Effects of radiotherapy on parotid salivary sialochemistry in head and neck cancer patients

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Abstract

Aim To determine the effects of high dose irradiation on parotid salivary sodium and pH concentration at subsequent duration of 1.5, 3 and 6 months following radiotherapy.

Materials and methods Eighty parotid glands of head and neck cancer patients were irradiated with mean dose of 66 Gy. The stimulated parotid flow (PF) was collected by a cannulation of Stenson's duct followed by analysis of sodium (PF sodium) by Easylyte Sodium/Potassium auto analyzer and pH by litmus narrow band pH paper.

Results A steep elevation of PF sodium was found in post-RT period after 1.5 months of starting RT followed by gradual increase up to 6 months and pH changed towards acidity.

Conclusions A high dose of 66 Gy causes irreversible damage to parotid salivary duct system.

Keywords Radiotherapy · Head and neck cancer · Parotid gland · Sodium

Introduction

The research on every aspect of cancer has always been a challenge to the medical field. Cancer is still one of the major killers of human being. No part of the human body is immune to cancer. The incidence of head and neck cancers is rather higher (5%) in comparison to involvement of other part of body. In India, the most common head and neck cancer are those of the oral cavity and pharynx. The age adjusted incidence for these sites, in the Indian males range from 10.8 to 38.8 per 100,000 males; and for the females it is 6.4 to 14.9 per 100,000 females [1]. Head and neck cancers are more significant to our country because of peculiar habits in population. Together with surgery or alone radiotherapy is the main treatment for malignant tumors in the head and neck region. In patients with head and neck cancer, radiation treatment also involves the tissues of the oral cavity and the major and minor salivary glands, either because of the site and extension of the primary tumor or due to the path of lymphatic spread. Exposing the salivary glands to radiation often results in salivary gland hypofunction and changes in saliva composition, leading to a number of acute and long-term complications. Besides the quantity of saliva, radiotherapy also results in a change of salivary composition. Saliva turns into very viscous, white, yellow or brown fluid. The obvious qualitative salivary changes are a reduced pH and buffering capacity, altered salivary electrolyte levels, and changed non-immune and immune antibacterial systems [2, 3]. Their compromise is intrinsically related to changes in the oral flora of irradiated patients and predisposes to dental caries [4–7].

Materials and methods

The prospective study including 40 patients (36 men and 4 women) was conducted on the histopathologically confirmed advanced head neck cancer admitted in the wards of the department of otorhinolaryngology and head neck surgery, S.R.N. Hospital, M.L.N. Medical College and

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K.N.M. Hospital, Allahabad. All patients were treated with radiotherapy alone or in combination with chemotherapy. The mean age was 54.12 years (range: 35–75 years). Most of the patients suffering from head and neck cancer by fifth decade (50%) followed by forth decade (24%) and sixth decade (12%) of life. Inclusion criteria consisted of the following: i) histopathologically confirmed patients of cancer of the head neck regions; ii) treatment planning with curative intent that included radiation therapy with two opposing lateral fields that encompassed all major salivary glands; and iii) patients who did turn up for postirradiation evaluation of parotid flow (PF) rate and sialochemical changes within 1.5, 3 and 6 months of completion of radiotherapy. Exclusion criteria consisted of - i) previous cancer treatment in the head and neck area; ii) histological findings other than squamous cell carcinoma; and iii) history of drug intake or any pathosis affecting salivary gland function.

In all the patients, bilateral parotid gland saliva samples were collected in pre-RT period and at 1.5, 3 and 6 months after the end of radiotherapy. The patient was instructed not to drink, eat, smoke and take any medicine at least 90 minutes before the collection of saliva. After that both parotid gland Stenson's duct was cannulated with silicon catheter with an inside diameter of 0.38 mm. Parotid flow rate was stimulated by 5% citric acid on the dorsolateral surfaces of the tongue at 30 seconds interval for 5 minutes during which gustatory stimulus was maintained. Two drops of 5% citric acid was placed on dorsum of patient's tongue at interval of every 30 seconds for 5 minutes. Parotid saliva was collected in a sterile calibrated test tube for 5 minutes (Fig. 1).

