A comparison of two saliva substitutes in the management of xerostomia during radiotherapy for cancer of the head and neck

Johann Georg Lochner

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Department of Oral Medicine and Periodontology

Faculty of Dentistry

University of the Western Cape

Supervisor: Dr J C Marnewick

Co-supervisor: Prof LXG Stephen

Abstract

Radiotherapy of the head and neck often results in complaints of xerostomia. Xerostomia is a condition characterized by a dry feeling of the mouth and is quite common in patients after radiotherapy of the head and neck. These patients often drink various liquids to alleviate these symptoms, but this could remove mucus from the mucosa and thus intensify the xerostomia. Saliva substitutes may give some relief with resulting improvement in their oral function and quality of life.

The aim of this study is to compare the palliative efficacy of two saliva substitutes (Sinspeek and Xerostom®) in patients during radiotherapy for cancer of the head and neck.

This crossover randomised controlled clinical trial was carried out on twenty five patients with malignant tumours of the head and neck, following four weeks of radiotherapy at Tygerberg Hospital. Two different artificial saliva substitutes (Sinspeek and Xerostom®) were tested. Inclusion criteria were consenting adults complaining of xerostomia. Exclusion criteria were patients with allergies to the test substances. Patients were evaluated at baseline, at the beginning of the second test period and after the second test period, by measuring the unstimulated whole salivary flow rate to determine the severity of xerostomia. Each patient was given both artificial saliva products and they were evaluated at baseline and after each test period by means of a questionnaire to report on the level of xerostomia.

Patients in the test group were between the ages of 48 and 78. In 21 of patients the diagnosis of the malignancy was squamous cell carcinoma. All patients received a cumulative radiation dose of at least 32 Gy by the start of the first test period. Unstimulated whole salivary flow rates were on average lower in the females compared to males. Unstimulated salivary flow rates (USFR) diagnostic of xerostomia (less than 0,2ml/min), were present in only eight of the patients who had subjective complaints of xerostomia. There were no statistically significant differences between sexes or age groups with relation to unstimulated salivary flow rates. There were no statistically significant changes in USFR collected at baseline, after the first test period and after the second test period. Results showed that the period of relief obtained from either test substance was not found to be statistically significant. All patients found saliva substitutes useful for the management of xerostomia. Sinspeek and Xerostom® were found to be equally useful for the management of xerostomia, with no statistically significant difference between them during radiotherapy.

The benefit of saliva substitutes to ameliorate the effects of xerostomia is well established and proper advice and access to relevant preparations is essential. Factors such as taste and cost are important. It may be useful to make up samples of different saliva substitutes so that patients could decide which substitute they prefer.

Declaration

I, Johann Georg Lochner, declare that the work contained in this research report is my own original work. I have not previously submitted this research report to any university for a degree or examination.

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J G Lochner

_____ **Day of** _____ **of 2007**

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Chapter One

Introduction and Literature Review

1.1 Introduction

Xerostomia is a condition characterized by a dry feeling of the mouth and is fairly common in dental practice (Cassolato & Turnbull, 2003). Patients often drink various liquids to alleviate the symptoms, but this could remove mucus from the mucosa and thus worsen the xerostomia (Samarawickrama, 2002).

Patients undergoing radiotherapy for head and neck cancer may receive significant doses of radiation (Regelink, *et al*, 1998). Radiotherapy as part of head and neck oncotherapy is aimed at destroying the relevant cancer cells. Unfortunately healthy tissue may also be destroyed in the process. Tissue damage of the mucosa, salivary glands and bone manifest clinically as mucositis, hyposalivation and osteoradionecrosis. Salivary glands undergo early and late changes during radiation therapy and, unlike the other tissues affected they do not recover. The damage results in both the amount and composition of saliva being affected (Regelink *et al*, 1998).

Until recently saliva substitutes have not been readily available in South Africa. Most substances were imported and therefore the costs were prohibitive for patients needing to use a substitute for a long period (Touyz, 1988). For these reasons saliva substitutes have been developed and manufactured locally at affordable cost (Van der Bijl & De Waal, 1994).

Visits to pharmacies by the author of this thesis made it apparent that the supply of saliva substitutes in South Africa has improved in recent years and various saliva substitutes are now readily available. The cost to patients varies and this may have an impact on the long-term maintenance for xerostomia.

1.2 Literature Review

1.2.1 The salivary glands

1.2.1.1 Embryology

All salivary glands are of similar embryological (ectodermal) origin. Epithelial buds of ectodermal origin start to develop in the sixth week of embryogenesis forming an epithelial groove that later transforms to an epithelial tunnel. This tunnel is the primitive mouth and extends into the surrounding mesenchyme. At the end of this blind tunnel the parotid gland develops by branching, budding and proliferation of the epithelium. Salivary gland tissues are thus of ectodermal origin, and the surrounding capsule and connective tissue is of mesenchymal origin. The development of the parotid gland is closely associated with the pharyngeal arches, clefts and pouches. Embryogenesis results in the formation of these salivary glands and the disappearance of the pharyngeal arches, clefts and pouches. Development of blood vessels and nerves are closely associated with the development of salivary glands and the facial nerve is associated with the parotid gland like a river delta flowing through it (Carlson, 2000).

1.2.1.2 Anatomy

The macro anatomy of the salivary glands is of particular importance during the treatment of cancers of the head and neck. The parotids, submandibular and sublingual salivary glands are often in the path of radiation during radiotherapy of malignant tumours of the head and neck. Consequential tissue damage of these glands frequently results in xerostomia (Carlson, 2000). The micro anatomy of the various glands is similar. Salivary glands consist of secretory acini which form the terminal ends of the glands supported by myoepithelial cells. Ducts link the secretory components, which ultimately merge to form the major duct. The glands are usually surrounded by a fibrous capsule which branches inward to separate the gland into lobules, with loose connective tissue between the ducts and secretory components. The nerves, lymph and blood vessels also run within this connective tissue component (Cooper *et al*, 1995; Van Rensburg, 1981).

1.2.1.2.1 The major salivary glands

1.2.1.2.1.1 The parotid glands

The parotids are the largest of the salivary glands and consist of mainly serous acini (Sinnatamby, 1999). A few mucous cells can sometimes be seen in salivary glands of children (Van Rensburg, 1981). The parotid glands extend from the zygomatic arch to the upper part of the neck. In the neck area it overlaps with the posterior belly of the digastric and the anterior border of the sternocleidomastoid muscles (Sinnatamby, 1999). The anterior part of the gland overlaps the masseter muscle. The gland extends posterior to the mastoid process and also to below the external auditory meatus. The parotid gland occupies the space between the ramus and the mastoid and styloid processes and is close to the lateral wall of the oropharynx. The gland is surrounded by a fibrous capsule and covered with overlying skin and are both innervated by the greater

auricular nerve. The parotid wraps around the posterior border of the ramus and also extends around the capsule of the temporomandibular joint. Both the parotid duct and facial nerve emerge at the anteromedial surface of the gland and run forward. The facial nerve runs in the parotid gland with all its branches anastomosing with each other forming a plexus (Sinnatamby, 1999). The facial nerve is most superficial with the veins deeper and arteries deepest in relation to each other (Carlson, 2000). The parotid duct is about 5 cm in length running forward over the masseter through the buccal fat pad and buccinator muscle and opens in the buccal mucosa in the region of the second upper molar. Blood supply is via branches from the external carotid artery and venous drainage to the retromandibular vein (Sinnatamby, 1999).

Sympathetic nerve supply is for vasoconstriction and parasympathetic nerve supply is for secretory function (Carlson, 2000). Nerve supply for secretory motor function is from the otic ganglion running along the auriculotemporal nerve. Sympathetic fibres come from the superior cervical ganglion. Pre-gangliotic fibres come from the inferior salivary nucleus in the medulla, via the glossopharyngeal nerve's branches. Lymphatic drainage is to parotid nodes and then to the upper group of deep cervical nodes (Sinnatamby, 1999).

1.2.1.2.1.2 The submandibular glands

The submandibular glands lie around the posterior part of the mylohyoid muscle with a smaller deep and larger superficial part connected to each other. These glands produce both serous and mucinous saliva and are a truly mixed gland. The superficial part of the submandibular gland lies against the submandibular fossae laterally, the inferior part is covered by skin and the medial part lies against the mylohyoid muscle. The facial artery dents this gland in the posterior part, before it curves upward at the inferior border of the mandible. The deep part of the submandibular gland extends forward between the mylohyoid and the hyoglossus muscles, under the lingual and above the hypoglossal nerves. The submandibular duct is five centimetres in length, running forward and upwards, and opens

in the front of the mouth under the tongue on the sublingual papilla. Blood supply is from and to the facial artery and veins and lymphatic drainage is to the submandibular glands. Nerve supply for secretomotor fibres is from the submandibular ganglion which is suspended from the lingual nerve. Pre-ganglionic fibres come from the superior salivary nucleus in the pons with chorda tympani, nervus intermedius and the lingual nerve. Post-ganglionic fibres run with the lingual nerve and secretomotor fibres originate from the nerve plexus surrounding the facial artery (Sinnatamby, 1999).

1.2.1.2.1.3 The sublingual glands

The sublingual glands lie just under the oral mucosa, between the genioglossus and mylohyoid muscles. These two almond shaped glands converge and almost meet anteriorly. On the lateral borders they lie in the sublingual fossae. The nerve supply is from the postganglionic parasympathetic secretomotor fibres via the lingual nerve, which originates from the submandibular ganglion, in the region where chorda tympani preganglionic fibres synapse. The sublingual gland secretes mucous saliva and has over a dozen ducts of which some open directly in the oral cavity and others into the submandibular duct (Sinnatamby, 1999).

1.2.1.2.2 The minor salivary glands

The minor salivary glands are found throughout the mouth. Labial, buccal, palatal and lingual variants are present. These glands are mostly mixed in nature except for the palatal glands which are mucous in nature. The salivary glands of Von Ebner are associated with the circumvalate papillae on the posterior part of the tongue and are purely serous. The other lingual minor salivary glands to the anterior part of the tongue and on the dorsum of the tongue are mucous glands (Van Rensburg, 1981).

1.2.2 Saliva production

Saliva production varies greatly between individuals and is influenced by age, sex, time of day (Epstein & Scully, 1992). The measurement of salivary production or flow rate is also affected by the method and site of collection

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Adults produce over 500ml of saliva every day. This production is quite variable depending on demand and the physiological status of individuals. An unstimulated or resting whole salivary flow rate of 0,3ml/minute is considered to be normal, with a range of 0,29 ml/min – 0,41 ml/min (Sreebny, 2000), however the flow rate can be as low as 0,1ml/min during sleep and as high as 4,0 - 5,0ml/min during mastication or stimulation (Epstein & Scully, 1992; Porter *et al*, 2004). The average stimulated salivary flow rate varies between 1 - 2 ml/min (Sreebny, 2000).

Saliva is produced predominantly (90%) by the major salivary glands (parotid, submandibular and sublingual glands). The other 10% is produced by the minor salivary glands. The main ingredient of saliva is water and the other parts are organic and inorganic factors. Saliva consists of two major types of secretions (serous and mucous). The serous component is produced predominantly by the parotid gland (75%) and the submandibular gland (25%) and consists of a protein rich secretion of proteolytic enzymes and antibodies which have a bactericidal function. The second component is mucous in nature and is produced predominantly by the submandibular, sublingual and minor salivary glands. Mucous saliva consists of water, glycoconjugates and mucin. The main functions of this component are to prevent dehydration of the oral mucosa as well as aiding lubrication (Cassolato & Turnbull, 2003).

Salivation is completely under nervous control. However hormones, such as the thyroid hormones and adrenocortical hormones have an influence

on the constituents of saliva. Salivation can occur due to psychological stimuli, such as the thought, smell and visualization of food. Several factors also influence the amount of salivary secretion such as the taste, consistency and smell of food. Mastication and different chemical stimuli present in food also affect salivary secretion. Additionally pregnancy, nausea, oesophageal irritation and trauma to the oesophagus could result in increased salivation (Van Rensburg, 1981).

There is a relationship between sympathetic and parasympathetic nerve stimulation for salivation. Parasympathetic stimuli are responsible for vasodilatation and secretory function, but sympathetic stimuli are responsible for vasoconstriction which also results in salivation. Parasympathetic stimuli results in production of large quantities of saliva with a watery consistency. Sympathetic stimulation results in salivation with a higher organic material content with less water. The phenomenon that stress results in a dry mouth is not due to sympathetic stimulation of the salivary glands, but rather due to higher autonomic control (Van Rensburg, 1981).

1.2.3 The composition of saliva

Most studies evaluate whole saliva to investigate the composition of saliva (Tabak, 2006). The main ingredient of saliva is water, comprising over 99% of the salivary volume (Cooper *et al,* 1995). The study of the constituents of saliva is however much more complex and it is advisable that glandular secretions be collected separately for the effective evaluation of the composition of saliva. With the advent of electrophoresis the perception that saliva consisted merely of a few ingredients such as water, salts, amylase, and mucin was proven to be incorrect. Saliva is an extremely complex fluid with over 40 identifiable proteins. A few of the

main proteins will be mentioned below (Mandel, 1989). Salivary proteins are identified by a procedure termed proteomics which employs Edman degradation to identify salivary proteins. This recent advance has led to the identification of many previously undetected proteins in saliva (Tabak, 2006). Acinar productions are genetically determined and consist of families of molecules which are polymorphisms of the same family of proteins. The proline-rich proteins are of particular interest and are the main parotid glycoproteins. Other proteins such as histidine rich peptides, cysteine, containing phosphoproteins, and tyrosine rich peptides with statherin as the main peptide, are also found. Amylase, a well known protein, has different families as well as numerous isoenzymes. Peroxidases have different molecular weights that are genetically determined. Mucin has both high- and low-molecular weight forms being secreted by the salivary glands. Numerous other proteins produced by the acinar cells include: lactoferrin, gustin, aggregating glycoproteins, secretory component, parotid zinc binding protein, antileukoprotease and epidermal growth factor (Mandel, 1989).

