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Longitudinal scintigraphic study of parotid and submandibular gland function after total body irradiation in children and adolescents

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Objective. Total body irradiation (TBI) and cyclophosphamide (CY) during allogeneic stem cell transplantation (ASCT) cause salivary gland dysfunction in children. The aim of this investigation was to study the scintigraphic functional changes over time of the parotid and submandibular glands in children and young adults one year after treatment with CY and TBI at ASCT.

Methods. Salivary gland scintigraphy (SGS) was performed before ASCT, and 3–6 months and 12 months after ASCT. The three male patients who fulfilled the scintigraphic study had a mean age (± SD) of 17.3 ± 9.8 years at ASCT.

Results. The parotid secretion capacity (SPar) was 83.5 ± 3.2% before ASCT and 48.5 ± 25.8% during the next 3–6 months ($P < 0.05$). The SPar did not increase (48.1 ± 12.4%) during the rest of the first year after ASCT. The submandibular emptying capacity (SSub) was 91.3 ± 12.9% before ASCT and 35.4 ± 2.3% after 3–6 months ($P < 0.05$). The SSub was 87.9 ± 17.9% one year after ASCT.

Conclusions. The parotid glands were more sensitive to irradiation since they did not recover lost capacity to secrete saliva, while the submandibular glands recovered the secretion capacity at the one-year follow-up.

Introduction

The success rates of allogeneic stem cell transplantation (ASCT) have continued to improve, and this technique is now incorporated into the therapeutic management of an increasing number of children with haematological malignancies, selected solid tumours, severe aplastic anaemia and some inborn errors of metabolism[1,2]. Stem cell transplant preparative regimens including cyclophosphamide (CY), alone or in combination with Busulphan (BU), or total body irradiation (TBI), as well as graft-versus-host disease (GVHD) are known to induce oral complications[3–7]. Mucositis, oral infections, oral haemorrhage, pain, gingival inflammation and salivary gland dysfunction are common acute effects found in this patient group.

Irradiation is one major reason for salivary gland dysfunction in ASCT-treated patients[3,8]. In a study by Jones *et al.*[9], normal levels of salivary secretion rates returned 2 years after ASCT in adult patients conditioned with chemotherapy and TBI. Among paediatric ASCT recipients conditioned with 10 Gy single-dose TBI in combination with chemotherapy, a permanent dysfunction of the salivary glands is seen[10]. For this group of patients, a lifelong oral preventive care programme is necessary to avoid the development of oral complications.

To evaluate the degree of salivary dysfunction, 99 m-technetium pertechnetate (99mTc) salivary gland scintigraphy (SGS) has been used in patients with radiation-induced salivary gland dysfunction[11,12] and Sjögren's syndrome[13,14]. It is a well-documented method, and allows an objective, non-invasive, simultaneous and continuous functional study of

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the major salivary glands[15,16]. The authors have previously shown that the function of the major salivary glands of long-term surviving patients treated with ASCT before the age of 13 years is diminished, as shown by a reduced trapping rate and reduced emptying capacity of the salivary glands[17].

The aim of this investigation was to study longitudinal functional changes in the parotid and submandibular glands, respectively, in children and young adults during the first year after treatment with 10 Gy single-dose TBI and ASCT using 99mTc salivary gland scintigraphy.

Subjects and methods

Eight patients (seven males and one female) were examined using salivary gland scintigraphy prior to ASCT. They were all conditioned with 10 Gy single-dose TBI and CY (120 mg kg^{-1}). Three patients were not available for follow-up, two of whom (one male and one female) declined to participate in further scintigraphic examinations, and one patient died before the 3-month follow-up. Two of the remaining five patients died before the end of the study. Thus, scintigraphic data are available from three male participants. The characteristics of the patients are shown in Table 1. All participants and parents gave their informed consent. Approval was obtained from the ethical committee of Huddinge University Hospital, Huddinge, Sweden.

The methods for measurements of unstimulated (USSRs) and stimulated salivary secretion rates (SSSRs) have previously been presented[17]. A USSR below 0.1 mL min^{-1} or SSSR below 0.5 mL min^{-1} was considered to indicate salivary dysfunction.

Scintigraphy was performed using a gamma camera and the radioactive isotope 99mTc was used. Forty-five min after the injection of 99mTc, one millilitre of 5% citric acid was applied to the patient's tongue to accelerate excretion. Collection of the digitized data began immediately upon injection and was continued at 30-s intervals for 60 min[13,18]. The variables used from the time-activity curves are shown in Fig. 1.

