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Recent advances in prevention and treatment of post-radiotherapy xerostomia in patients with head and neck cancer

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Recent advances in prevention and treatment of post-radiotherapy xerostomia in patients with head and neck cancer

Short title: Treatment of dry mouth (xerostomia)

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Abstract

Xerostomia, or feeling of dry mouth is the most common (80%) of all complications of radiotherapy for head and neck cancer. Besides well-known artificial saliva and agents and therapies stimulating saliva production and salivary gland regeneration, new methods comprise the use of vitamin C and E, low level laser therapy, hyperbaric oxygen therapy and thyme honey. Recently, transplantation of the mesenchymal stem cells reported to be successful, and these may be, together with gene-transfer therapy the future therapies of xerostomia after salivary gland irradiation.

Key words: dry mouth, xerostomia, post-radiotherapy complications, head and neck cancer, artificial saliva

Introduction

Head and neck tumors account for approximately 3–5% of all malignancies diagnosed worldwide [1]. It is a heterogenous group of tumors with mortality rate of above 50% [1]. As most of tumors are cancers of epithelial or glandular origin and by the time of diagnosis are locally advanced, radiotherapy with or without previous surgery are the treatment of choice [2]. Dry mouth or xerostomia are frequent adverse effect of radiotherapy and depends of the rate of salivary gland damage and regeneration [3]. Regeneration of the gland tissue may be none or incomplete and the dry mouth may accompany the patient until death. It can profoundly affect patients' ability to chew, swallow and speak, as well as it may affect the teeth health and overall quality of life [3].

After surgery and/or radiotherapy salivary glands loose ability to produce saliva and 80% of all patients with head and neck cancers treated with these methods suffer of dry mouth or xerostomia [4]. Only in some of these patients there will be enough viable gland tissue amenable to stimulation and/or able to regenerate. Beside oncology, in medicine, there is a great interest in the treatment of xerostomia and hyposalivation in Sjögren syndrome [5]. Some data on the treatment of xerostomia cited in this paper may originate from this research.

Methods

In this review we shall present the data on the management of xerostomia after radiotherapy treatment for head and neck cancers. A combination of terms "xerostomia", "treatment" "radiotherapy" and "head and neck cancer" yielded in the National Library of Medicine 211 articles. Among them 26 (including systematic reviews) were about treatment methods and were published in the last 10 years. Three articles were systematic reviews of different treatments of xerostomia.

Topical agents and saliva substitutes

Taking sips of water, sometimes with ice or lemon, is the oldest treatment method of dry mouth. However, it is seldom successful on the long run as water washes out the mucus and decreases the lubrication of the mucus membrane which is than prone to drying. This is why new formulations of artificial saliva were prepared and are already in use for decades. Artificial saliva ideally resembles the natural one and is usually a mix of buffering agents, cellulose-like derivatives and flavoring agents [6]. Saliva replacements are accessible as different agents such as liquids, sprays, gels, oils, mouthwash, chewing gums, and toothpastes. Typically, they are not toxic and can be applied by the patient as needed, many

times a day. Their main purpose is to lubricate the mucous membrane and facilitate chewing, swallowing and speaking. Some preparations may be combined with pilocarpine which stimulate salivary gland to produce more natural saliva [7, 8]. Artificial saliva was in the past only rarely a subject of a clinical controlled trial as such. More often it was used as a placebo to be compared with [7].

Seventy-two patients with Sjögren syndrome (most of them women) and xerostomia and dry eyes were assigned randomly to receive either 10 pilocarpine drops (5 mg) or 10 drops of artificial saliva three times daily for 12 weeks [7]. The primary outcome was the measurement of non-stimulated salivary and lacrimal flow. The secondary endpoint was the patients' subjective assessment. Patients receiving pilocarpine had a statistically significant improvement in their salivary flow ($p < 0.001$), lacrimal flow ($p < 0.001$) and their subjective global assessment ($p < 0.001$), compared with patients who received artificial saliva. The most common side-effects were sialorrhea and nausea.