Ductal cells produce secretory IgA, lysozyme, kallikrein, vitamin B-12, fibronectin and vitamin D binding proteins. The von Ebner glands of the tongue produce lipase. Albumin and IgG leak from the serum, through the gingival crevice, into the saliva (Mandel, 1989).

Other ingredients include non-electrolytes such as urea and ammonia as well as numerous electrolytes (Mandel, 1989).

All these constituents have specific functions, however it is their collective functioning which enhances intra-oral homeostasis (Mandel, 1989; Tabak, 2006).

1.2.4 Functions of saliva

It was previously thought that the most important function of saliva was its role in digestion. Saliva is however much more complex than previously conceived and it is debatable whether its digestive function is the most important (Mandel, 1989). Saliva consists of families of salivary molecules, each with multifactorial functions (Mandel, 1989; Samarawickrama, 2002).

In the past the ingredients of saliva were analysed and each molecule identified was assigned a specific putative function. This simplistic concept is incorrect. Saliva is complex in nature and all the various ingredients work collectively to maintain oral equilibrium and health (Tabak, 2006).

1.2.4.1 Lubrication

Mucin, glycoproteins, proline-rich proteins, which complex with albumim, as well as several other molecules lubricate the oral cavity. This lubrication is important to facilitate chewing, bolus formation and swallowing and when absent, difficult and uncomfortable eating results, as well as retention of foods onto teeth (Mandel, 1989). Mucins bind to each other and form very large molecules. This process of complexing creates molecules which are an important factor responsible for the lubricating function of saliva (Samarawickrama, 2002).

1.2.4.2 Mucous membrane and soft tissue integrity

The mouth heals very rapidly after mucosal trauma, and it is thought that saliva, with the aid of epidermal growth factor, facilitates and enhances this process (Mandel, 1989). The viscosity of saliva also minimizes

chemical and mechanical damage by covering and lubricating the mucosa (Cassolato & Turnbull, 2003).

1.2.4.3 Rinsing action

The salivary flow caused by the action of muscles around the mouth and tongue is responsible for a washing effect of the mouth. This washing effect removes harmful bacteria and chemicals from the teeth and mucosa and is also important to eliminate debris from the mouth (Mandel, 1989).

1.2.4.4 Maintenance of ecological balance

Saliva is essential to the maintainance of ecological balance. The adherence and elimination of bacteria should be in a critical balance. During radiotherapy there is often a shift from less harmful bacteria, for example *Streptococcus sangius*, to the overgrowth of harmful bacteria and other organisms such as Candida, S *mutans* and *Lactobacillus* species. Saliva is important here to maintain homeostasis and to prevent the overgrowth of harmful pathogens (Mandel, 1989).

1.2.4.5 Bacterial attachment

Bacteria are dependant on colonizing surfaces for their survival (Mandel, 1989). The mucins and amylase aids interaction between the mucosa, hard surfaces and certain bacteria. This is essential for bacterial homeostasis and survival (Samarawickrama, 2002). The mechanism by which saliva controls adhesion of bacteria is dependant on certain molecular interactions. Secretory IgA agglutinates certain bacteria which then cannot adhere to intra-oral surfaces. This is important as a protective mechanism where bacteria, which could cause caries for example are prevented from adhering to tooth surfaces. Mucins also compete with bacteria for binding space to surfaces and also agglutinate bacteria, which

further protect against bacterial damage. There are also other molecules, lysozyme and parotid basic glycoprotein, which aggregate bacteria. Other mechanisms such as calcium binding also inhibit bacterial adhesion (Mandel, 1989).

1.2.4.6 Antibacterial, antifungal and antiviral activity

Saliva protects the oral mucosa against infectious agents such as bacteria and fungi and viruses. This is facilitated by lysozyme, lactoperoxidase, immunoglobulin A and histatins (Cassolato & Turnbull, 2003).

Lysozyme, lactoferin, salivary peroxidase as well as other salivary proteins and histidine-rich proteins kill bacteria, prohibit acid production and interfere with bacterial growth and adhesion. Lysozyme is a potent cationic enzyme which causes bacterial lysis by interacting with other salivary components and is responsible for bacterial cell membrane breakdown. It also reduces acid production by certain bacteria that protects against demineralisation and chemical damage to mucosal surfaces (Mandel, 1989).

Histidine-rich proteins also kill bacteria directly and inhibit bacterial growth (Mandel, 1989).

Lactoferrin has bacteriostatic properties. It works by binding iron and is responsible for what has been termed “nutrition immunity” because of the competition between bacteria and lactoferrin to bind iron. Lactoferrin is also responsible for a bactericidal effect on *Streptococcus mutans* by binding iron (Mandel, 1989).

Salivary peroxidase is a catalysing agent in the oxidizing pathway of bacterial glucolysis. By interference in this pathway, acid production and growth of bacteria are seriously affected. The antibacterial proteins in

saliva all interact with each other and with mucin. This interaction defends the oral environment against damage. There are also protective molecules and cells from the gingival crevicular fluid which protect against bacterial damage. These include serum antibodies, for example IgG, phagocytic cells, as well as lysozyme, lactoferrin and myeloperoxidase from the phagocytes themselves (Mandel, 1989). The antifungal effect of histidine-rich peptides against damage by Candida albicans is well-known. These peptides are found in parotid fluids and they inhibit growth of these fungi (Mandel, 1989).

Antiviral effects of saliva can be directly attributed to the effect of secretory IgA, which neutralizes viruses, in particular HIV, polioviruses and rhinoviruses. Mucins also have antiviral effects against the herpesvirusses and HIV (Mandel, 1989).

1.2.4.7 pH Balance

Saliva aids remineralisation of teeth by providing calcium and phosphate ions in a neutral pH provided by the bicarbonate phosphate buffer systems, thus inhibiting tooth decay (Cassolato & Turnbull, 2003; Samarawickrama, 2002). The pH in the mouth is almost neutral and bacterial and other acids are neutralized by bicarbonates, phosphates and histidine-rich peptides. Mastication pumps saliva into the oral cavity when eating, increasing the amount of saliva needed for neutralization of harmful acids (Mandel, 1989).

1.2.4.8 Tooth maintenance

Saliva has a protective function for teeth as it forms a protective pellicle consisting of glycoprotein (Cassolato & Turnbull, 2003; Samarawickrama, 2002). The protective pellicle formed by salivary ingredients, consisting of phosphoproteins, mucin, albumin, lipids, glycolipids and phospholipids,

binds hydroxyapatite. This pellicle shields, lubricates and protects against tooth wear and prevents mineral loss from teeth. Saliva is supersaturated with calcium phosphate and remineralisation is regulated by staterin, histidine-rich peptides and cysteine-containing peptides which are responsible for the crystal stability and growth of calcium phosphate (Mandel, 1989). Proline-rich proteins further facilitate mineralisation of enamel (Samarawickrama, 2002). The anti-acid and buffering effects are also important to prevent demineralisation of the teeth (Mandel, 1989).

1.2.4.9 Other functions

A very important function of saliva is the preparation of a food bolus. Functions like speech, swallowing and chewing are also dependant on saliva (Cassolato & Turnbull, 2003; Samarawickrama, 2002). Saliva lubricates buffers, mineralises, facilitates taste, is antimicrobial and aids hydration (Mandel, 1989; Samarawickrama, 2002).

1.2.5 Collecting saliva

The accurate measurement of salivary flow rates is essential for experimental purposes. Salivary collections may be carried out under resting or stimulated circumstances. When stimulated salivary collections are required citric acid, paraffin wax, elastic bands, and gum base can be used as stimulants. Additionally pharmacological stimulants and electric stimulation may also be done. When unstimulated salivary collections are done no salivary gland stimulation should be present (Navazesh, 1993).

Saliva collections could also be divided into whole saliva collection or collection of saliva from individual glands. When whole saliva is collected it consists of saliva from the major as well as the minor salivary glands. Saliva could also be collected from individual major glands. When saliva is

collected to evaluate the composition of the saliva, individual gland sampling is preferred. Whole saliva collection is the preferred method to investigate xerostomia (Navazesh, 1993).

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It is important to standardize saliva collection methods because of the huge variation in normal salivary secretion between individuals. Factors such as the patient's hydration status, time of day, body position, season of the year, smoking habits and the smell of food can have an effect on salivary production (Navazesh, 1993).

There are different methods of collecting whole saliva samples. The draining method is done by letting saliva drain from the mouth over a specific time and at the end all saliva is expectorated into a pre-weighed container. The patient spits into a pre-weighed container in the spitting method every 60 seconds. Saliva can also be aspirated, as it forms in the mouth, and put in a test tube. Absorbent pre-weighed swabs can be used to absorb saliva and weighed again to determine the amount of saliva collected (Navazesh, 1993).

Of all the techniques described, the spitting and draining methods provide the most reproducible results to quantify whole saliva. It is recommended that the spitting method be used when whole saliva is collected. Salivation could be stimulated as described earlier or samples could be collected without stimulation. It is also advised that a trial run be done to allow the patient an exercise period for up to two minutes before the actual saliva collection period of five minutes starts. The saliva collected during a trial run should be discarded and not form part of the test sample (Navazesh, 1993).

To collect salivary secretions from individual glands specialized and customized apparatus is needed for salivary collection. Patients often find these methods uncomfortable and they could also be technique sensitive (Navazesh, 1993).

The subject of salivary gland function has attracted considerable attention in recent times. It is difficult to compare the work done by different authors

because standardized methods were not used for collection of salivara. It is therefore important to use standardized methods for saliva collection to make comparison of results between different studies possible (Navazesh, 1993).

1.2.6 Xerostomia

1.2.6.1 Aetiology

Causes of dry mouth can be temporary or chronic in nature. Temporary xerostomia affects the resting salivary secretion only and these patients are not affected during mastication. Smell and taste is not affected either (Cassolato & Turnbull, 2003). In chronic hyposalivation resting and stimulated salivary flow rates are affected and these patients are adversely affected and mucosal and dental diseases are more prevalent (Cassolato & Turnbull, 2003).

Xerostomia has many causes. Common causes are systemic medications, high dose radiation to the head and neck and specific diseases such as Sjögren's syndrome (Cassolato & Turnbull, 2003; Porter *et al*, 2004). Chronic xerostomia can also be caused by iatrogenic factors such as chemotherapy and chronic graft versus host disease (Porter *et al*, 2004). Salivary gland diseases such as Sarcoidosis, HIV, Hepatitis C infections, Cystic fibrosis, and primary biliary cirrhosis could also cause symptoms of a dry mouth (Porter *et al*, 2004). Other causes include dehydration (Frost *et al*, 2002; Samarawickrama, 2002), and diabetes (Porter *et al*, 2004; Samarawickrama, 2002). Other rare factors responsible for xerostomia include amyloidosis, haemochromatosis, Wegener's disease, Triple A syndrome and salivary aplastic states where the salivary glands did not develop (Porter *et al*, 2004).

Head and neck cancer radiation therapy and Sjögren's syndrome cause the severest levels of xerostomia (Cassolato & Turnbull, 2003).

1.2.6.1.1 Radiotherapy

The main modalities for the treatment of malignancies of the head and neck are surgery and radiotherapy (Chambers *et al,* 2004). Unfortunately radiotherapy damages healthy tissue as well as the cancer cells. Blood vessels, the mucosa, nerves, bone and salivary glands are affected (Chambers *et al*, 2004). The complications of radiotherapy could manifest during or after therapy. During treatment patients may suffer from mucositis, xerostomia, pain, infections, and neural disturbances such as hypersensitivity and dysgeusia (Chambers *et al*, 2004; Cooper *et al*, 1995). Other acute complications include altered taste, redness and desquamation of the skin (Cooper *et al*, 1995).

Salivary glands are easily damaged by radiation and the parotids are most affected (Porter *et al*, 2004). Radiation results in acinar atrophy as well as in chronic inflammation. Radiation induced apoptosis causes atrophy of the secretory acinar cells and this is responsible for early salivary changes after radiation. Radiation induced necrosis causes late changes after radiotherapy (Samarawickrama, 2002). A single dose of 20 Gy could damage salivary glands permanently and stop salivary flow (Porter *et al*, 2004). Irreversible radiotherapy damage occurs at a dose of 40 Gy when given as separate doses of 2 Gy per day (Regelink *et al*, 1998). As early as the first week of radiotherapy salivary flow could be reduced and after a treatment period of five weeks salivary flow may be reduced by as much as 95%. Salivary glands do not recover from this damage and stimulated as well as unstimulated flow rates are affected (Porter *et al*, 2004).

The treatment of squamous cell carcinoma for instance involves doses of between 50 and 70 Gy given at increments of 2 Gy per day. These doses of radiation will ultimately result in irreversible damage to the salivary glands (Regelink *et al*, 1998). If some salivary glands are irradiated and some escape radiation the latter may undergo hypertrophy which to some extent may compensate for the symptoms of xerostomia, but after a year

little further improvement is seen (Porter *et al*, 2004). Advances in the use of cone radiation techniques somewhat restrict the damage to salivary glands, and preservation of contralateral glands may be achieved (Porter *et al*, 2004).

Radioactive iodine used in the treatment of thyroid disease can also cause permanent damage to salivary glands because iodine is secreted by them, with consequent xerostomia (Porter *et al*, 2004).