Statistical analysis

The Wilcoxon signed-rank test was used to compare the salivary secretion rates and scintigraphic values from the different examinations.

Results

The salivary secretion rates for the individual patients are shown in Table 2. The mean USSR and SSSR at baseline ($n = 8$) were

Table 1. Patient characteristics, diagnoses, conditioning treatment, graft-versus-host (GVH) prophylaxis and time of scintigraphic examination.

Patient number	Age at ASCT (years)	Sex	Diagnosis	Conditioning	GVH prophylaxis	Time from ASCT at scintigraphic examination (+) (months)		
						0	3	12
1	8.0	M	Lymphoma	CY, TBI, ATG	MTX, CsA	+	+*	+
2	16.3	M	AML	CY, TBI	MTX, low-dose CsA	+	+	+
3	27.6	M	Lymphoma	CY, TBI, ATG	MTX, CsA	+	+	+
4	12.3	F	ALL	CY, TBI, OKT3	MTX, CsA	+	+	–†
5	11.7	M	CML	CY, TBI, ATG	MTX, CsA	+	+	–†
6	7.8	M	ALL	CY, TBI, VP16	MTX, low-dose CsA	+	–‡	–‡
7	10.6	M	ALL	CY, TBI, ATG	MTX, CsA	+	–‡	–‡
8	8.2	M	SAA	CY, TBI, OKT	MTX, CsA	+	–†	–†

(ASCT) allogeneic stem cell transplantation; (M) male; (F) female; (AML) acute myeloid leukaemia; (ALL) acute lymphoblastic leukaemia; (CML) chronic myeloid leukaemia; (SAA) severe aplastic anaemia; (CY) cyclophosphamide; (TBI) 10-Gy total body irradiation; (ATG) antithymocyte globulin; (OKT3) orthoclone; (VP16) etoposide; (OKT) octreotide; (MTX) methotrexate; and (CsA) cyclosporine A. *Examined after 6 months. †Deceased. ‡Did not accept scintigraphy.

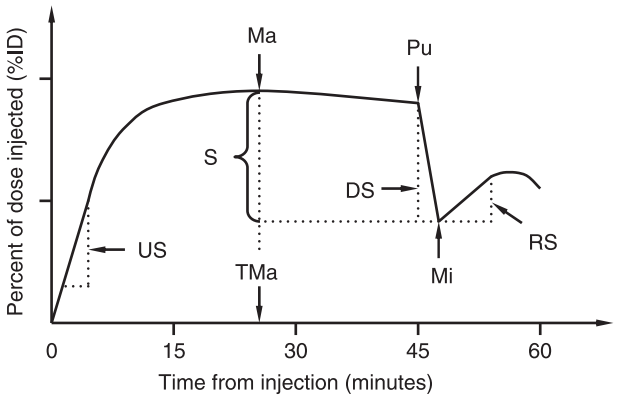

Fig. 1. All variables in the time-activity curve (TAC) were calculated using a computer. Maximum uptake (Ma) was defined as the highest uptake value in the TAC. Prestimulated uptake (Pu) was measured as the uptake value immediately before stimulation and minimum uptake (Mi) as the lowest uptake value after stimulation. The up-slope (US) represents the direction coefficient (DC) between 1.5 and 3.5 min after injection of the isotope. The stimulated down-slope (DS) was defined as the DC between the application of citric acid (Pu) and Mi. The reaccumulation-slope (RS) was defined as the DC between Mi and the level reached 6.5 min later. The stimulated secretion capacity (S) was calculated as $S = (1 - Mi/Ma) \times 100\%$[15]. The time to Ma (TMa) was measured from injection of the isotope until Ma was reached. All values are presented as the per cent of the total dose injected (%ID). [Reproduced with permission; *DentomaxillofacRadiol* 2000; **29**: 264–271]

Table 2. Unstimulated (USSRs) and stimulated salivary secretion rates (SSSRs).

	Time after TBI/ASCT (months)					
	USSR (mL min^{-1})			SSSR (mL min^{-1})		
Patient number	0	3	12	0	3	12
1	0.53	0.00*	0.07	1.50	0.00*	0.10
2	0.17	0.00	0.11	1.72	0.15	0.38
3	0.93	0.20	0.17	3.20	0.40	1.50
4	0.25	0.03	–‡	0.92	0.28	–‡
5	0.50	0.01	–‡	1.10	0.03	–‡
6	0.50	0.15†	0.33†	1.20	0.50†	1.10†
7	0.70	0.30†	0.15†	2.10	0.40†	0.44†
8	0.30	–‡	–‡	3.00	–‡	–‡

(TBI) total body irradiation; and (ASCT) allogeneic stem cell transplantation. *Examined 6 months after ASCT. †Did not accept scintigraphy. ‡Deceased.