Recently, several clinical trials with different formulations of artificial saliva with or without pilocarpine were published which suggests developments of new and improved preparations [8–10]. A study by Sarideechaigul et al. [8] aimed to compare the efficacy and safety for xerostomia treatment of two artificial saliva formulations containing 0.1% pilocarpine, and, either sodium carboxymethylcellulose or, sodium polyacrylate. Thirty-one xerostomia patients with xerostomia were randomly allocated into either a carboxymethylcellulose-treated group (15 patients) or, a polyacrylate-treated group (16 patients). The xerostomia could be secondary to radiotherapy but also could result from different, usually, autoimmune disorders. The artificial saliva formulations were taken at the volume of 0.5 mL four times daily for six weeks in a double-blind fashion. The results were assessed using stimulated and unstimulated salivary flow rates and xerostomia inventory and clinical oral dryness score. After treatment, the carboxymethylcellulose-treated group had significantly lower clinical dryness scores and higher unstimulated and stimulated whole salivary flow rates ($p < 0.001$), while the polyacrylate-treated group showed significantly lower clinical oral dryness scores only ($p = 0.004$). The effects of both formulas ceased after discontinuation of therapy.

In another single blinded randomized controlled trial concerning efficacy of an oral moisturizing jelly and topical commercial mouth gel was tested in 56 patients with postradiotherapy xerostomia [9]. Primary endpoints were *Candida* colonization, stimulated salivary flow rate, salivary buffering capacity and salivary pH. Secondary endpoints included subjective patients' reports. Both tested saliva gels improved saliva pH, decreased the number

of *Candida* species and stimulated salivary flow rate. A total of 56 participants in oral moisturizing jelly (n = 30) and commercial mouth gel (n = 26) groups completed the study. Oral moisturizing gel significantly increased saliva pH ($p = 0.042$) and buffering capacity ($p = 0.013$) after one month of use, while commercial mouth gel only improved saliva pH ($p = 0.027$). Both interventions tended to increase stimulated salivary flow rate but only commercial gel had a significant increase at two months ($p = 0.015$). Both commercial gel and oral moisturizing jelly significantly decreased the number of *Candida* species at 1 and 2 months, but not counts. Comparison of similar preparations was performed by Nuchit et al. [10]. These authors concluded that the new oral moisturizing gel tested by them was significantly better than the control commercial mouth gel and it improved better patients' salivary flow rate and subjective experience.

Finally, in a controlled clinical trial [11] including 94 survivors of nasopharyngeal cancer a xerostomia Oral7® mouthwash, (an immunologically active saliva substitute formulated with natural enzymes such as lactoperoxidase, lysozyme, glucose oxidase, and lactoferrin, similar to naturally occurring saliva) was compared to commercially available Colgate Plax® mouthwash with biocidal properties but no immunologic active ingredients. The trial lasted for 4 weeks. The endpoints were xerostomia inventory and unstimulated whole saliva. There was a significant difference in xerostomia inventory ($p < 0.0001$) and unstimulated whole saliva ($p < 0.0001$) between control and interventional arm. The immunologically active mouthwash (intervention arm) was significantly better than the control mouthwash but the study lasted only for a short time and it is difficult to judge about the long-term effects.

In conclusion. New developments of artificial saliva preparations, step by step, improve their palatability and efficacy. Pilocarpine added to the artificial seem to have an additional effect. However, this particular aspect was not tested in the controlled trials discussed here. On the other hand, the market is flooded with different preparations (tested and untested) available without prescription, which may leave the patient with xerostomia in a great confusion.

Pharmacological treatment

Patients with head and neck cancers survive longer and also suffer xerostomia for a longer time [12], but the data on the results of pharmacological treatment cover usually short periods of time. Earlier months than years. A systematic review of the xerostomia pharmacological treatments had been published in Cochrane database by Riley at al. [13].

Amifostine

Two drugs were discussed extensively in this paper. The first is amifostine, a selective-target cytoprotective agent and the second was pilocarpine, and old pro-cholinergic drug. Amifostine was studied in 3520 patients in 39 controlled trials. The authors conclude, that there is some low-quality evidence to suggest that the drug amifostine prevents the feeling of dry mouth in people receiving radiotherapy to the head and neck (with or without chemotherapy) in the short- (end of radiotherapy) to medium-term (three months after completion of radiotherapy). However, it is less clear whether or not this effect is sustained to 12 months after radiotherapy. The benefits of amifostine should be weighed against its high costs and frequent adverse effects. Nausea, vomiting, low blood pressure, and allergic response were all more frequent in those receiving amifostine than placebo. There was insufficient evidence to show that any other treatment is beneficial.

Pro-cholinergic drugs

Pilocarpine is an old and cheap pro-cholinergic drug used in ophthalmology and it can be used for xerostomia orally as a capsules [14] or topically as drops [7, 15]. However, the controlled trials performed on only 389 patients and reviewed by Riley at al. [13] revealed data of low quality and only a minor effect, accompanied by some unpleasant adverse effects like runny nose, increased lacrimation and sweating as well as nausea and vomiting.