Fig. 1 Collection of parotid saliva in a sterile calibrated test tube

After the collection saliva sample was immediately send for sodium and pH measurement. Sodium was measured by Easylyte Sodium/Potassium analyzer and pH was measured by litmus narrow band pH paper.

Statistical analysis

Parotid salivary sodium and pH were recorded as individual absolute mean value, standard deviation and ranges were calculated for entire control, pre-RT and post-RT patients. The difference among groups was analyzed by using Student t-test. P values of ≤ 0.05 were considered statistically significant.

Results

The study included the analysis of 80 parotid glands in pre-RT period, 56 at 6 weeks, 46 at 3 months and 18 at 6 months after the commencement of radiation course. Among the 50 patients, 42% were suffering from laryngeal carcinoma, 32% from oropharyngeal carcinoma, 14% from hypopharyngeal carcinoma and 12% from oral cavity carcinoma. Thirty-six patients with stage III and IV were irradiated comprehensively to both neck sides combined with full course of chemotherapy. Six patients with stage II were given irradiation alone. The median prescribed dose to primary targets was 66 Gy (range 60–72 Gy) at 2 Gy/fraction/day given for 5 days a week with the theratron 780 C complete cobalt 60 teletherapy unit. Saliva became thickened, viscous, curdy and scanty in post-RT period which leads to deterioration of quality-of-life QOL.

Parotid salivary flow sodium PF sodium

The mean stimulated PF sodium concentration in 10 healthy non-irradiated controls (20 parotid glands) and 40 patients (80 parotid glands) of head neck cancer before the commencement of irradiation was almost same ranging from 8 to 26.1 mEq/l. Michels [8] observed that sodium concentration is much higher in stimulated (citric acid) PF as compared to resting PF due to transepithelial transport which is time consuming, hence values are flow-dependent. Sodium concentration is proportional to flow rates from 0.1 to 2.5 ml/min followed by plateau phase. In post-RT period mean stimulated PF sodium concentration of 56 parotid gland was 45.9 mEq/l at 6 weeks, 49.63 mEq/l at 3 months (46 parotid gland) and 50.4 mEq/l at 6 months (18 parotid glands) as listed in Table 1. On comparison, pre-RT results, post-RT group exhibited the strongest increment in mean stimulated PF sodium concentration. The mean PF sodium for all patients increased sharply after irradiation by 3 times at 6 weeks as compared with

Table 1 Comparison of mean PF sodium in pre-RT and post-RT period at different interval

Study groups	No. of parotid glands	Mean stimulated PF sodium mEq/l	Range
Pre-RT	80	15.19 ± 0.909	8–26.1
Post-RT 6 weeks	56	45.9 ± 2.43	26.1–67
Post-RT 3 months	46	49.63 ± 2.08	29.8–67
Post-RT 6 months	18	50.4 ± 3.46	36.1–61.7

Table 2 Comparison of mean PF pH in pre-RT and post-RT periods

Study groups	No. of parotid glands	Mean stimulated PF pH	Range	Statistical significance compared with pre-RT
Pre-RT	80	7.67	6.9–8.8	
Post-RT 6 weeks	56	7.04	6.2–7.7	p = 0.00 t = 11.07
Post-RT 3 months	46	7.01	6.2–8	p = 0.00 t = 9.1
Post-RT 6 months	18	6.8	6.2–7.2	p = 0.00 t = 11.1

mean pre-RT levels. Absence of recovery of PF sodium concentration was supported by correlation analysis, which further reveals a significant difference between pre-RT and post-RT as $p < 0.05$.

Parotid Salivary flow pH (PF pH)

Reduction of pH to acidic levels by irradiation had previously been documented for whole saliva [5]. However, to our knowledge, only few authors [9–11] had studied the late effects of irradiation on pH of saliva collected selectively from parotid glands. Despite our attempts to control factors to alter pH, such as eating, smoking just before collection of saliva, we found wide variation in the pH of parotid saliva. However, the mean stimulated PF pH collected from healthy non-irradiated controls and head neck cancer patients before irradiation was almost same ranging from 6.9 to 8.8. Following irradiation to dose of 60–70 Gy, there was a significant ($p < 0.05$) fall in mean PF pH as compared to pre-irradiation period. Results of PF pH are illustrated in Table 2.