0.48 ± 0.25 and 1.84 ± 0.54 mL min^{-1}, respectively. None of the eight patients participating at the start of the study had salivary gland dysfunction before ASCT.

For the three patients completing the study, the mean USSR decreased from 0.54 ± 0.38 mL min^{-1} before ASCT to 0.07 ± 0.12 mL min^{-1} 3–6 months later. A recovery of USSR to 0.12 ± 0.05 mL min^{-1} was seen one year after ASCT. The mean SSSR decreased from 2.14 ± 0.92 mL min^{-1} before ASCT to 0.18 ± 0.20 mL min^{-1} 3–6 months later, and one year after BMT, the mean SSSR was still only 0.66 ± 0.74 mL min^{-1} ($n = 3$).

After 3–6 months, 43% (three of seven subjects) had abnormally low USSRs and 86% (six of seven) had abnormally low SSSRs. At the 12-month follow-up, 20% (one of five) had an abnormally low USSR and 60% (three of five) had abnormally low SSSRs (Table 2).

Table 3 shows the mean values of the measured variables from the time-activity curves of the parotid and submandibular glands, respectively, in the three patients who completed the study. During the first 3–6 months of follow-up, these variables showed significant changes: the up-slope (US) for the parotid glands decreased; the time to maximum uptake (TMa) for the parotid glands was delayed; the secretion capacity for both the parotid and submandibular glands decreased; the minimal uptake level (Mi) in submandibular glands increased; and the maximal uptake level in submandibular glands increased.

Figure 2 shows the secretion capacity during the study period in the parotid (SPar) and submandibular glands (SSub), respectively, in the three patients who completed the study. The SPar was $83.5 \pm 3.2\%$ before ASCT and $48.5 \pm 25.8\%$ over the next 3–6 months ($P < 0.05$), and the SPar did not recover ($48.1 \pm 12.4\%$) during the rest of the first year after ASCT. On the other hand, the SSub was $91.3 \pm 12.9\%$ before ASCT and $35.4 \pm 2.3\%$ after 3–6 months ($P < 0.05$), but recovered to $87.9 \pm 17.9\%$ one year after ASCT. During the period from 3 to 6 months after ASCT until the end of the study at 12 months, there was a better recovery for the submandibular glands (98%) compared to the parotid glands (0%).

There was also an indication of large inter-individual differences with regard to secretion capacity 3–6 months after TBI since the secretion capacity in the parotid glands (SPar) varied between 24% and 75%.

Table 3. Mean values and standard deviations of scintigraphic variables from the time-activity curves of the parotid and submandibular glands in the three patients who participated until the one-year follow-up.

Variable	Time point		
	Before ASCT	3–6 months after ASCT	One year after ASCT
Parotid glands			
Up-slope (%ID/s × 10^{-3})	2.69 ± 1.17	2.38 ± 0.47*	2.58 ± 1.13
Down-slope (%ID/s × 10^{-3})	–6.05 ± 2.46	–6.41 ± 7.95	–5.47 ± 1.36
Reaccumulation-slope (%ID/s × 10^{-3})	0.63 ± 0.40	0.48 ± 0.01	0.82 ± 0.23
Time to maximum uptake (min)	33.0 ± 13.0	49.2 ± 8.6*	34.5 ± 12.1
Maximum uptake (%ID)	1.44 ± 0.37	2.90 ± 1.54	2.00 ± 0.30
Minimum uptake (%ID)	0.25 ± 0.10	1.58 ± 1.49	0.87 ± 0.54
Secretion capacity (%)	83.5 ± 3.2	48.5 ± 25.8*	48.1 ± 12.4*
Submandibular glands			
Up-slope (%ID/s × 10^{-3})	1.25 ± 0.66	0.81 ± 0.32	2.46 ± 3.10
Down-slope (%ID/s × 10^{-3})	–3.02 ± 0.85	–2.80 ± 2.46	–2.87 ± 2.50
Reaccumulation-slope (%ID/s × 10^{-3})	0.25 ± 0.12	0.60 ± 0.76	0.82 ± 0.23
Time to maximum uptake (min)	31.5 ± 21.2	40.3 ± 2.8	9.2 ± 4.2
Maximum uptake (%ID)	0.81 ± 0.27	2.00 ± 2.02*	1.03 ± 0.86
Minimum uptake (%ID)	0.08 ± 0.10	1.33 ± 1.38*	0.20 ± 0.31
Secretion capacity (%)	91.3 ± 12.9	35.4 ± 2.3*	87.9 ± 17.9

(TBI) total body irradiation; (ASCT) allogeneic stem cell transplantation; and (%ID) percentage of total dose injected. *Significant difference from before TBI/ASCT ($P < 0.05$).