A study performed at the University of Sao Paulo (Brazil) [16] showed that bethanechol (another old pro-cholinergic drug, similar to pilocarpine) used to treat post-radiotherapy salivary gland dysfunction, improved xerostomia symptoms, and induces some changes in saliva composition. In this study 45 post-radiotherapy patients complaining of xerostomia used 50 mg/day of betanechol for 3 months, and the salivary parameters were evaluated before, and at 1, 2 and 3 months of therapy. Biochemical analysis included buffering capacity of saliva; pH; total salivary protein concentration; amylase and catalase concentrations; catalase and peroxidase activity. Patients showed improvement in xerostomia experienced prior and after 1, 2 and 3 months of therapy. The percentage of severe xerostomia decreased to 80.5%, 75.7% to 70% of the pretreatment values respectively. Inversely, the frequency of mild xerostomia increased from 19.5% (background value), to 24.3% after 1 month and to 30% after 3 months. This despite no changes in stimulated and unstimulated salivary flows. In addition, some changes were observed in chemical composition of saliva. In stimulated whole saliva, total protein increased significantly after one month ($p < 0.0001$) but decreased later on in the study. At the end, after 3 months the total protein values were similar to the background values ($p = 0.51$). In unstimulated whole saliva collection, there was a decrease in peroxidase

activity by comparing the background values with those after 1 month ($p = 0.026$), 2 months ($p = 0.007$) and 3 months treatment ($p = 0.018$). For stimulated whole saliva collections there was also a decrease in this peroxidase activity comparing to the background values. In unstimulated whole saliva there was no significant change of catalase activity during the study ($p < 0.05$). However, in stimulated whole saliva, catalase was increased after 2 ($p < 0.0001$) and 3 months ($p = 0.003$). Amylase activity in unstimulated whole saliva collection was increased after 1 ($p = 0.002$), 2 ($p < 0.0001$) and 3 months ($p = 0.029$). In conclusion, betanechol appeared in this study to reduce the severity of xerostomia despite lack of increase of the salivary flow rates. It is thus possible that qualitative changes in salivary biochemistry were responsible for the observed effects.

Vitamins C and E

Vitamins C and E (alone or in combination) were used in prevention and treatment of xerostomia for a longer time. However, these drugs were never trustworthy tested in a clinical trial. A prospective, double-blind, randomized study with the vitamins C and E [17] was studied in South Korea in 45 patients before radiotherapy due to head and neck cancers. The patients were randomized in two groups. The intervention group ($n = 25$) received 100 IU of vitamin E and 500 mg of vitamin C (in one capsule), administered twice daily. The control group ($n = 20$) received identical capsule with placebo, also twice daily. Both groups started treatment one week before and continued it for one month after completion of radiotherapy. Patients were assessed with a Patient-reported xerostomia questionnaire, patient-reported xerostomia score and salivary scintigraphy. The intervention group showed greater improvements in xerostomia questionnaire and scores at 6 months post-radiotherapy when compared with those at one month post-radiotherapy ($p = 0.007$ and 0.008, respectively). In contrast, the control group showed no changes between 1- and 6-months post-radiotherapy. By salivary scintigraphy, there was no difference in maximal accumulation or ejection fraction between the two groups. At the final follow-up, there was no difference in overall survival and disease-free survival between the two groups. So, it is probable that vitamins C and E may protect patients from post radiotherapy xerostomia. More studies should be done in the future. The vitamins were not studied separately so we do not know which (if not both) vitamins are responsible for the observed effect.

Alternative treatments

Low level laser therapy

An exciting, but not yet fully proven in clinical trials method is illumination with a low-level laser therapy (LLLT). LLLT is a cheap method used for photo-bio-modulation of tissue in many medical specialties, including pain control [18]. In the study performed in Sao Paulo (Brazil) [19] on 29 patients with post-radiation hyposalivation and dry mouth a continuous wave indium-gallium-aluminum-phosphorus diode laser device was used punctually on the major salivary glands (808 nm, 0.75 W/cm^2, 30 mW, illuminated area 0.04 cm^2, 7.5 J/cm^2, 10 s, 0.3 J). Six extraoral points were illuminated on each parotid gland and three on each submandibular gland, as well as two intraoral points on each sublingual gland. Each patient received two sessions in a week for three months. Stimulated and unstimulated salivary flow rate, salivary pH, and quality of life questionnaire were assessed at baseline and at the end of the treatment. There were significant increases in both mean salivary flow rates (unstimulated; $p = 0.0012$; stimulated; $p < 0.0001$), mean pH values (unstimulated; $p = 0.0002$ and stimulated; $p = 0.0004$), and mean score from the quality-of-life questionnaire ($p < 0.0001$). Low-level laser therapy seems to be effective to mitigate salivary hypofunction and decrease of xerostomia. One should remember, that this was not a controlled study and the study lasted only for three months. There are no data on long term effects after discontinuation of photo-bio-modulation.