Mucosal damage results from radiation effects on the epithelial, connective tissue and vascular components irradiated. The epithelium of both mucosal surfaces and skin has a high turnover rate in comparison to the vascular and connective tissue components. Tissues in a rapid cycle of renewal have numerous cells undergoing mitosis and are more affected by radiation. The epithelial basal cell layer is affected by radiation-induced cell death, but because the cells take up to two weeks to mature the clinical signs of mucositis are rarely seen earlier than two weeks after radiation. However both mucosa and skin are very tolerant to radiation and damage is typically seen with doses over 50 Gy. The oral mucosa can tolerate doses of about 65 Gy before it ulcerates.

It is now accepted that acute and chronic radiation changes should be seen as a continuum and not as separate entities. Hyperaemia of irradiated skin results from vasodilatation and increased permeability of the vessels leading to oedema and the release of fibrin into the tissue. The fibrin undergoes fibrotic changes in the involved tissue. The vasodilatation has the effect of lowering perfusion of the tissues and this leads to further damage. Collagen deposition due to increased fibroblast activity in the connective tissue was thought to be a late result of radiotherapy, but collagen deposition actually occurs as early as the first week after radiotherapy (Cooper *et al*, 1995).

Chronic complications of radiotherapy include osteoradionecrosis, soft tissue necrosis, rampant caries due to xerostomia and malnutrition (Chambers *et al*, 2004). There is also soft tissue ulceration, scar tissue formation, thinning of the mucosa, and altered taste due to damage of the taste buds. Fibrosis can lead to trismus and loss of elasticity of the tissues and even chondroradionecrosis.

The management of pain due to radiotherapy complications is difficult and rarely effective. Topical Xylocaine rinses may be beneficial, but often systemic analgesics are needed. Preventative measures are important to limit complications and thorough follow up is needed to treat pain early before complications such as malnutrition develop (Cooper *et al*, 1995).

The salivary glands are very sensitive to radiation damage and a single dose of over 1 Gy may lead to transient acinar damage. The serous components are more readily damaged and it appears that the mucinous components are more resistant to radiation damage. Necrotic changes that occur after radiotherapy results in acinar necrosis, atrophy, ductasia, accumulation of inflammatory cells and fibrosis, all resulting in salivary gland dysfunction (Cooper *et al*, 1995).

The management of patients who is about to have radiotherapy must include pre-radiation preventative treatment modalities as well as treatment during and after radiation therapy. Before radiation therapy commences any necessary extractions and routine dental treatment must be done. Emphasis must be placed on the provision of pre-operative teaching of plaque control methods, which will need to be reinforced and maintained throughout the life of the patient. For patients that are not able to achieve adequate maintenance before radiation therapy commences extraction of the remaining teeth is advised. During radiotherapy topical fluoride should be applied every second day to prevent tooth decay. During radiotherapy rinsing with a mixture of salt and sodium bicarbonate is advised to remove deposits and to dissolve thick mucous. Pain relief can be obtained by rinsing with a sucralfate suspension of 1 g per 15 ml of water. During radiotherapy there is often mucositis and yeast infections

and the use of a lozenge containing antifungal and antibacterial agents is advised from the start of, and for the duration of radiotherapy. Some patients will suffer from trismus. Exercising the muscles during radiotherapy is important to prevent trismus, because once established it is very difficult to treat. Patients must continue with these exercises for up to 6 months after therapy. It has been noticed that the occurrence of trismus may be initiated long after therapy was completed (Jansma *et al*, 1992*).* Xerostomia, resulting from cancer treatment, must be managed effectively otherwise it may lead to a decline in the quality of life of patients (Chambers *et al*, 2004).

1.2.6.1.2 Other

The most common reason for xerostomia is the use of certain systemic drugs (Cassolato & Turnbull, 2003; Porter *et al*, 2004). It is outside the scope of this discussion to address all drugs causing xerostomia. More than 500 medications have been implicated (Porter *et al*, 2004). The elderly are often affected because of their higher intake of single or combined medication (Cassolato & Turnbull, 2003; Porter *et al*, 2004). Examples of drug groups include antidepressants, antihypertensives, antihistamines and antipsychotics. Patients receiving radiation for head and neck cancer may be using some of these medications with a summation of the effects of radiation and medication resulting in increased xerostomia (Samarawickrama, 2002; Porter *et al*, 2004).

Often radiotherapy is combined with chemotherapy which could lead to more severe xerostomia (Chalmers *et al*, 2004) as well as additional complications where the actions of the chemotherapy and radiotherapy overlap (Cooper *et al,* 1995). Both radiotherapy and chemotherapy have a damaging effect on mucosal surfaces and patients that receive these therapies simultaneously have exaggerated effects of mucositis, ulcerations and pain. These individuals may have ulcerations that are more prone to infections and these patients should be monitored closely to prevent such infections (Cooper *et al,* 1995).

Symptoms of xerostomia are reported in up to 78% of patients receiving chemotherapy; their fourth most-common complaint. The number and dosage of different chemotherapeutic drugs used can be correlated to the severity of their xerostomia. Chemotherapeutic agents could change the consistency of saliva which further complicates xerostomia (Porter *et al*, 2004).

Chronic graft-versus-host disease is a common cause of xerostomia. Microscopically fibrosis can be seen in the parotids with resulting diminished salivary flow rates as well as changes in the composition of saliva. Both the oral epithelium and salivary epithelial cells are damaged in the early stages of this disease. The disease also causes damage to water transport, calcium ion transport and muscarinic receptors in the salivary glands with resulting complaints of xerostomia (Porter *et al*, 2004).

Sjögren's syndrome (SS) is a chronic immune modulated condition and has effects on exocrine glands as well as multiple other organs. The effects on the exocrine glands result in symptoms of dry mouth and dry eyes. SS can be divided into primary and secondary disease. Patients with primary SS have symptoms of dry eyes and dry mouth only whereas patients with secondary SS have additional connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus (Porter *et al*, 2004).

The salivary glands are damaged by dense infiltration of lymphocytes with resulting xerostomia and xerophthalmia. The diagnosis of SS depends on the presence of subjective complaints of dry eyes and dry mouth as well as objective ocular signs, microscopic signs of sialadenitis and autoantibodies to Ro/SSA and/or La/SSB. The diagnosis is still difficult because a large proportion of the population has autoantibodies to Ro/SSA and/or La/SSB. The aetiology of this disease is still speculative and factors such as viral disease have been suggested in the literature to be implicated in the aetiology, however this speculation has proven not to be a cause of the disease (Porter *et al*, 2004).

Patients with chronic sarcoidosis also have complaints of dry mouth, dry eyes and salivary gland enlargement. There are overlapping symptoms between SS and sarcoidosis, but in SS more symptoms of Raynaud's phenomenon are seen and in sarcoidosis more parotid enlargement. The main distinguishing factors are however pulmonary symptoms and raised blood pressure due to raised angiotensin-converting enzyme in patients with sarcoidosis (Porter *et al*, 2004).

Both children and adults with HIV disease could develop salivary gland disease in the presence of HIV infection. HIV salivary gland disease with symptoms of glandular enlargement and xerostomia, salivary gland enlargement due to Kaposi sarcoma, non-Hodgkin lymphoma, intraglandular lymphadenopathy and acute suppurative sialadenitis is seen. All of these entities could cause symptoms of dry mouth. Patients under treatment with reverse transcriptase inhibitors or protease inhibitors for HIV infection also often complain of xerostomia (Porter *et al*, 2004).

Hepatitis C virus (HCV) infections often result in salivary and other extra-hepatic diseases more frequently in comparison with other hepatic viruses. HCV infection causes inflammatory damage, similar but less pronounced than in SS, which results in xerostomia (Porter *et al*, 2004).

Both Epstein Barr virus and human T-lymphotropic virus 1 has been shown to be a potential cause for symptoms of xerostomia (Porter *et al*, 2004). Mumps and cytomegalovirus infections could also cause transient xerostomia (Cohen-Brown & Ship, 2004).

Any age group can be affected, from children to the elderly. Women aged from 40-60 years of age, make up the largest proportion (90%) (Samarawickrama, 2002). It is not necessarily the age of these patients, but the effects of medications, salivary gland diseases, immunological disorders, cancer treatments as well as other systemic diseases which make xerostomia more prevalent in the older age group (Ship *et al*, 2007).

Patients with myelodysplastic syndromes could progressively develop sicca syndrome. Iron overload due to regular blood transfusions will cause haemosiderosis in these patients. The iron deposition in the salivary glands is a reason for the development of xerostomia in these individuals. Patients with haemochromatosis often suffer with diabetes too and the development of xerostomia in these patients can often be attributed to the diabetes (Vrielinck *et al*, 1988).

Triple A syndrome or Allgrove syndrome is a very rare condition characterized by alacrima, achalasia, adrenocortical insufficiency and neurological abnormalities. In a report of five cases all individuals were found to suffer from xerostomia in addition to their other symptoms (Dumić *et al,* 2000).

Conditions where the salivary glands do not develop are very rare, but cause symptoms of xerostomia in children and youngsters. The diagnosis of this condition of salivary gland agenesis is often made later when the patient presents with rampant caries (Hodgson *et al*, 2001).

Patients with diabetes often complain of a dry mouth, but this could be attributed to the general state of dehydration of these patients or possibly the medications they use (Cohen-Brown & Ship, 2004; Porter *et al*, 2004; Rees, 1994).

Salivary dysfunction is also reported in patients with Alzheimer's, Parkinson's disease and in patients who had strokes (Cohen-Brown & Ship, 2004).

The following conditions have also been mentioned as causes of xerostomia and include: amyloidosis, primary biliary cirrhosis cystic fibrosis, acute sialadenitis, chronic sialadenitis, salivary stones, salivary tumours, cysts, and sialadenosis due to malnutrition, alcoholism and hyperlipidemia (Cohen-Brown & Ship, 2004).

1.2.6.2 The diagnosis of xerostomia

The feeling of a dry mouth is very subjective. The correlation between objective sialometry and the subjective complaint of dry mouth is poor (Thomson, Chalmers, Spencer & Williams, 1998; Samarawickrama, 2002). Of all patients who complain of dry mouth, 35% have no objective evidence of xerostomia (Frost *et al*, 2002).

When patients complain of dry mouth during the night or during daytime it is not indicative of xerostomia. Objective measurements of salivary function show that over 80% of patients who complain of xerostomia during the day or night do not have compromised salivary function, but complaints of a dry mouth during mastication are almost always a sign of salivary gland hypofunction. Even with masticatory and gustatory stimulation these patients have diminished salivation and their complaints of xerostomia are more often corroborated by the objective measurements of salivary dysfunction (Fox *et al*, 1987).

Clinical, radiographic and laboratory tests could be used to confirm the diagnosis of xerostomia. It is important to take a thorough history and do a detailed clinical examination. After these, specific special investigations could be done to aid in the diagnosis. Special tests include haematological, biochemical, imaging and histological investigations (Porter *et al*, 2004).

The average unstimulated salivary flow rate is approximately 0,3ml/min as quoted by Frost *et al,* (2002) from a study by Edgar & O'Mullane (1996). Navazesh *et al* (1992) proposed an unstimulated whole salivary flow rate of not more than 0,2ml/min for a diagnosis of xerostomia. Frost *et al* (2002) suggested that an unstimulated whole salivary flow rate of approximately 0,15ml/min could be indicative of xerostomia. This is 50% of the usual flow rate (Frost *et al*, 2002). Ghezzi *et al* (2000) established in a study that a reduction of 45% in the normal stimulated salivary flow rate be referred to as hyposalivation and that this level of salivary flow reduction can be used as a reference level for further studies. It can therefore be

useful to do salivary sampling before radiotherapy commences to have a reference point for further comparisons.

Sometimes the complaint of xerostomia is not due to lower production of saliva, but due to the altered consistency of saliva and this by itselfcould trigger a complaint of xerostomia. The quality of saliva is thus as important as the quantity, as this establishes the hydration and lubricating potential of saliva (Samarawickrama, 2002).

The measurement of the level of xerostomia is difficult. Thomson *et al*, 1998 reported that measuring saliva flow is an exact science due to the fact that different tried and tested methods exist. The quantification of xerostomia is subjective and patients with the same salivary flow will respond different to xerostomia related questions. Questionnaires were developed to estimate the level of xerostomia of patients as well as to study and compare the potential benefits of possible treatments (Thomson *et al*, 1998).

1.2.6.3 The clinical effects of xerostomia

Patients suffering from xerostomia are affected in many ways, including altered oral function, pain, infections and caries (Cassolato & Turnbull, 2003; Porter *et al*, 2004). Other symptoms include nocturnal oral discomfort, speech problems (Temmel et al, 2005), difficulty in swallowing (Momm, et al 2005), higher rates of oral infection (Porter *et al*, 2004) and caries (Regelink *et al*, 1998). Patients often complain of mucosal soreness, burning tongue and sometimes de-papillation of the tongue could be observed (Porter *et al*, 2004). Taste can also be affected and this affects patients' quality of life (Temmel *et al*, 2005). Individuals with xerostomia have viscous and foamy saliva. This type of saliva has lost its lubricating ability and adheres to the mucosa and teeth. Food and plaque adhere to the teeth and mucosa, resulting in difficulties with mastication and a higher incidence of mucosal infections.

These persons also present with periodontitis (Cassolato & Turnbull, 2003) and acute gingivitis (Porter *et al*, 2004). Salivary gland enlargement occurs often as a result of a compensatory effect leaving the lips dry, cracked and sore (Porter *et al*, 2004).

Saliva is essential in many important functions of health. Any condition which affects the composition or the amount of saliva will contribute to diminished quality of life and will adversely affect the well being of patients. It is therefore imperative that xerostomia be diagnosed and treated early and effectively (Cassolato & Turnbull, 2003).

Xerostomia will ultimately affect patient's general well being (Momm *et al*, 2005). The quality of life of such patients is affected due to interference with normal masticatory function as well as altered taste. They tend to avoid certain foods because of the difficulties encountered during mastication and this could lead to malnutrition. Speech problems, cracked lips, halitosis and problems with denture wearing are often encountered (Cassolato & Turnbull, 2003).