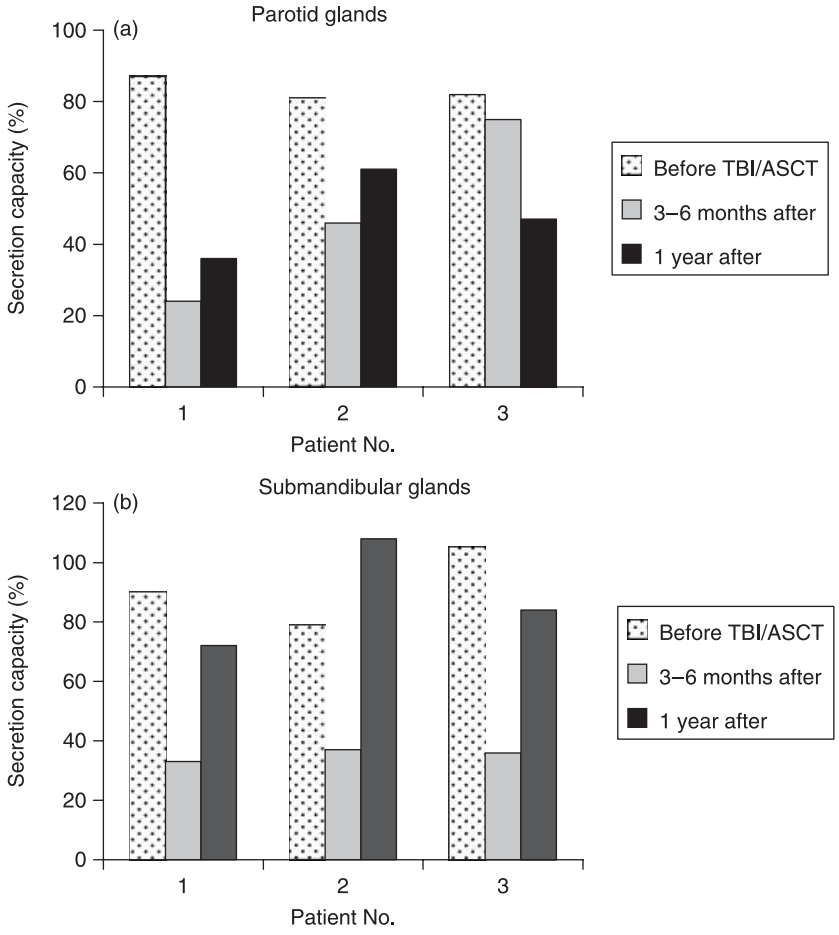

Fig. 2. Secretion capacity (S) in the (a) parotid (SPar) and (b) submandibular glands (SSub) in the three patients who fulfilled the study. The definition of S is given in Fig. 1.

Because of the limited number of patients, it was not possible to find any significant ($P < 0.05$) correlations between values of salivary secretion rates and scintigraphic variables in the three patients who completed the study.

Discussion

The role saliva plays in well-being and quality of life is obvious in patients with salivary gland dysfunction. Oral complaints and dry mouth are sometimes described as the most debilitating symptoms in some patient groups. Salivary gland dysfunction may lead to taste alterations, difficulties in eating and swallowing, and problems with oral hygiene and speech. Ulceration and sometimes burning sensations of the oral mucosa as a result of dry mouth may lead to avoidance of particular foods, increasing the risk for malnutrition. Bacterial and fungal infections in the oral mucosa are easily established, and the defence against dental caries is reduced in a mouth with salivary gland dysfunction[19]. Patients with subjective xerostomia sometimes try to relieve their symptoms by frequent intakes of fluids or candies, which will, in turn, increase the risk of dental caries if these products contain carbohydrates.