In this view it is important to mention the older but uncontrolled study by Loncar et al. [20] who showed on 16 patients that photo-bio-modulation with LLLT was not only stimulating salivation but also positively influenced regeneration of the salivary glands. However, more recently, a well-designed placebo controlled clinical trial did not show any effect on salivary glands in Sjögren syndrome [21]. In another uncontrolled study, exposure to photo-bio-modulation during radiotherapy period probably limited hyposalivation [22]. So, it is possible, but not proven, that regeneration of the salivary gland may be different in Sjögren syndrome and in post-radiation xerostomia.

One should also reflect on the issue that until recently the LLLT was never used in oncology as the LLLT was feared to stimulate the remaining tumor cells to grow and metastasize. The data about this issue are still preliminary and controversial [23, 24]. On the other hand, illumination with LLLT is performed on the salivary glands that did not contain any tumor. Taking all of this into account further studies and well controlled studies are needed, but this method has its potential.

Hyperbaric oxygen

Another alternative method is the use of hyperbaric oxygen therapy. Lovelace et al. [25] in a metanalysis of the literature on this subject found that hyperbaric oxygen improves subjective experience of xerostomia. After this, number of clinical trials were performed and a systematic review confirmed the long-term effects on xerostomia [26]. Interesting is that with this method the need of tooth extraction due to hyposalivation and caries was reduced [27]. The limitation of this methods is that number of hyperbaric chambers, used in diving medicine, is limited, and many countries do not have these facilities at all.

Thyme honey

Thyme honey was used in a traditional medicine for many ailments. Among others: wound healing and xerostomia. A single center, randomized clinical trial was performed with thyme honey on inpatients with head and neck cancers subjected to radiotherapy [28]. It was anticipated that the presence of honey in the oral cavity before and after radiotherapy can have a sialagogue effect by stimulating the salivary glands to produce more saliva and can prevent xerostomia. Seventy-two patients with head and neck cancer receiving radiotherapy or/and chemotherapy or/and surgery were recruited in a specialized cancer center. Patients were randomized prior to the oncological therapy to either thyme honey or saline groups. Patients had oral rinses (20 mL of thyme honey diluted in 100 mL of purified water) just before the radiotherapy session, immediately after the radiotherapy session and 6 hours after the session. The control group received rinses with saline according to the same protocol. The study was evaluated after 1 and 6 months. Analysis of results revealed the statistically significant effect of the thyme honey on xerostomia ($p < 0.001$) and overall quality of life ($p < 0.001$) in comparison to placebo. Thyme honey was safe in use and was effective in the treatment of not only xerostomia but also dysphagia, intractable pain, postradiotherapy changes in the taste and significantly improved the quality of life. This is a single trial and more trials should be done before these methods, although very interesting, can be presented to the great public. In the above study blinding was not ideal as saline tastes different from honey. This could have influence on the final results. Also, unintended beneficiary effect on so many other symptoms should always be treated with suspicion.

Acupuncture

In the past it was claimed that acupuncture is able to mitigate post-radiotherapy xerostomia in head and neck cancer patients. Ni et al. [29] performed a systematic review of acupuncture in the treatment of xerostomia in cancer patients. Eight clinical trials (725 participants) were analyzed, and 3 were included in the meta-analysis. All included trials had a high risk of bias,

such as selection, performance, and detection bias. Analysis indicated favorable effects of Acupuncture regarding the improvement of xerostomia symptoms (MD −3.05, p = 0.02, 95% CI −5.58 to −0.52), compared with sham acupuncture. However, there were no differences between acupuncture and sham acupuncture regarding the stimulated salivary flow rate (MD 0.37, p = 0.08, 95% CI −0.05 to 0.79) and unstimulated salivary flow rate (MD 0.09, p = 0.12, 95% CI −0.02 to 0.21), which were whole salivary flow rate compared with no acupuncture (standard oral care, usual care, or no treatment). Acupuncture produced a significant improvement in patient-reported xerostomia, without causing serious adverse effects. Authors concluded that overall quality of analyzed data was low. In conclusion; acupuncture is probably effective against xerostomia, but its effect could be caused not by acupuncture itself but by placebo effect. Acupuncture cannot yet be recommended for radiation-induced xerostomia in cancer patients until more solid evidence is produced.