Discussion

Quality-of-life after cancer treatment is becoming more and more of consideration. The present study confirms that

mean high dose of 66 Gy altered the chemical constituents of parotid saliva. Unfortunately, the radiotherapy literature is quite scarce and too confusing to allow to predict the intensity and duration of this complication when particular treatment is recommended [12]. The parotid gland is almost entirely composed of serous cells, whereas the submandibular comprises both the mucinous and serous types [13]. The average daily flow of whole saliva varies between 0.5–1 liter in normal physiological conditions [14]. Secretion of saliva is an active and continuous process.

A two stage model for saliva production is widely accepted [15–17]. First stage: in the acinus, a chloride shift is followed by sodium and water transport across the membranes and cell junctions. Second stage: the primary fluid is rendered hypotonic in the ductules by active sodium and bicarbonate reabsorption. Some water is presumed to follow. In exchange, potassium and some proteins are secreted. This process is assisted by membrane K-Na-ATPase. It is interesting to note that reabsorption processes take time and reach steady-state values at a given flow rate. Within normal functional limits, salivary flow rate and sodium concentration show a good proportional relationship. At high flow rates, the primary secretion will pass through the pars striate too quickly to allow much reabsorption to occur, and hence the sodium concentration will also be high [8].

The most interesting result was the rise of PF sodium concentration inspite of diminished parotid flow rate. This is significant, since normally sodium concentration decreases with the reduction of flow rate [8, 17, 18]. The PF sodium concentration increased sharply after irradiation by 3 times at 6 weeks followed by gradual increase up to 6 months as compared with mean pre-RT levels. Our study had also investigated the effects of radiotherapy on parotid flow rate (PFR) in same patients which shows steep drop in PFR in post-RT period. Mean values of PFR at 6 weeks, 3, 6 and 12 months shows significant relationship with PF sodium concentration (Fig. 2). This confirms that PF sodium concentration increases with decline of PFR in post-RT

▲ Parotid flow sodium concentration, (meq/l)

▲ Parotid flow rate (ml/min)

Fig. 2 Correlation between PFR and PF sodium concentration (Present study, 2006)

period. Spijkervet [19] reported steep elevation of sodium with decline of PFR in post-RT period. This was followed by initial recovery of PFR with decreased PF sodium due to early repair but it never return to pretherapy values. However, in our study there is no recovery of salivary ductal segments due to exposure to very high dose of cobalt 66 Gy. Salivary ducts do not reabsorb electrolytes adequately following radiation as ionizing radiation damages cell membrane permeability to ions, reabsorption ability of the tubuli and chronic periductal inflammation caused by lymphocytes or their products surrounding ductal cell which causes increased sodium concentration [20].

As seen already for pH values, the mean pH in patients with head and neck cancer was indistinguishable from that of healthy subjects. A wide range of buffering capacities was measured, which also occurs in healthy populations [21]. After radiotherapy the mean PF pH changed towards acidity after exposure to mean high radiation dose of 66 Gy. These results were comparable with other studies as there was significant reduction of pH was observed after radiotherapy [9, 10]. The mean value of pH remained at a low level, fluctuating between 7.04 and 6.8 until the end of study (Table 2). A permanent decrease in pH was not unexpected, because it is well known that low salivary secretion rates are accompanied by low buffering capacity [22]. We contributed this to reduction in bicarbonate levels which act as a buffering agent for saliva previously noted in the studies of whole stimulated saliva [3, 9]. Reabsorption of bicarbonate mainly takes place during passage through the intralobular duct. However, low values of bicarbonate were found coupled to small secretion rates, even where sodium concentration is high when exposed to high radiation dose [8]. A fall in salivary pH following irradiation results in an altered microflora that is highly cariogenic and contributes to dental decay [5].

Conclusion

Patients with head and neck cancer display PF sodium and pH values similar to those of healthy subjects. Cancer treatment that include high mean dosage (66 Gy) of conventional radiotherapy to all major salivary glands induce severe xerostomia, strong increment of PF sodium and significant decline of PF pH due to loss of buffering capacity. Saliva become thick, viscous and scanty which causes deterioration of quality-of-life. We found no recovery of salivary ductal segments in post-RT period up to 6 months. Further studies are warranted to determine the long-term effects of radiation on parotid gland function and ways to reduce salivary dysfunction through intensity modulated RT or use of radioprotectors such as amifostine.

References

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