rather than fungiform papillae. As a result of their minimal level of staining, it was relatively easy to differentiate fungiform papillae from filiform papillae, as their staining was darker.

The morphology of the blood vessels at the end of the anterior tongue apex was classified based on the classification of Negoro et al. [7]. Five types of morphology were found for the vessels, categorised in increasing order of morphological changes: Type A (clear loop and wooden branch shape), Type B (clear loop and wooden branch shape), Type C (stretched blood vessels), Type D (dotted or granular shape), and Type E (unclear blood vessels).

For the purpose of statistical analysis, where it was not possible to measure the EGM-threshold, a numerical value of 36 dB was assigned. IBM® SPSS® Statistics 26.0 software was used and significance level was fixed at $p < 0.05$. STROBE statement was followed as reporting guideline for this study.

Results

Patients' demographics

Acute mucositis and oral bacterial infections were not observed in any of the patients prior to commencing the therapy. From the 20 patients, one patient abandoned the measurements and another one died when RCT was being conducted. All other patients ($n=12$ pT3N2aM0-8 males and 4 females, $n=6$ pT3N2cM0-4 males and 2 females) finished the study.

The mean age of the patients included in the evaluation was 57 ($SD \pm 7$), and the d-Test value ($d=0,2189$) indicated that the analysis was slightly affected by the age distribution (mean and standard deviation).

EGM-thresholds

A statistically significance difference was observed between the values prior to starting the therapy and one week after ($p=0.02$, Cohen's d -Test=0.35). At that time, patients had complaints of hypogeusia ($n=6$), allogeusia ($n=1$) and dysgeusia ($n=1$). When the third measurements were made, hypogeusia was reported by every patient, while 3 patients also complained of dysgeusia. A further deterioration in EGM-threshold values was observed in the subsequent measurements, which included the follow-up measurements following RCT. Table 1 shows the mean EGM-thresholds of the evaluated patients.

Structural alterations associated with the fungiform papillae

The fPap shape and vascularisation of the tip of the tongue exhibited a significant deterioration when therapy was being delivered based on the classification criteria of Negoro. It appeared that the fPap parameters (form and vascularisation) had worsening tension once the treatment had been completed.

Prior to RCT, there were significant correlations among the EGM-thresholds and morphology ($r=-0.719$, $p<0.05$) as well as vascularisation of fPap ($r=-0.719$, $p<0.05$). Once RCT had been initiated, a strong positive correlation was only detected between EGM and vascularisation ($r=0.763$, $p<0.05$) one week subsequent to the initiation of therapy. In the follow-up measurements, no additional correlations were observed.

Discussion

In the current study, we demonstrated that an improvement in EGM thresholds does not occur concurrent to the morphology and vascularisation of fPap. Vascularisation is the first parameter that appears to show signs of improvement. A further important result is that additional deterioration of EGM-thresholds appears to occur even after the RCT treatment has been completed. Our findings support the theory that when nerve fibres responsible for innervating taste buds are damaged by irradiation, taste cells could be indirectly destroyed due to the fact that mature taste cells need functional nerve contact in order to be maintained [8].

After receiving RT treatment for HNC, patients commonly complain of taste dysfunction [1]. When receiving a 6-8-week daily radiotherapy course, a loss of taste generally manifests by weeks 3 to 4 and it is common for all taste modalities to be impacted. Previous studies have reported the worsening of EGM-thresholds during RCT for HNC [3]. The time at which taste cells are lost predominantly occurs when patients begin to experience functional taste loss, which is initially seen one week into the course of radiotherapy [9].

Low-level radiation delivered during the early stages could cause the receptors to be damaged. In a study, it was observed that when curative radiation therapy was given for HNC, salivary function had decreased by the end of week 1, and measurements clearly indicated that after the second week of treatment, taste function had been impaired [9]. Initial evaluations of taste changes reported by patients receiving radiation therapy have indicated that significant changes occur when the treatment is ongoing, and that taste sensations do not return to pre-treatment levels [1]. Such taste problems could be caused by direct impacts on the taste

receptors, the reduction in the production of saliva leading to secondary infection, and limited delivery of tastants to receptor areas.

With regard to chemotherapy, taste disorder aetiology is not only because of damage caused to taste receptors and neurons by RCT, but it is probable that it is caused by multiple factors. Apart from chemotherapeutic agents, other drugs can also alter taste and must be taken into account when assessing taste in such patients [10].

In summary, there is no improvement in EGM-thresholds concurrent with the morphology and vascularisation of fPap. There has been minimal focus in the literature on taste dysfunction in patients with HNC, and it is probable that they are underestimated. Additional long-term studies of nerve fibres at the tongue tip subsequent to chemotherapy or radiotherapy in patients diagnosed with tonsillar squamous cell carcinomas are therefore necessary.

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Table 1 EGM results.docx available at <https://authorea.com/users/313079/articles/710443-electrogustometry-and-contact-endoscopic-findings-in-patients-with-tonsillar-squamous-cell-carcinoma-and-radiochemotherapy>