Prevention, early intervention and appropriate management of complications are essential when treating xerostomia.

1.2.6.4 The management of xerostomia

The most important part of the management of patients with xerostomia is the maintenance of good plaque control to prevent further damage to the existing dentition. Oral hygiene instruction, modification of and correct plaque control methods are essential for these patients (Chambers *et al*, 2004; Cohen-Brown & Ship, 2004). Caries prevention is important and here fluorides and dietary modification play an important role (Porter *et al*, 2004).

Various saliva substitutes have been tested for the protective modalities against enamel demineralisation. Prevention of enamel demineralisation is

important, since many patients with xerostomia are elderly, the importance of dentine protection is just as important. Elderly patients often have marked gingival recession and cervical erosions and sometimes root caries. Effective treatment of these problems and prevention of xerostomic complications is mandatory (Meyer-Lueckel *et al,* 2002). Dentate patients who were treated with radiotherapy often suffer with rampant caries typically affecting the cervical areas of teeth (Meyer-Lückel & Kielbassa, 2006).

The choice of an oral lubricant could be important to combat caries for this group of patients. There are several products available, some with greater anticaries property. Preparations such as Oralube® have a marked advantage for caries prevention and will be a good choice for dentate patients (Meyer-Lueckel *et al*, 2002). Biotene containing preparations and Glandosane® are not indicated for patients with teeth because of poorer defense against caries and reduced remineralisation of defects. Saliva Orthana, which contains mucin (Meyer-Lückel & Kielbassa, 2006) as well as xylitol and fluoride (Wray, 2000) protects against caries due to the covering effects of the mucin as well as the remineralisation effects of the fluoride present. Products which contain both mucin and fluoride will be superior in protection against dentine caries in patients after radiotherapy (Meyer-Lückel & Kielbassa, 2006; Wray, 2000).

Xerostomic patients often complain of problems associated with the retention and fit of dentures. Cleanliness of dentures is also compromised. Candidal infections in these persons should be monitored and kept under control with antifungal agents (Porter *et al*, 2004).

Topical saliva substitutes and systemic medication forms the mainstay of the treatment for xerostomia. Where salivary function is poor and symptomatic relief is needed, topical preparations are of particular importance (Kam *et al,* 2005). Most topical agents used to manage the symptoms of xerostomia are rapidly removed from the oral environment resulting in a short transient period of relief and protection (Porter *et al*, 2004).

1.2.6.4.1 Topical agents

The composition of natural saliva is complex with a large number of constituents which are responsible for the numerous functions of saliva, in particular, lubrication. Topical agents and artificial salivas are often used to alleviate the symptoms of xerostomia. These products are not as complex and do not resemble normal saliva. They frequently provide one main ingredient responsible for improved oral lubrication. These substances are rapidly eliminated from the oral cavity. In this regard they only provide short-term relief and for this reason they need to be applied very often for the relief of symptoms (Temmel *et al*, 2005).

Patients treated with carboxymethylcellulose (CMC) based products found relief with regard to the severity of xerostomia which was marginally statistically significant (Temmel *et al*, 2005). CMC products are viscous but do not simulate other properties of saliva (Epstein and Stevenson-Moore, 1992). This type of preparation did not improve the taste disturbances caused by xerostomia (Temmel *et al*, 2005). Some patients prefer this type of preparation compared to products containing glycerine and lemon (Epstein & Stevenson-Moore, 1992). There are many different CMC preparations available commercially which have similar beneficial effects. However cost and taste of these different products influence the patient's preference (Vissink *et al*, 1983).

Mucin based saliva substitutes are reportedly superior in alleviating symptoms of xerostomia (Davies & Singer, 1994). Saliva Orthana is one such preparation which is commercially available (Davies & Singer, 1994; Davies, 2000). In some persons Saliva Orthana causes nausea, diarrhoea, vomiting and intra-oral tenderness of the mucosa. Despite these complications, many patients persist in using this product due to the beneficial alleviation of xerostomia related complaints (Davies, 2000). Patients who were treated with radiation therapy also preferred mucin-containing preparations because of the perceived superior protection capabilities to the mucosa when compared to CMC containing preparations (Meyer-Lückel & Kielbassa, 2006). Mucin containing

preparations are retained in the mouth for longer periods, smaller volumes are needed throughout the day and there is a noticeable improvement of oral function (Vissink *et al*, 1983).

Casein phosphoprotein-calcium phosphate complex preparations such as Dentacal®, reportedly have similar beneficial effects as fluoride, without the possible negative effects of fluoride ingestion. A fluoride containing product may potentially cause fluoride toxicity, since patients apply xerostomia products very regularly and some of the product may be swallowed. The casein phosphoprotein-calcium phosphate preparation, which is a processed by-product of milk, may be swallowed without any adverse reactions. Patients reported favourably on this product with regard to taste, improvement of xerostomia related symptoms in addition to its preventative function against caries (Hay & Morton, 2003).

The main consideration in manufacturing saliva substitutes is that it must have good lubrication properties. In a study by Shannon *et al* (2002) use was made of a formulation (V.A. Ora-lube) containing sodium, potassium, calcium, chlorine, fluoride and inorganic phosphorous. This, VA-Ora Lube preparation has no lubricating properties, but dentate patients had beneficial protective effects on their remaining teeth due to better remineralisation properties caused by the presence of fluoride (Shannon *et al*, 2002).

Polyox contains polyethylene oxide which has viscous, wetting and elastic properties similar to saliva. As mentioned before these favourable characteristics alone do not guarantee that patients would prefer such a product and that factors such as taste and cost could be more important (Epstein & Stevenson-Moore, 1992).

1.2.6.4.1.1 Mouthwashes

Preparations should preferably give long lasting relief and in dentate individuals provide protection against caries. Patient acceptance of preparations is important and factors such as the lubrication potential,

taste, duration of relief, severity of xerostomia, type of preparation and cost play a role. Available preparations include Saliva Orthana (AS Pharma, Sweden), Salivace, Luborant (Antigen, UK), Xerostom® (Biocosmetics laboratory, Spain) and Oral Balance (Anglian, UK). These have been approved for use in xerostomia due to Sjögren's Syndrome and radiotherapy (Cohen-Brown & Ship, 2004; Porter *et al*, 2004). Oralbalance Oral Lubricant (Laclede), Moi-Stir (Kingswood laboratories), Optimoist (Colgate Oral Pharmaceuticals) and Salivart (Xenex Laboratories) are well-known products, but not available in South Africa (Cohen-Brown & Ship, 2004).

1.2.6.4.1.2 Sugar-free gum

The chewing action when chewing gum results in increased salivary production. However patient compliance as well as the presence of sufficient functional salivary gland tissue could be limiting factors (Porter *et al*, 2004; Cohen-Brown & Ship, 2004). The stimulation of salivation by chewing gum is both mechanical and due to gustatory stimulation, and therefore flavoured gum is preferred (Davies, 2000). Products include Biotene dental chewing gum (Laclede) as well as other sugar free chewing gum (Cohen-Brown & Ship, 2004). In a comparative study of three different chewing gums, one placebo, one containing mucin and V6 gum, a commercial product, all three preparations were found to give relief to xerostomic patients (Aagaard et al 1992). The test substances tasted similar, however the xerostomia patients preferred the mucin-containing product. The mucin-containing product is not commercially available and comes at a higher price.

1.2.6.4.1.3 Gels

Some patients prefer gel preparations for the symptomatic relief of xerostomia (Epstein, Emerton, Le & Stevenson-Moore, 1999). Oral Balance® gel (Laclede Inc., Rancho Dominguez, CA, USA) has no known side effects and is one such product which is frequently prescribed (Epstein *et al*, 1999; Kam *et al*, 2005). Another example is Biotene moisturizing gel (Laclede) (Cohen-Brown & Ship, 2004). Oral balance gel

which contains hydroxypropyl methylcellulose, lactic acid, sorbitol, parabens and xylitol was preferred over CMC containing products by patients, although no statistical significant improvements in xerostiomia were found (Epstein *et al*, 1999). Xerostom® (Biocosmetics laboratory, Spain) is an example of a preparation available in South Africa. This product is eliminated from the oral cavity rapidly resulting in a shortened period of relief for the patient (Kam *et al*, 2005; Porter *et al*, 2004).

1.2.6.4.1.4 Sprays

Mucin spray has been found to be useful in patients after radiation therapy with resulting subjective and objective improvements in their xerostomia (Porter *et al*, 2004). Salivart® is an example of such a CMC based product, which does not contain alcohol or glycerine and gives relief to xerostomia related complaints (Epstein & Stevenson-Moore, 1992; ADA Division of Science, 2001). Xerostom® (Biocosmetics laboratory, Spain), Artificial saliva (Cipla Medpro, South Africa) and Dentacal (Phoscal holdings, Australia) are all available in South Africa. Sprays are preferred by some patients because they are easy to use discreetly (Epstein & Stevenson-Moore, 1992).

1.2.6.4.2 Intraoral devices

Saliva substitutes are swallowed and rapidly removed from the oral cavity. To provide an oral lubricant for longer periods of time intra-oral devices with reservoirs have been developed which provides a slow release of lubricant (Kam *et al*, 2005). Often xerostomia is most severe at night time, due to the normal nocturnal drop in salivary flow rate. Patients are usually restless and their sleep is disturbed by the need to lubricate their mouths. Patients often drink water to alleviate the dryness during these spells (Frost *et al*, 2002). Some studies have shown that intraoral lubricating devices are beneficial in combating this nocturnal dryness. These appliances differ in design for dentate and edentulous patients and are equipped with inbuilt reservoirs filled with artificial saliva which trickle out and thus allows a continuous supply of lubricant (Frost, Gardner, Price and Sinclair, 1997; Frost *et al*, 2002; McMillan *et al*, 2005). In the study by

Frost *et al* (2002) it was found that patients preferred such devices, especially at night time (Frost *et al*, 1997), but McMillan *et al* (2005) found that patients preferred normal lubricating methods above intraoral devices. A limitation to these appliances is their bulkiness which may interfere with speech during daytime (Frost *et al*, 2002). Another problem is accumulation of debris in these devices, if they are used when eating. It is advised that patients who wear dentures be provided with a separate set for use during mealtimes to prevent such contamination with food (Frost *et al*, 1997). Often the viscosity of substitutes used in these devices could cause poor compliance because the release of the lubricant cannot be controlled from the device. The use of gels in these devices are preferred, in particular Oral balance gel, and were found to be of benefit to patients suffering from xerostomia after radiotherapy (Kam *et al*, 2005).

1.2.6.4.3 Others

Substances such as evening primrose oil, available as Efamol®, has not shown any statistically significant benefits when compared to a control in xerostomia related to SS patients (Brennan, Shariff, Lockhart & Fox, 2002). Preparations could also be available as Sugar-free sweets (Porter *et al*, 2004).

Pastilles which stimulate salivary production have been proven to be useful for patients using oxybutynin chloride for treatment of detrusor instability (a neurological condition). Salivix (Provalis, UK), a preparation for xerostomia, allows higher doses of the oxybutynin to be tolerated (Porter *et al*, 2004).

Interferon-α lozenges (150 IU of Interferon-α 3 times per day) have been found useful to increase both unstimulated and stimulated salivary flow in patients suffering from xerostomia related symptoms with no side effects (Porter *et al*, 2004).

Toothpastes are also available for the relief of xerostomia. Biotene dry mouth toothpaste (Laclede) (Cohen-Brown and Ship, 2004) is an example

as well as Xerostom® (Biocosmetics laboratory, Spain), which is available in South Africa (Epstein *et al*, 1999).

1.2.6.4.4 Systemic preparations

Many different medications and substances have been researched, but inconsistent methods have made it difficult to compare results of these studies. Well-designed, randomized, controlled trials for the use of pilocarpine in the management of xerostomia in SS and radiotherapy patients have been reported.

1.2.6.4.4.1 Cholinergic agonists

Salivary production can be increased with the aid of oral muscarinic M3 receptor agonists. Pilocarpine and Cevimeline have been in use for some time and both have proved to increase saliva production. Pilocarpine is being used in post radiation patients and more recently also in SS patients with promising effects (Porter *et al*, 2004).

Pilocarpine is an acetylcholine muscarinic M3 receptor parasympathetic agonist and stimulates secretion by different glands. This stimulatory effect is not limited to salivary gland stimulation only, but also sweat glands, lacrimal glands and respiratory mucous glands (Porter *et al*, 2004).

Pilocarpine also effects contraction of smooth muscle of the gall bladder, urinary tracts, biliary ducts, bronchi and the gastrointestinal tract which limits the prescription of this drug to severe cases. Side effects such as weating, nausea, headaches, gastrointestinal upsets, polyuria, increased lacrimation, influenza type symptoms, flushing, and palpitations are all unpleasant side effects. However, Pilocarpine does not have serious adverse reactions nor does it have serious interactions with other drugs (Chambers *et al*, 2004). It is generally well tolerated but it is advised not to be used in patients with asthma and other chronic obstructive pulmonary diseases (Porter *et al*, 2004). Oral pilocarpine is given at 5 mg 4 times per day or 10 mg 3 times per day and should be used for 8 to 12 weeks before

positive effects are noted (Chambers *et al*, 2004; Davies & Singer, 1994; LeVeque, et al (1993); Porter *et al*, 2004).

Pilocarpine can also be prepared as a rinse and swallow preparation four times per day, 5 mg per rinse. Some patients may prefer this type of rinse above a conventional salivary replacement rinse (Davies & Singer, 1994).