Transcutaneous electrical nerve stimulation

Salimi et al. [30] performed a systematic review on the studies investigating effects of transcutaneous electrical nerve stimulation (TENS) in xerostomia experienced by patients with head and neck cancer. Five studies (928 patients) were included in the systematic review. Most of the studies presented in this review suggest that there is a benefit in producing saliva by stimulating the salivary glands with TENS. However, all the studies with TENS used different protocols and this is why the results are impossible to compare.

New non-pharmacological methods in development

Mesenchymal Stem Cell therapy

Mesenchymal stem cell (MSC) therapy has shown promising results in pre-clinical studies. It was hypothesized that MSCs could have a paracrine, angiogenic and antiapoptotic effect on the salivary glands [31]. In a single-center, phase I/II, randomized, first in humans, placebo-controlled, double-blinded clinical trial using MSCs or placebo injected directly into the submandibular salivary glands [32]. The primary end point was the unstimulated salivary flow rate. Secondary end points were subjective patients reports, safety and efficacy measures. The effects were evaluated at the baseline and 1 and 4 months after the MSC or saline injection. The results of this feasibility phase 1 study were promising and will be used to design further trials. Similar promising results were obtained with effective mononuclear cells [E-MNC]

[33]. E-MNC could influence regeneration of the atrophic cells probably better than the MSC. The results should be further validated in the phase II and III trials.

Gene transfer therapy

Salivary gland gene-transfer into the salivary glands is safe and can be beneficial in humans. Applications to treat and prevent radiation damage show considerable promise. A first-in-human clinical trial was recently successfully completed [34]. The results are promising as a proof-of-the concept, but we need to wait until controlled studies will be published.

Discussion

Feeling of dry mouth or xerostomia is one of the most annoying, common complication of radiotherapy due to head and neck cancers [1–4]. It influences significantly patients' quality of life and it may last life-long. It may induce caries and result in compulsory tooth extraction and oral/gingival infections. Because treatment of established xerostomia is often unsatisfactory or incomplete and the condition lasts sometimes life-long it important to address in the clinical trials problem of prevention. Such trials are now slowly coming up and some are promising. Potential of xerostomia prevention was observed in the trial with C and E vitamins [17] and thyme honey trials [28]. But these findings need confirmation. Also, there are only few trials which address regeneration of the salivary glands. Potential for regeneration was suggested in the LLLT trial [20]. However, this finding could not be confirmed for the patients with xerostomia due to Sjögren syndrome [21]. It is possible that regeneration differs in these two conditions. Although tempting, extrapolation from Sjögren syndrome to post-radiotherapy xerostomia is risky and should not be accepted without caution. Regeneration, or at least maintenance of the improved glandular function after discontinuation of treatment has been evidenced for hyperbaric oxygen only [25, 26]. In contrast many studies reviewed in this paper lasted only for a relatively short time and there is paucity of data on xerostomia after discontinuation of therapy.

Traditionally xerostomia is treated with artificial saliva or other topical preparations which needs to be applied many times a day. But the effects of these topical preparations are often disappointing. Recently, different new and improved preparations were introduced on the market and there is a considerable progress in this field. Many preparations available on the market, sometimes without prescription, were never clinically tested. The patients are often overwhelmed by this and making a rational choice can be challenging. Some of the Artificial

saliva preparations are combined with pilocarpine topically, while its account is still controversial [13]. In case of the salivary glands rest function is available stimulating measures can be tried. Here are the pro-cholinergic drugs like pilocarpine, or betanechol applied systemically, the standard. However, efficacy of these methods is limited, and new drugs and new methods are needed. Amifostine was the most promising new stimulating and cytoprotective drug which was expected to replace pilocarpine, but its effects are only moderate and are accompanied by frequent adverse effects [13].