Different strategies have been suggested to minimize damage to the salivary glands during TBI. Some have suggested injection of the cytoprotectant drug amifostine prior to radiation treatment[20]. Others have proposed stimulation of the glands using the parasympatomimetic drug pilocarpine before and after irradiation[21]. Another strategy has been to inhibit salivary secretion with the parasympatiolytic drug biperiden during irradiation and stimulate with pilocarpine after radiotherapy[22].

In cases in which salivary dysfunction can not be eliminated, treatment is usually multifactorial. Treatment of salivary gland dysfunction should primarily be stimulation through tastants and/or chewing. Frequent intake of water is essential and lip balm can help to relieve some symptoms of dry mouth. Saliva substitutes could be considered if salivary secretion cannot be stimulated, but individual preferences must be taken to consideration to find the most appropriate substitute for each individual patient[23]. Oral pilocarpine and other drugs, as well as acupuncture[24], have been used to improve salivation after irradiation.

Only three of the eight initial participants completed the study. Two patients did not want to continue after the initial scintigraphic examination. These two patients showed higher USSRs and SSSRs after 3–6 and 12 months in comparison to the others. During the scintigraphic examination, the patient is examined under a gamma camera in a fixed position during 60 min. The procedure itself may have contributed to these individuals' decision to not participate in the repeated scintigraphic examinations of the salivary glands. According to ethical protocols, a patient participating in a scientific study is not asked for the reason why she or he does not want to continue. The patients who did not continue the present study might have found the procedure uncomfortable or time-consuming. Their general health status or general level of anxiety, or simply not being in the mood for continued study participation may also have influenced the patients' decision not to participate further. At present, there is no other non-invasive method available for the study of the physiological function of the salivary glands. Girls have generally lower salivary secretion rates[25].

The authors have previously shown that significantly more girls than boys have salivary dysfunction one year after ASCT and TBI[8]. In this study, the results are based on three boys completing the study. Total body irradiation is known to cause severe salivary dysfunction after ASCT[8]. Children are particularly at risk of a permanent reduction in salivary flow after 10 Gy single-dose TBI[10]. The three children who completed this study showed similar changes. Two patients had no measurable unstimulated salivary output 3–6 months after ASCT. Both unstimulated and stimulated salivary output increased during the following 6–9 months. This is in agreement with the authors' previous findings[10].

The authors have previously found a decreased secretion capacity in long-term follow-up of children treated with 10 Gy single-dose TBI at ASCT, with a decreased capacity to empty the glands after stimulation, possibly

caused by inflammation and accumulation of fibrotic tissue[17]. The initial decrease of the function of the salivary glands seen a few months after irradiation injury[10] is caused by the acute inflammation.

The submandibular glands showed a trend during the last months of the study – from the 3–6 month examination to the one-year examination – towards a better recovery of capacity to secrete saliva compared to the parotid glands. There have been contradictory reports regarding the sensitivity of human parotid and submandibular glands to irradiation. Some have found that the parotid glands are as equally sensitive to irradiation as the submandibular glands[26,27], while the results from the authors' scintigraphic study correspond with the results described by Liem *et al*.[28], who found that the submandibular glands are less sensitive to irradiation than the parotid glands. Why the serous cells of the salivary glands seem to be more sensitive to ionizing radiation, as compared to the more resistant mucous cells, remains unknown. The histopathological changes seen after radiation injury are loss of serous acini, distortion or dilation of acinar ducts, aggregation of plasma cells and lymphocytes, and fibrosis[29]. Exactly how the inflammation and eventual fibrosis are related to injury to the parenchymal cells, and vascular and connective tissue remains uncertain[29].

The authors also found large inter-individual differences with regard to parotid function after TBI. This is in agreement with Franzén *et al*.[30], who studied parotid function following radiotherapy of malignancies in the head and neck.

The authors conclude that secretion capacity was reduced 3 months after 10-Gy single-dose TBI in both the parotid and submandibular glands. The ability to recover lost emptying capacity seems to be present in the submandibular glands, but not in the parotid glands, indicating that the serous cells in the parotid gland are more sensitive to irradiation than the mucous cells in the submandibular gland. The reduced recovering capacity of the parotid glands is a possible contributing factor to the reduced whole-salivary secretion rate seen after TBI at ASCT.

What this paper adds

- This paper adds unique knowledge of longitudinal functional changes in the major salivary glands during the year following total body irradiation.

Why this paper is important for paediatric dentists

- Paediatric dentists are important for the maintenance of patients' oral health during and after treatment with total body irradiation. This paper highlights the time when salivary gland function is most severely affected.
- The authors also discuss different methods for minimizing the problems associated with salivary gland dysfunction.

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