Pilocarpine increased salivary flow in post radiation patients, but the effect was not significant (Chambers et al 2004). Xerostomia symptoms improved for patients and this could be attributed to altered saliva secretion when pilocarpine was used (LeVeque *et al*, 1993). Many patients' mouths are so dry that even minimal improvement in salivation will lead to less complaints of xerostomia (LeVeque *et al*, 1993). There is evidence in the literature that in some randomised placebo controlled trials, pilocarpine is of benefit for both SS and post radiotherapy treatment. Patients had significantly less xerostomia related complaints and oral soreness (Brennan *et al*, 2002). Pilocarpine is a preferred drug for treatment of radiotherapy and SS induced xerostomia. The use of this medication in drug-induced xerostomia is inconclusive. The oral effect of pilocarpine is due to increased release from glands, in particular minor glands which were not damaged by radiotherapy and is not responsible for increased activity from damaged glands (Chambers *et al*, 2004; Porter *et al*, 2004).

Cevimeline is an analog of acetylcholine with high affinity for M3 muscarinic receptors of salivary and lacrimal glands. Its effect on M2 cardiac and respiratory receptors is modulated with potentially less adverse reactions. Conflicting evidence has been reported regarding its efficacy in reducing symptoms of xerostomia. Cevimeline is available as Evoxac® (Kahn & Johnstone, 2005), and when given at a dose of 30 mg 3 times per day has been reported to be well tolerated with an improvement of xerostomia related symptoms (Chambers *et al*, 2004; Porter *et al*, 2004).

1.2.6.4.4.2 Thiol-containing substances

Research has shown that thiol-containing substances such as Amifostine® (WR-2721, Ethyol; Medimmune Oncology, Inc, West Conshohocken, PA) can be useful to limit radiation damage to salivary glands due to their accumulation in salivary epithelium and a scavenging effect on radiation induced free-radicals (Brizel *et al*, 2000; Kahn & Johnstone, 2005; McDonald *et al*, 1994). Side effects such as nausea, vomiting and hypotension have been recorded, but levels of xerostomia were found to be significantly less when patients received amifostine. This type of treatment shows great promise for future treatment and prevention of xerostomia for this group of patients (Brizel *et al*, 2000; Chambers *et al*, 2004).

1.2.6.4.4.3 Miscellaneous Drugs

Bethanechol is suggested as a treatment for drug induced xerostomia. It is a muscarinic and nicotinic agonist and is given at 25 mg 3 times per day. At this dose both unstimulated and stimulated salivary flow increases were reported (Porter *et al*, 2004). Correlations between flow rate increases and improvement of symptoms could not be determined in post radiation patients, but adverse reactions such as nausea and diarrhoea were limited (Porter *et al*, 2004).

Interferon-α used for the treatment of xerostomia with parenteral and intra-muscular preparations was found to give rise to some adverse reactions like nausea and vomiting etc. (Porter *et al*, 2004). Preparations at a dose of 150 IU of interferon-α resulted in no improvements for oral dryness or unstimulated whole saliva, but only for stimulated whole saliva when compared with placebo (Brennan *et al*, 2002). When Interferon was used in a lozenge preparation, alleviation of xerostomia was found without the adverse reactions. It is notable that although interferon is inactivated in the gastrointestinal tract and was not detectable in blood after the lozenge preparations, it still resulted in positive xerostomia related improvements (Porter *et al*, 2004).

Anethole trithone is another drug which is useful in increasing pilocarpine induced salivary production. It increases muscarinic receptor availability and therefore makes cholinergic stimulation by drugs such as pilocarpine stronger with resulting increased salivation and reduction of xerostomia related symptoms. Patients with radiation damage could find this drug useful, but its use in SS patients is not clear (Porter *et al*, 2004).

Pyridostigmine, a cholinesterase inhibitor which has nicotinic and muscarinic agonistic actions is useful for patients with drug induced xerostomia (Porter *et al*, 2004).

There is limited data for the use of **Bromhexine** for xerostomia, but it is suggested that benefits, with increased salivary and lacrimal flow can be achieved in patients with SS, with a dose of 32-48 mg per day, (Porter *et al*, 2004). In other studies there was no increase in salivation with the use of this preparation and only lacrimal function was improved (Brennan *et al*, 2002).

Trials are currently conducted to establish a potential benefit for **Carbacholine** in the treatment of xerostomia in post radiation patients (Porter *et al*, 2004).

The use of **Corticosteroids** in the treatment of SS is not advocated until further studies have been conducted (Porter *et al*, 2004).

Hydroxychloroquine given at doses of 6 – 7 mg/kg/day has produced variable benefits when given for a period over a year. Therefore further long term studies are required to test its use for the treatment of xerostomia in patients with SS (Porter *et al*, 2004).

Other drugs which have been mentioned for the management of xerostomia includes **Azathioprine**, **Cyclosporine**, **Cyclophosphamide**, **Sulfasalazine**, **Methotrexate** and **Thalidomide**, but studies proving the benefit of their use are still inconclusive (Porter *et al*, 2004).

1.2.6.4.5 Other methods

Parotid sparing radiation techniques show great promise and a variety are available, including shrinking field approaches, the use of lead blocks and masks and stents to reproduce patient position and shield peripheral tissue against damage. Two-dimensional radiation could also be used, sparing one parotid, but this technique depends on the position of the tumour. A new technique which makes use of three dimensional (3D) intensity modulated radiotherapy (IMRT) provides a higher dose to the tumour site, sparing other tissue from radiation damage. The contra lateral parotid can thus be spared with the result of less xerostomia related complaints and complications (Chambers *et al*, 2004). When patients were treated with IMRT there were no initial benefits with relation to xerostomia, but when patients were assessed 6 months later a clear benefit was found for this salivary gland sparing radiotherapy (RT) modality. Patients must be informed of the late benefit of IMR above conventional RT in the treatment or oral cancer (Jabbari *et al*, 2005).

The prevention of the intensity of xerostomia is important to achieve better quality of life (QOL). Patients who are treated with IMRT will eventually have less xerostomia than patients treated with conventional radiotherapy. This technique is not indicated for all head and neck cancer patients, but where possible it will ultimately have better QOL outcomes for these patients (Jabbari *et al*, 2005).

The use of electrostimulation has shown limited benefit (Brennan *et al*, 2002) in patients with SS in alleviating symptoms of xerostomia and further testing is advisable (Porter *et al*, 2004). Acupuncture resulted in increased salivation in patients with SS and some improvement in symptoms was noticed, but more investigations are needed (Porter *et al*, 2004).

Dietary modification and supplements could be of benefit to patients with xerostomia. Vitamin supplements, cappuccino coffee, evening primrose

oil, rich fatty acids and linseed extract, for example Salinum, have been mentioned as aids to reduce symptoms of xerostomia (Porter *et al*, 2004).

Salivary glands can surgically be moved to an area away from where radiotherapy needs to be done. Research is being done where parotid and submandibular tissue is transplanted to the submental area, where shielding techniques are used to protect this area (Kahn & Johnstone, 2005). The transplanted tissue has shown promise to stay functional during and after radiotherapy, resulting in less xerostomia related complaints (Chambers *et al,* 2004; Kahn & Johnstone, 2005).

With the development of gene transfer techniques in medical research, it might in future be possible to repair damaged salivary glands. No projects are currently done in this area, because it is such a new field, but the hypothesis shows great promise (Chambers *et al,* 2004). Although saliva substitutes alleviate the symptoms of xerostomia, Rhodus & Bereuter (2000) found that some patients using a saliva substitute showed increased whole salivary secretion rates in comparison to when a substitute was not used. The reason for this finding is not known, but could be investigated in future studies.

The treatment of xerostomia for post radiation patients is symptomatic in nature, because the irreversible damage cannot be prevented nor managed with medication like pilocarpine which is used prophylactically or after radiation therapy (Regelink *et al*, 1998). More recently this notion has been disputed and a benefit for these drugs has been mentioned (Porter *et al*, 2004). Saliva stimulating drugs are only helpful if there is residual functional salivary gland tissue left after radiation therapy (McMillan *et al*, 2006). Both dentate and edentulous patients have problems with speech, mastication, swallowing, sleeping and there is a higher prevalence of oral infections. In the case of denture wearers, soreness, looseness of dentures and denture induced ulceration of the oral mucosa are common complaints (Olsson & Axéll, 1991).

Chapter Two

Aims, Objectives, Materials and Methods

2.1 Aims

The aim of this study is to compare the palliative efficacy of two locally available salivary substitutes (Sinspeek and Xerostom®) in patients during radiotherapy for head and neck cancer.

Figure 2.1
Sinspeek and Xerostom®

2.2 Objectives

1. To measure the whole unstimulated salivary flow rates at baseline.
2. To measure the whole unstimulated salivary flow rates after the first and second test weeks.
3. To compare these whole unstimulated salivary flow rates at baseline and after the first and second test weeks.
4. To evaluate the efficacy of both salivary substitutes by comparing patient's responses using a standard questionnaire.
5. To establish if any patient factors have an influence on the efficacy of the two salivary substitutes (e.g. age, gender, and baseline salivary flow rate).
6. To establish whether patients found it beneficial to use a salivary supplement.
7. To determine if patients would like to continue using salivary substitutes.
8. To develop a protocol for the use of salivary substitutes in the management of radiotherapy induced xerostomia.

2.3 Null hypothesis

There is no statistical significant difference between the two salivary substitutes.

2.4 Materials and methods

2.4.1 Study Design

The study is designed as a prospective crossover randomised clinical trial.

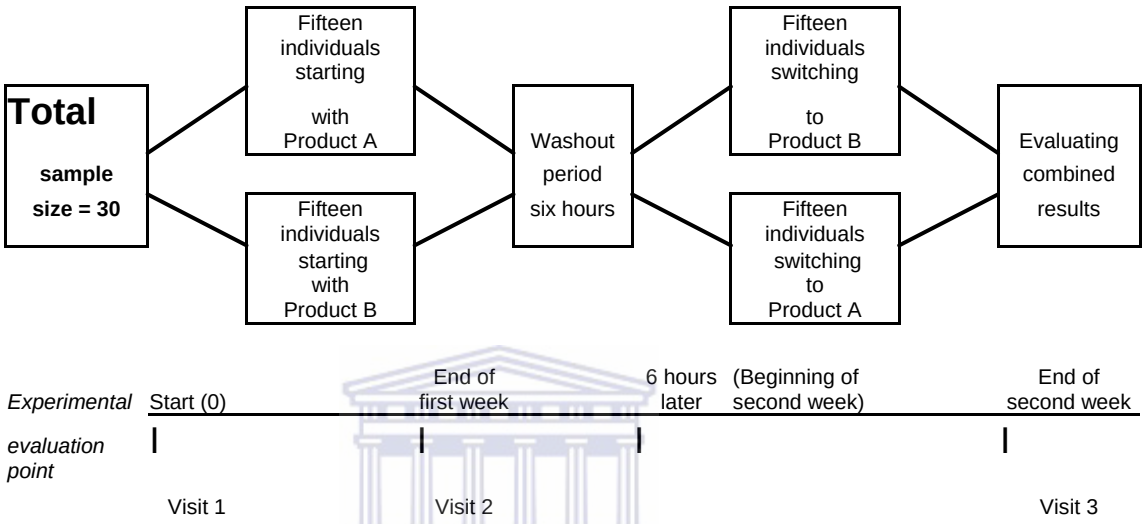

Figure 2.2
Experimental design and study population.

A computer generated randomisation list was created to randomly allocate patients to either salivary substitute group.

The patients will use both substitutes in a crossover design for a period of one test week for each substitute. Each patient therefore reported on the efficacy of each product. Salivary substitutes are usually used *ad libitum* because they are readily eliminated from the oral cavity (Van der Bijl & De Waal, 1994).

There was a washout period of 6 hours between the test periods of the two salivary substitutes.

Some of the test subjects were hospitalised and others travelled to the hospital daily for treatment. A longer washout period was not logistically possible.

Subjects were blinded to the salivary substitutes, i.e. they were packaged in identical white containers marked A and B.

An independent person labelled the bottles. The key which showed which salivary substitute was marked as A and B respectively was placed in an envelope and sealed for safekeeping by the independent person till after all data were captured.

Both the patient and examiner will thus be blinded to which substance is used at any given time.

Figure 2.3
Pre-weighed salivary substitutes bottled in identical white plastic containers.

2.4.2 Study Sample

Twenty-five patients receiving radiotherapy for cancer of the head and neck at Tygerberg Hospital Radiotherapy Department formed the study population.

Mcmillan *et al* (2005) compared different salivary substitutes and different methods of application of salivary substitutes. A study population of 15 was needed to show a 20% improvement in “the score”, with a significance level of 0,05, with a power of at least 90%, when a crossover study design was used. More subjects were used in this study to achieve results which will be more significant. The sample size in this study was calculated in consultation with a competent statistician.

2.4.3 Inclusion and exclusion criteria

2.4.3.1 Inclusion criteria

1. Patients undergoing radiotherapy who have reported symptoms of xerostomia.
2. Patients who have completed four weeks of radiotherapy.
3. Patients must be consenting adults.
4. Patients willing to sign the relevant informed consent form.
5. Patients must be willing to provide the relevant information for completion of the questionnaires at the specified time intervals.
6. Patients must be willing to provide whole saliva samples when required.

2.4.3.2 Exclusion criteria

1. Patients who do not have symptoms of xerostomia.
2. Patients who are not willing to participate.
3. Patients who are allergic to any of the substances which are to be used in the study.
4. Patients presently using a salivary substitute.
5. Patients who are unwilling to sign the relevant consent as well as those not willing to provide information relevant for completion of the questionnaires.
6. Patients unwilling to provide whole saliva samples when required.

2.4.4 Identification of patients

After four weeks of radiotherapy for cancer of the head and neck twenty-five consecutive patients were selected as a convenience sample from patients undergoing radiotherapy for head and neck cancer according to the inclusion and exclusion criteria.