Among the alternative methods of stimulation, the hyperbaric oxygen looks most promising. [26, 27]. Its lasting effect is confirmed beyond any doubt. However, the drawback of this method is poor availability of hyperbaric oxygen chambers in countries without access to the sea. Many new clinical trials should be performed, also with emerging alternative treatments. Clinicians, however, have even now a wide choice of methods available to choose from. From the new, but not yet sufficiently investigated, and hence poorly available methods, are mesenchymal cells therapy as well as gene-transfer therapy [31–33]. If the preliminary results will be conformed, these methods may be the future of therapy of post-radiation xerostomia.

Table 1. Treatment of xerostomia

Method of treatment, how it works?	**Appearance**	**How often and how should be applied?**	**Availability**	**Is the action proven?**
Formulations of artificial saliva Topical, lubricating [6–11]	Liquids, drops, sprays, gels, mouthwash, chewing gum, toothpaste	Treatment is non-toxic so the formulations may be applied many times a day	Very good	Not always, there are many formulations and only few were tested clinically. Clinical trials were probably sponsored by the pharmaceutical industry
Amifostine [13] This is a well know cytoprotective drug. It generates tissue thiols. It is used during chemo- and radiotherapy	Ampoules for parenteral use	Intravenous injection 200 mg/m^2 prior to radiotherapy	It is available in the hospitals. it is quite expensive	In many controlled clinical trials, the activity against xerostomia is only moderate and the adverse effects are frequent. It does not work against established post-radiation xerostomia
Pilocarpine [7, 8, 14, 15]	Tablets [14],	Usually 3 × 5 mg	Tablets and	In the controlled studies the

It is an old pro-cholinergic drug stimulating salivary production. It works only when the salivary glands are intact (not after surgery). Tablets act systemically while drops act topically with less adverse effects	drops [7, 8, 13, 15]	With higher doses frequent adverse effects as nausea and vomiting, increased sweating and increased lacrimation. Increased production of gastric acid [13]	capsules are not easily accessible in the pharmacies. Drops are used by ophthalmologists and are available in every pharmacy	stimulation of the salivary glands is minimal and adverse effects are common [13]
Betanechol A pro-cholinergic drug [16]	Tablets [16]	50 mg a day [16]	Fewer adverse effects in comparison to pilocarpine [16]	In controlled studies it has similar effects as pilocarpine but less adverse effects [16]
Vitamin C and E [17]	Capsules	Vitamin C 500 mg and vitamin E 11 IU, twice daily [17]	Cheap. Easily accessible in every pharmacy	This was a single trial on a limited number of patients. The results should be repeated and confirmed.[17]
Photo–bio–modulation by the low–level laser therapy [19–21]. It works probably by bio–stimulation and regeneration of the salivary glands	Exposition to the laser light beam	Therapies in the office. Usually 20–30 minutes. Couple times a week. Different protocols. The treatment is not toxic unless excess advised doses	Availability is limited. LLLT is used in physiotherapy, sports and pain medicine	The results of clinical trials are scarce and are not consistent as every author uses different equipment and doses. Stimulation of regeneration of the salivary glands is not yet proven [20, 21]
Hyperbaric oxygen [25, 26] Stimulates regeneration of	Oxygen applied under high pressure in a hyperbaric tank. The	Up to 5 times a week. [27]. This method is not suitable for claustro-phobic patients. The	Availability is limited to large cities. Some countries do	Clinical trials revealed a consistent positive and long-lasting results [25, 26, 27]

the salivary glands	session lasts 20–30 minutes	treatment is not toxic	not have even one chamber	
Thyme honey [28] The mechanism of action is unknown	Honey dissolved in water	Couple of times a day. Its working is limited to prevention of xerostomia [28]	Cheap, easily available in specialized shops	Positive preventive effect was seen in a single centre trial (not well blinded) with a limited number of patients [28]. Authors reported positive effect also on intractable pain. The trial should be repeated with a better design
Acupuncture [29] It Is not clear how it works	Needle insertion	Twice weekly sessions	Cheap, available	Difficult to differentiate what is the effect of placebo and what is the effect of true acupuncture. The results of a systematic review shows that most trials used different protocols [29]
Mesenchymal stem cells [31, 32, 33]. The cells are able to stimulate regeneration of the salivary glands	The cells are injected directly into the gland	Once in the operation theatre	Experimental. Availability is limited to research centres. Single centres in Europe	The working, although promising, is not yet proven in clinical trials
Gene transfer therapy [34]	The genes are injected into the salivary gland	Once in the operation theatre	Experimental	The results are promising but until now we have only a proof-of-the concept trial [34]

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

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