Patients were asked to answer the following question. “Is your mouth dry? Are there any problems that you experience which are associated with this dryness?” If the answer to this question was “yes” patients were asked to join the study. This question and method was also used by Momm *et al* (2004), when they identified patients for their study to compare different salivary substitutes.

This was a subjective complaint of the patients. If there were any dropouts from the study, additional patients were recruited.

Examples of the patient information and consent forms are included as appendix 1 and appendix 2 respectively.

The study was described to the patient and his/her role was explained in detail so that he/she was well informed.

Patients selected to participate were asked to sign the consent form.

Patients were allocated a number in sequence when entering the study. A computer generated randomisation list was used to assign patients to the two different test groups that determined who received which test substance first.

The computer generated randomisation list is included as appendix 3.

2.4.5 Patient examination

Patients were examined by experienced consultants in the radiotherapy department and were referred for dental treatment before radiotherapy commenced. Where deemed necessary, dental clearances were advised to limit post radiation complications. Patients were evaluated every week by consultants in the radiotherapy department. This included an oral examination as well as a general medical examination. At this visit patient complications or symptoms were addressed, patients were referred for additional treatments and medications were prescribed as needed.

2.4.6 Saliva collection

The resting unstimulated whole saliva secretion rate was established to determine the severity of xerostomia. This was done at the beginning of the study when patients have completed four weeks of radiotherapy, at the beginning of the second test period when the patients would have completed five weeks of radiotherapy and after the second test week when the patients would have completed six weeks of radiotherapy.

Patients were asked to rinse their mouths with sterile water before saliva collection started. After rinsing with sterile water a rest period of five minutes was allowed. A one-minute period of saliva collection followed and was used as a practice period, and the saliva expectorated during this initial minute was discarded.

Pre-weighed specimen bottles were then provided and patients were asked to expectorate saliva into the specimen bottles over a five minute period.

The weight of the saliva expectorated was converted from gram per minute (g/min) to millilitre per minute (ml/min) on the basis that one gram weight of saliva has a volume of one millilitre. This method is similar to that described by Navazesh, Christensen & Brightman (1992); Navazesh (1993); Thomson *et al* (1998) when they established the unstimulated whole saliva secretion rate in their studies to determine criteria for salivary gland hypofunction.

2.4.7 Questionnaire

Patients were questioned by the principal investigator who then completed the questionnaire at baseline, after the first test period, and after the second test period. The questionnaire was developed by modifying questionnaires used in the WR-38 study as reported by Thomson *et al* (1998); Thomson & Williams, (2000), questionnaires used by Momm *et al,* (2005); Van der Bijl & De Waal, (1994), to allow for comparison between this and their studies. The completed questionnaire contained relevant patient information such as age, gender, type of tumour, the affected site, medications used, period since radiotherapy commenced and radiation dose. There were also specific questions relevant to the xerostomia at baseline and after each test period. The questionnaire is included as appendix 3.

The medication the patient took during the course of their treatment was also listed. Xerostomia related questions were asked at baseline, after the first test period and after the second test period. Patients were asked to rate their complaints on a four point scale with regard to dry mouth, difficulty in speaking, chewing, swallowing, dry mouth during sleeping, taste disturbances and pain or burning sensations in the mouth.

Patients were asked what the effect of the salivary substitute on their mouth was, for how long the test substance provided relief and how they rated the substance in general and with regard to taste. The patients had to decide whether the test substance provided relief to such an extent that they wished to continue using it.
This process was repeated for the first and second test periods and ultimately the patient had to decide which product they preferred.

2.4.8 Test materials

Two different saliva substitutes were tested. Both are available as rinses:

1. Xerostom® (Biocosmetics laboratories, Madrid, Spain). The main ingredients of Xerostom® are: Betaine, Allantoin, Xylitol, Fluoride, Olive oil, Vitamin B5 and Vitamin E. It is imported by Unique Dental on behalf of Biocosmetics laboratories, Madrid, Spain.

2. Sinspeek (Carboxymethylcellulose based saliva substitute made within the Department of Oral Medicine, University of Western Cape, South Africa)

Both salivary substitutes were dispensed in identical white plastic bottles to allow for blinding of the patients and examiner.

Salivary substitutes were manufactured locally to reduce cost and because of the poor supply of salivary substitutes in South Africa. These locally manufactured substitutes contained polysaccharides such as carboxymethylcellulose (CMC) as well as other ingredients which were similar for the different recipes of artificial saliva. The additional ingredients, such as flavourings and artificial sweeteners, differed in concentration in the different recipes (Touyz, 1988; Van der Bijl & De Waal, 1994).

The main constituents of commercial products are CMC, animal mucins (Van der Bijl & De Waal, 1994) or glycerine (Wiesenfeld, Stewart & Mason, 1983), all with the addition of different electrolytes, flavouring agents and non-cariogenic sweeteners (Van der Bijl & De Waal, 1994).
In some products fluoride was added to offer additional dental protection for dentate patients (Hatton, Levine, Margarone & Aguirre, 1987). Care has to be taken when a fluoride-containing supplement is used to avoid ingestion, as high fluoride intake levels could be harmful to the patient (Van der Bijl & De Waal, 1994). There is a critical fluoride concentration which is necessary to aid in remineralisation of tooth structure. The concentrations at which fluoride is present in saliva substitutes may be too low to aid in remineralisation and the true benefit therefore is questionable. It is advisable that professionals do fluoride applications as a preventative action against caries for dentate patients with xerostomia (Van der Bijl & De Waal, 1994). Fluorides in artificial salivas could have toxic effects if present at concentrations of over 2 mmol/l. Fluoride levels of 3 mmol/l shifts the balance from demineralisation to remineralisation for enamel. The levels for dentine will be different, and dentine is also more susceptible to demineralisation than enamel. Fluoride concentrations of 2 mmol/l will also stop demineralisation of dentine when the oral environment is slightly acidic (Meyer-Lückel & Kielbassa, 2006).

Different saliva substitutes have been studied extensively and these are available as gels, sprays, oils or liquids (Momm *et al*, 2005). Patient preference to the taste, cost and other rheological properties influence the choice of a salivary substitute. This is the same for preparations containing CMC which is proven to reduce the symptoms of xerostomia in subjects with radiation induced xerostomia (Chambers *et al*, 2004).

The main constituents are responsible for the lubrication and viscosity properties which are the most important properties required for a saliva substitute (Van der Bijl & De Waal, 1994). Wiesenfeld *et al* (1983) showed that there were no statistical significant differences in xerostomia scores between mucin based, CMC based or glycerine based supplements when used to alleviate the symptoms of xerostomia.

The two salivary substitutes which will be tested in this study differ in composition.

2.4.8.1 Sinspeek

Sinspeek is made from a recipe as described by Touyz (1988); Van der Bijl & De Waal (1994); Wiesenfeld *et al* (1983) with the main constituent being carboxymethylcellulose (CMC) with the addition of electrolytes, flavourings and non-cariogenic sweeteners. This type of preparation was available commercially before as Glandosane®, but was removed by the suppliers due to financial reasons (Van der Bijl & De Waal, 1994). It was therefore decided to manufacture a salivary substitute similar to this product from ingredients readily available in South Africa, deriving the name from the words “sintetiese speeksel”.

Low molecular weight, low-viscosity grade, CMC is preferred as a base (Meyerov & Touyz, 1987), but was not readily available in South Africa and replaced with a high molecular weight CMC of food grade (Van der Bijl & De Waal, 1994). The pH of Sinspeek is 6,7 which compares well with

some of the products available commercially for example Luborant® (pH=6,86) and Saliva Orthana (pH=6,69) and would give favourable results for remineralisation if fluoride was added. It was decided not to add fluoride in this preparation because patients needed alleviation of xerostomia by administering the substitute *ad libitum*, with the potential effect of fluoride toxicity, especially in the warm South African weather (Van der Bijl & De Waal, 1994). The ph of Glandosane® was much lower at 5,06 (Van der Bijl & De Waal, 1994) and this is why this product is not advisable for dentate patients because of poor remineralisation properties (Meyer-Lueckel *et al*, 2002).

It was manufactured as a high viscosity salivary substitute and the main ingredient is a high molecular weight CMC of food grade ('KICCOLATE' F-170 Nichirin chemical industries, Itami city, Japan). Other ingredients include KCl, NaCl, $MgCl_2.6H_2O$, $CaCl_2.2H_2O$, K_2HPO_4, sorbitol solution (70%), methyl p-hydroxybenzoate, solution of egg (1%) and oil of lemon (Van der Bijl & De Waal, 1994)

Table 2.1
The composition of Sinspeek

Component	**Weight in (g)**
CMC	9,0
KCl	1,2
NaCl	0,84
$MgCl_2.6H_2O$	0,06
$CaCl_2.2H_2O$	0,16
K_2HPO_4	0,34
Sorbitol solution (70%)	42,80
Methyl p-Hydroxybenzoate	2,0
Solution of egg yellow (1%)	2,0
Oil of lemon	0,4
Distilled water	1000 mL

This preparation is relatively inexpensive and is sold to patients at a nominal price of R20 per 200ml bottle to cover costs of manufacturing.

2.4.8.2 Xerostom®

Xerostom® (Biocosmetics laboratories, Madrid, Spain) is the other test compound and is available commercially as a mouthwash, toothpaste, spray and saliva substitute. For the purposes of this study design it was decided to use the Xerostom® mouthwash. Xerostom® contains the ingredients listed in the table below.

Table 2.2
The composition of Xerostom®

Component	Function
Betaine	Lubricant
Olive oil	Anti-infective, coating and anti-caries effects. Prolong retention in the mouth.
Fluoride	Remineralisation
Calcium	Remineralisation
Xylitol	Control pH, prevents plaque formation and retention, inhibits *Streptococcus Mutans* and stimulates salivation.
Vitamin E	Antioxidant, limits mucositis.
Allantoin	Healing and regeneration properties.
Vitamin B5	Healing and soothing properties, prevents water loss through the mucosa.
Potassium	Limits tooth sensitivity
Citrus medica	Stimulates salivation

Betaine is a human amino-acid (trimethylglycerine). It is also present as a natural sugar beet extract with skin lubricating (Ship, 2007) and skin lubricating properties (Söderling, Le Bell, Kirsolä & Tenovuo, 1998). It also reduces skin irritation and when combined with sodium lauryl sulfate, a normal ingredient of toothpastes, has been found to improve xerostomia related complaints (Söderling *et al*, 1998). Betaine has an osmoprotecting effect against chemical and other irritants because of its ability to bind humidity from air. It's biggest use is in the cosmetics industry where it is used in skin, cosmetic and hair care products (Ship, 2007).

Allantoin, a uric acid derivative, promotes soft tissue healing and is clinically proven as a treatment for numerous dermatological conditions. It also has soothing, non-irritating and healing properties (Lubowe & Mecca, 1959).

Xylitol is an anticariogenic sweetener, controls pH, inhibits plaque adherence to tooth substance, promotes remineralisation and stimulates salivary flow rates (Masalin, 1992).

The sour taste of citrus medica is a gustatory stimulant and stimulates salivation (Ship, 2007).

The leaves and fruit of the plant *Olea europaea* is a source of olive oil (Bisignano, Laganá, Trombetta, Arena, Nostro, Uccella, Mazzanti & Saija, 2001). Olive oil contains long-chain aldehydes which have been proven to have antibacterial and antifungal effects. It therefore has the potential to have anti-infective properties (Bisignano *et al,* 2001). Plaque growth and adherence was inhibited by olive oil which will add to its protective effects against caries and gingivitis in patients suffering from xerostomia (Pretty, Gallagher, Martin, Edgar & Higham, 2003). The anticariogenic effect of olive oil might also be attributed to a covering effect of this substance. Oral

bacteria will also produce fewer acids, in the presence of lipids in the diet, in comparison with fermentable carbohydrates. These factors will result in an overall protective effect against caries and demineralisation. Olive oil also reduces attrition due to its covering and lubricating effects (Buchalla, Attin, Roth & Hellwig, 2003). When olive oil containing products were tested, significant improvements were also found in the reduction of halitosis (Kozlovsky, Goldberg, Natour, Rogatky-Gat, Gelernter & Rosenberg, 1996).

Vitamin B5 stimulates healing and it was also found to have an antibacterial effect and it stimulated epithelial growth (Kline & Caldwell, 1952). Vitamin B 5 also reduced water loss through the oral mucosa due to its hygroscopic properties as well as its barrier function (Gehring & Gloor, 2000).

Vitamin E was found to be helpful in the management of gingivostomatitis and its effect was studied for the management of mucositis. Vitamin E is an antioxidant, reduces the recovery time of mucositis and has anti-ageing properties (Wadleigh, Redman, Graham, Krasnow, Anderson & Cohen, 1992).

Fluoride is proven to have anticariogenic effects owing to its remineralising effects on decalcified enamel and dentine (Stookey, DePaola, Featherstone, Fejerskov, Möller, Rotberg, Stephen & Wefel, 1993).

Xerostom® is available to patients at a cost of R115 per 250ml bottle.

As far as could be established this was the first study, comparing the efficacy of locally available salivary substitutes, in South Africa.

2.4.9 Test period

The two different artificial saliva substitutes were tested in a prospective crossover randomised controlled trial.

The test substances Xerostom® and Sinspeek were presented in the same packaging to allow for blinding of the test subjects and marked as substance A or B respectively by an independent person.

Patients were provided with verbal instructions on the use of the salivary substitutes according to the manufacturers. Patients received 250ml artificial saliva for *ad libitum* use for a one-week period.

Patients were provided with a register, which had to be completed every time they used the salivary substitute, of which a copy is enclosed as appendix 4.

Data from this register was captured on the questionnaire and provided the information on how many times per day they used the salivary substitute.

An independent person allocated the patients to the relevant test group by means of the randomisation list to determine which test substance they will receive first. An independent person dispensed the relevant test substance and gave instructions to the patient on its usage.

The randomisation list was designed by utilizing Microsoft Excel® software with the help of an independent statistician.

An independent person indicated which substance was used first by using the code A or B on the questionnaire.

Patients were evaluated at baseline (Visit 1) and after each test period (Visit 2 and Visit 3) by means of the questionnaire to report on their level of xerostomia.

The test compound was used for one week by every patient. After using the first substance for one week an independent person collected the remaining test substance from the patients on the morning of the seventh test day (Visit 2) and the amount of artificial saliva used was calculated.

A washout period of six hours was allowed.

An independent person dispensed the next test substance, again giving the relevant instructions on its usage.

The independent person noted the second test substance on the questionnaire as A or B.

Patients again completed the register to determine how many times the artificial saliva was used per day.

At the end of the second test period (Visit 3) the amount of artificial saliva used was determined and captured.

The researcher was thus blinded to what substance the patient received at any time.

All questionnaires were filled in by the author. The information provided in the questionnaires was captured on a spreadsheet to provide the data for statistical interpretation.

Only after capturing the data was it possible for the author to establish in which sequence substances were tested for the different individuals.

2.4.10 Data Analysis

The data obtained from the questionnaires was entered in an Excel® spreadsheet. A statistician was consulted to analyse the data by utilising SPSS® software. Most of the measurements were nominal or ordinal in nature. Rates and proportions were calculated by utilizing the SPSS® software. The Chi-squared test was used to decide whether differences were statistically significant. In cases of ordinal measurements the Wilcoxon signed rank test was used to draw the relevant conclusions. Other applicable non-parametric techniques were used to investigate the patients' experience of the two different products. The results from this study will be compared to other appropriate literature.

2.4.11 Ethical Considerations

Approval for the study was obtained from the Research Ethics Committee of the University of the Western Cape. Informed consent was obtained from all participants after explaining the possible advantages, aim and procedures that were to be used.

Patient confidentiality was strictly enforced and patients were able to exit the study at any time for any reason without prejudice.

The test substances have been used extensively with no adverse reactions reported. Results will not be available for examination by any supplier prior to publication.

The author declares that he had no financial interest in any of the products used or tested in this study.

Chapter Three

Results

In Table 3.1 below the joint and marginal frequencies with respect to Gender and Treatment Order are noted. Furthermore, descriptive statistics such as the Mean Age, Standard Deviation, Minimum and Maximum are given in each respective cell four joint cells (AB, Male); (AB Female); (BA Male); (BA Female) and two marginal cells (AB Total); (BA Total).

Table 3.1
Descriptive Statistics with relation to the Age of 25 patients participating in the evaluation of two different salivary substitutes

		Gender		
Treatment order	**Data**	**Female**	**Male**	**Total**
AB	Number of subjects	6	7	13
	Average Age	62	56.	59.
	Standard Deviation	8.89	10.84	10.01
	Minimum	49	47	47
	Maximum	71	75	75
BA	Number of subjects	3	9	12
	Average of Age	58	59	59
	Standard Deviation	16.77	10.45	11.44
	Minimum	48	46	46
	Maximum	78	76	78

From table 3.1 it is apparent that the Average Age of the experimental group was 59. The average age of the males were 3 years older than the average age of the females. The patients in the two treatment groups (AB and BA) had similar Mean Ages. More Males were included in the study.

Table 3.2
Demographic data: Frequency Distribution of Tumour sites and Histology

Tumor sites	Frequencies		Tumour Histology	Frequencies
Mouth	11		Squamous Cell Carcinoma	21
Larynx	6		Adenocarcinoma	1
Hypopharynx	3		Acinic cell adenocarcinoma	1
Oropharynx	2		Lymphoepithelioma	1
Salivary Glands	2		Schwannoma	1
Maxillary Sinus	1			

From Table 3.2 above it is apparent that the majority of patients had cancer of the Oral Cavity, followed by the Larynx, Hypopharynx, Oropharynx, Salivary glands and the Maxillary sinus. The most common histological diagnosis was that of Squamous Cell Carcinoma though some rare tumours are also listed in the above table.

Table 3.3
Descriptive Statistics of the Radiation Dose for the complete group of 25 patients participating in the evaluation of two different salivary substitutes

Average Radiation Dose	36 Gy
Standard Deviation	3.35 Gy
Minimum	32 Gy
Maximum	44 Gy

From Table 3.3 above it is apparent that all the Radiation Doses ranged between 32 to 44 Gy and with a mean of 36 Gy. The Minimum Radiation Dose reported was 32 Gy and the Maximum Radiation Dose was 44 Gy.

Table 3.4
Descriptive Statistics of Salivary Flow Rates in ml/min

Gender	Data	Baseline	End of First Week	End of Second Week
Female	Number of Unstimulated Saliva	9	9	9
	Average of Unstimulated Saliva	0.29	0.35	0.27
	Standard Deviation of Unstim. Saliva	0.25	0.27	0.20
	Minimum of Unstim. Saliva	0.00	0.02	0.02
	Maximum of Unstim. Saliva	0.80	0.65	0.61
Male	Number of Unstimulated Saliva	16	16	16
	Average of Unstimulated Saliva	0.54	0.54	0.59
	Standard Deviation of Unstim. Saliva	0.41	0.35	0.41
	Minimum of Unstim. Saliva	0.08	0.08	0.06
	Maximum of Unstim. Saliva	1.33	1.09	1.66

From the data presented in Table 3.4 it is apparent that the Females' Average Unstimulated Salivary Flow Rates were consistently lower than that of the Males. The differences between the Baseline Unstimulated Salivary Flow Rates, Unstimulated Salivary Flow Rates after the First Test Week and Unstimulated Salivary Flow Rates after the Second Test Week did not vary significantly in either the Male or Female groups. The complaint of subjective xerostomia was reported by all the test subjects, but the objective measurements of the Average Unstimulated Salivary Flow Rates were consistently higher than 0,2ml/min in both Males and Females.

Table 3.5
Descriptive Statistics of the Average of the three Unstimulated Saliva collections with respect to Treatment Order and Gender in ml/min

		Gender		
Treatment order	**Data**	**Female**	**Male**	**Total**
AB	Number of saliva collections	6	7	13
	Average of Unstim. saliva collection	0.26	0.46	0.36
	Standard Deviation	0.17	0.31	0.27
	Minimum	0.03	0.09	0.03
	Maximum	0.45	0.89	0.89
BA	Number of saliva collections	3	9	12
	Average of Unstim. saliva collection	0.39	0.64	0.58
	Standard Deviation	0.31	0.37	0.36
	Minimum	0.04	0.10	0.04
	Maximum	0.59	1.30	1.30
Number of collections		9	16	25
Average of Unstimulated saliva collection Average		0.30	0.56	0.47
Standard Deviation		0.22	0.35	0.33
Minimum		0.03	0.09	0.03
Maximum		0.59	1.30	1.30

From table 3.5 above it was apparent that a clear tendency existed for a lower unstimulated salivary flow rate for the Females in comparison to the Males. This tendency was found regardless of which treatment sequence, (AB) or (BA), was followed.

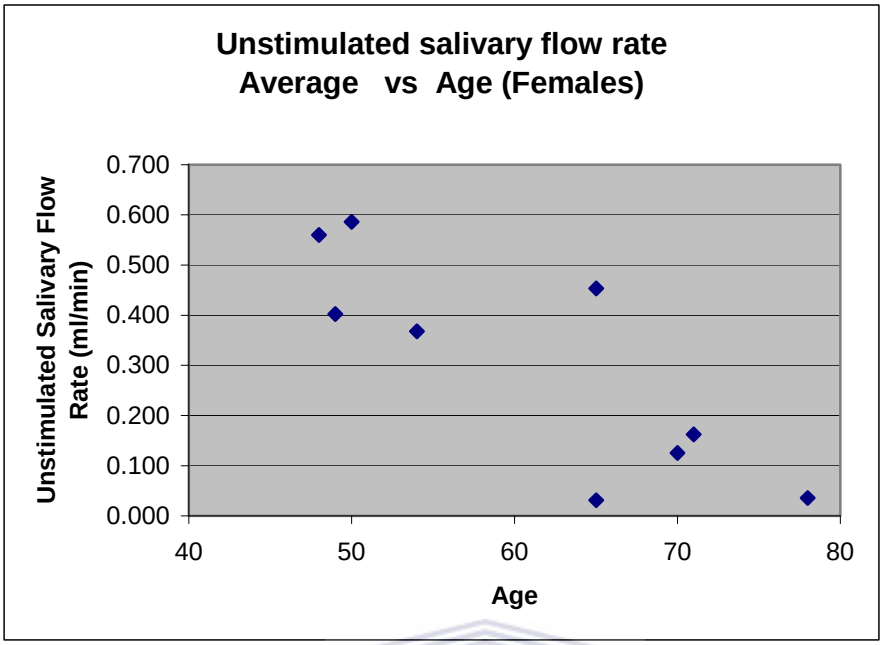

Figure 3.1
Scatter Plot of Average Unstimulated Salivary Flow versus Age for Females

From figure 3.1 above it was apparent that the age of the females did not play a role in the subjective reporting of xerostomia by the test subjects. Only four Females had objective measurements of xerostomia with a tendency towards the older age group. This tendency was not statistically significant.

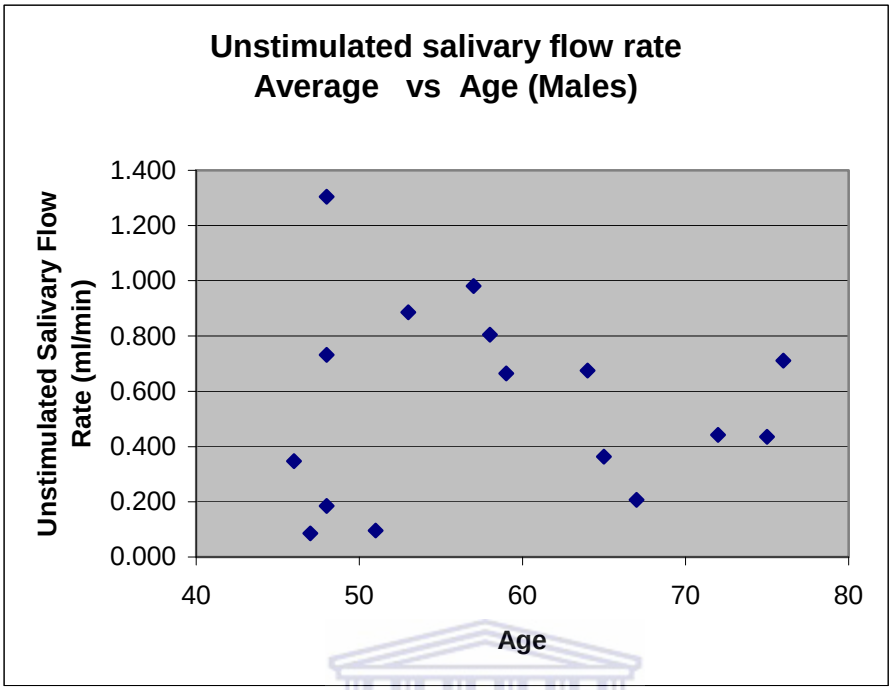

Figure 3.2
Scatter Plot of Average Unstimulated Salivary Flow versus Age for Males

Males reported subjective xerostomia related complaints more often than the Females. The Average Unstimulated Salivary Rate was not related to age for the Male patients. Only four Male patients had objective measurements of Average Unstimulated Salivary Flow rates consistent with a diagnosis of xerostomia and the distribution of these patients was not related to their age.

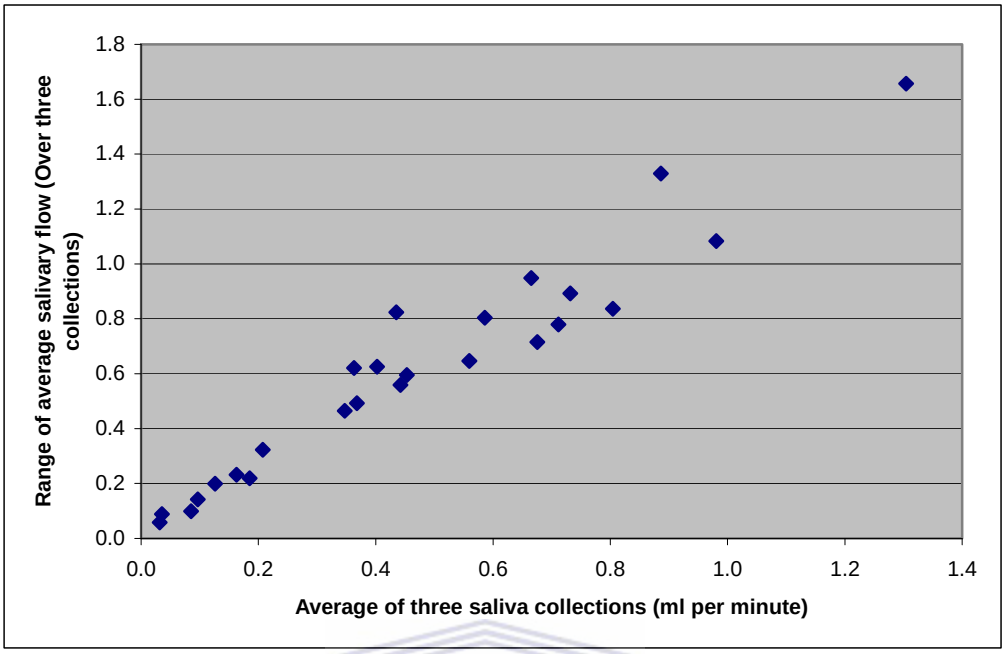

Figure 3.3
Average of three saliva collections (ml/per minute) versus the Range of these measurements

From the empirical distribution of the Average of the saliva collections it was clear that approximately 30% of these Averages were equal to or less than 0.2 ml/min, illustrating that the majority of patients participating in this study had a saliva flow rate of more than 0.2 ml/min. From figure 3.3 above it was clear that the Range of the three measurements increased directly proportional as the Average increased. With respect to variability (distributional properties) it was of importance that the Range was larger than all of the corresponding Averages of the three collections.

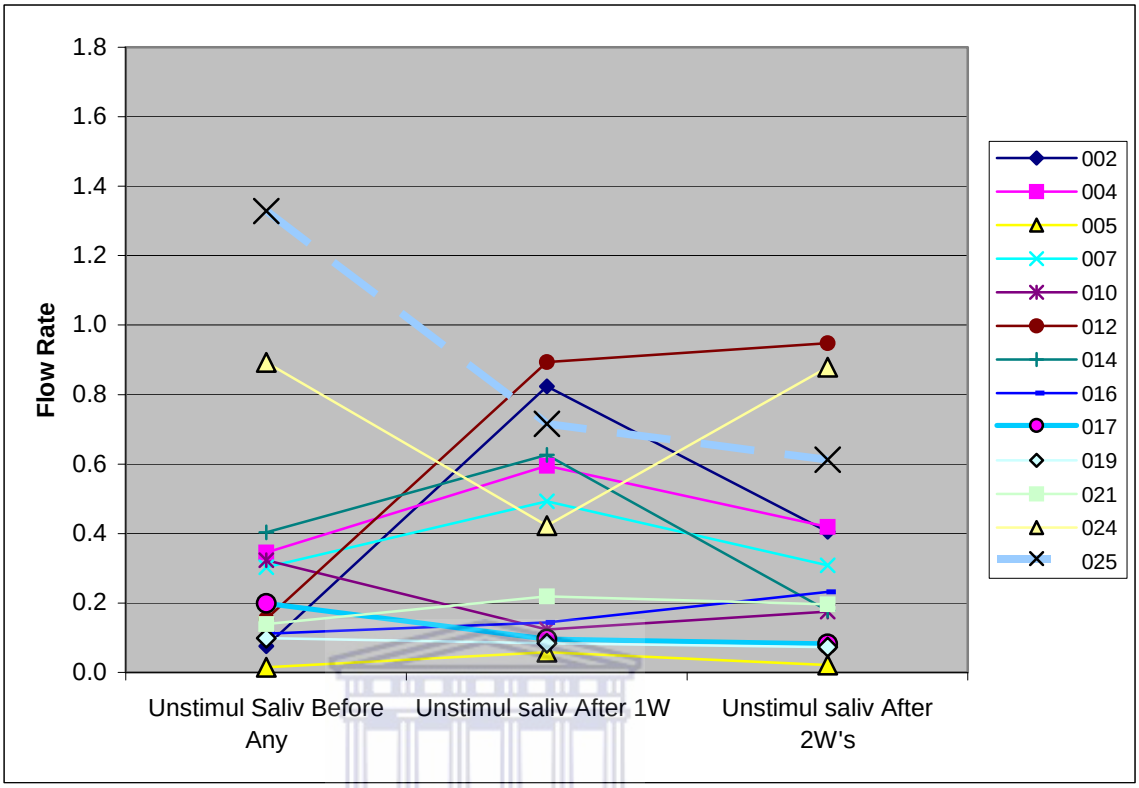

Figure 3.4
Salivary Flow Rate over Treatment AB Sequence

Figure 3.4 above depicted the salivary flow rates for baseline, after the first test period and after the second test period for the AB test group. It is apparent that the Unstimulated Salivary Flow Rates of none of the patients changed significantly over the course of the test period. Individual patients (25) and (12) showed major deterioration and improvements respectively, with regard to objective measurements of Unstimulated Salivary Flow Rates, but this was not of statistical significance.

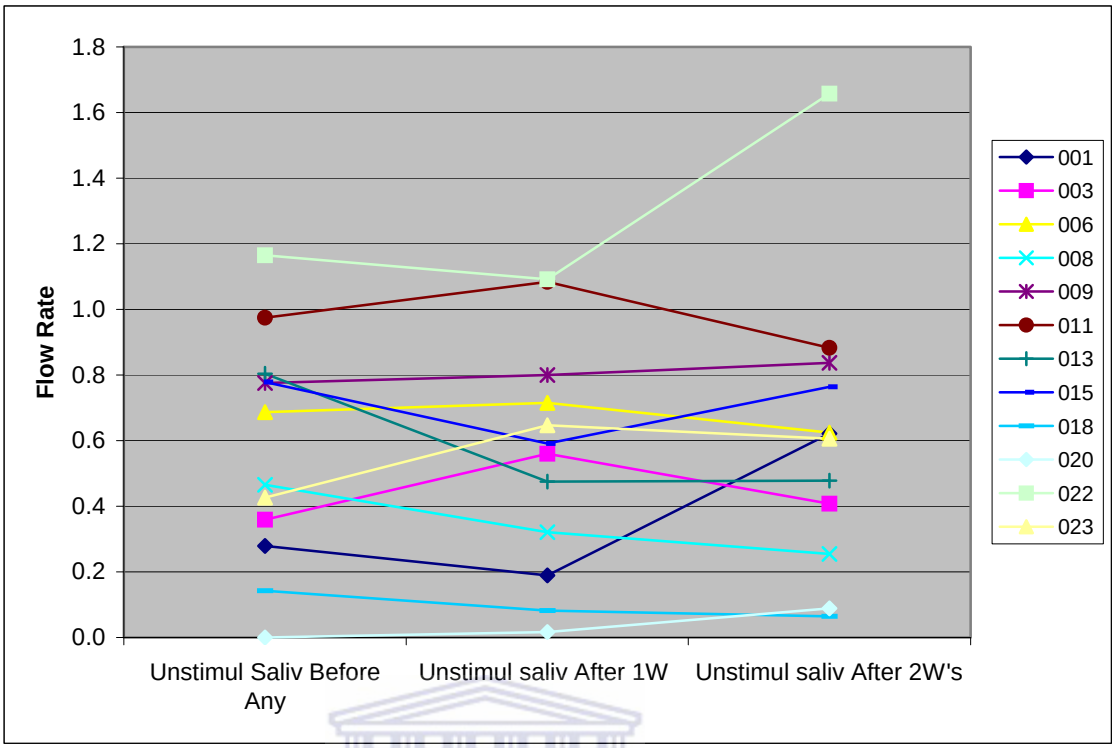

Figure 3.5
Salivary Flow Rate over Treatment BA Sequence

Figure 3.5 above depicted the Salivary Flow Rates at baseline, after the First and after the Second Test Period, for the BA test group. It was again apparent that the Unstimulated Salivary Flow Rates in none of the patients changed significantly over the course of the test period. Only one patient (22) showed a major improvement with regard to the objective measurement of Unstimulated Salivary Flow Rate, but this was not statistically significant. For the rest there were no statistically significant changes in Unstimulated Salivary Flow Rates over the duration of the test period.

From figures 3.4 and 3.5 above it was evident that only **nine** patients had Unstimulated Salivary Flow Rates of 0,2 ml/min or less at baseline; **eight** had Unstimulated Salivary Flow rates of 0,2 ml/min or less after the first treatment period and **eight** had Unstimulated Salivary Flow Rates of 0,2 ml/min or less after the second test period.

Table 3.6

Descriptive Statistics of the Range (Maximum minus Minimum) of the three saliva collections from 25 participants (ml/min)

Average of Range of three collections	0.61
Standard Deviation	0.40
Minimum Range	0.06
Maximum Range	1.66

Table 3.6 indicates that there were some patients with a low variability (Range) but even in these cases the corresponding Range was more than the Average.

Table 3.7

Descriptive Statistics of the Duration of Relief measured in Minutes experienced by the patients using artificial saliva A or B respectively during the **First Week** of the crossover study.

		Gender		
Treatment order	**Data**	**Female**	**Male**	**Total**
AB				
	Number of subjects with relief	6	7	13
(While using A)	Average of duration of relief	25.83	23.57	24.62
	Median	27.50	20.00	—
	Standard Deviation	11.58	18.87	15.34
	Minimum	15	0	0
	Maximum	45	60	60
BA				
	Number of subjects with relief	3	9	12
(While using B)	Average of duration of relief	20.00	32.56	29.42
	Median	30.00	27.50	—
	Standard Deviation	34.64	25.05	26.59
	Minimum	0	3	0
	Maximum	6	80	80

From the raw data it was evident that the participants in this study estimated the duration of Relief in rounded numbers for example five minutes, ten minutes, and so on. This again was a subjective estimation of the time they had relief from symptoms of a dry mouth.

In Table 3.7, in two of the four cells (both belonging to Males), the distribution of the Period of Relief was skewed towards the longer periods, comparing the Averages and Medians within each of the four cells.

For the females in two of the four cells the distribution of the Periods of Relief was skewed toward the shorter periods of relief, when comparing the Averages and Medians within the four cells.

A non-parametric test (Wilcoxon Signed Rank) was used to investigate whether the two Medians of Relief differs (the one reflecting the Relief from Product A and the other from Product B) of Relief differs. The paired differences were not statistically significant (p>0.05).

Table 3.8
Descriptive Statistics of the Duration of Relief measured in Minutes experienced by the patients using artificial saliva A or B respectively during the **Second Week** of the crossover study

		Gender		
Treatment order	**Data**	**Female**	**Male**	**Total**
AB				
	Number of patients with relief	6	7	13
(While using A)	Average of duration of relief	23.83	25.00	24.46
	Median	20.00	20.00	—
	Standard Deviation	23.46	17.56	19.59
	Minimum	3.00	10.00	3.00
	Maximum	70.00	60.00	70.00
BA				
	Number of patients with relief	3	9	12
(While using B)	Average of duration of relief	15.00	43.33	36.25
	Median	15.00	20.00	—
	Standard Deviation	5.00	30.52	29.09
	Minimum	10.00	5.00	5.00
	Maximum	20.00	80.00	80.00

As can be seen from table 3.8 above, the distribution of the period of relief is skewed towards the longer periods in all four cells (Median less or equal to the Averages), indicating that some subjects made more liberal estimates. The result of the Wilcoxon Signed Rank Test confirmed that there was no difference between the reliefs reported between the test subjects.

Table 3.9a
The joint Frequency Distribution of the Dry Mouth complaint prior to the First Treatment Period and After the First Treatment Period (Treatment order AB)

Treatment order	**AB**

Count	**Complaints - Dry Mouth_Post 1st Treatment**				
Complaints - Dry Mouth_Pre Any	1_None	2_Minor	3_Moderate	4_Severe	Total
1_None					
2_Minor	1		2		3
3_Moderate		2	3		5
4_Severe		2	1	2	5
Total	1	4	6	2	13

For the AB group, in Table 3.9a, the diagonal cells were indicated by means of yellow and their condition did not change with respect to the First Treatment Period (5 patients). The presence of subjects above the diagonal indicate that their subjective estimations of dry mouth deteriorated during the First Treatment Period (2 patients), and the condition improved for those individuals counted below the diagonal of the frequency table (6 patients). The improvement of the 13 patients using Product A (first) was not statistically significant.

Table 3.9b
The joint Frequency Distribution of the Dry Mouth complaint prior to the First Treatment Period and After the First Treatment Period (Treatment order BA)

Treatment order	**BA**

Count	**Complaints - Dry Mouth_Post 1st Treatment**				
Complaints - Dry Mouth_PreAny	1_None	2_Minor	3_Moderate	4_Severe	Total
1_None					
2_Minor		2	2		4
3_Moderate		1	4	1	6
4_Severe			2		2
Total		3	8	1	12

For the BA group, the condition of six patients did not change over the Second Period with relation to Dry Mouth, three deteriorated and three improved. Clearly the improvement showed no statistical significant difference.

Table 3.9c
The joint Frequency Distribution of the Dry Mouth complaint After finishing the First Treatment Period and After completing the Second Treatment Period (Treatment order AB)

Treatment order	**AB**

Count	**Complaints - Dry mouth_Post 2nd Treatment**				
Complaints - Dry Mouth_Post 1stT	1_None	2_Minor	3_Moderate	4_Severe	Total
1_None		1			1
2_Minor	1	2	1		4
3_Moderate	1	2	3		6
4_Severe		1		1	2
Total	2	6	4	1	13

The condition of six patients did not change over the Second Period with relation to Dry Mouth, two deteriorated and five improved. There was no statistical significance in this finding.

Table 3.9d
The joint Frequency Distribution of the Dry Mouth complaint After finishing the First Treatment Period and After completing the Second Treatment Period (Treatment order BA)

Treatment order	**BA**

Count	**Complaints - Dry mouth_Post 2ndtTreatment**				
Complaints - Dry Mouth_Post 1stT	1_None	2_Minor	3_Moderate	4_Severe	Total
1_None					
2_Minor	1	1	1		3
3_Moderate		4	4		8
4_Severe		1			1
Total	1	6	5		12

The condition of five patients did not change over the Second Period with relation to Dry Mouth, one deteriorated and six improved. Again no statistical significance was found in this finding.

Table 3.10a
Pearson Correlation Matrix of the AB Group of seven measurements including two derived measurements, Unstimulated Salivary Collection Average (from three collections) as well as the Range thereof

AB	Unstimul Salivary Coll. A	Unstimul Salivary Coll. B	Unstimul Salivary Coll. C	Unstimul S. Coll. Average	Range A to C	Relief First Week	Relief Second Week
Unstimul Salivary Coll. A	1						
Unstimul Salivary Coll. B	0.3410	1					
Unstimul Salivary Coll. C	0.5156	0.7099	1				
Unstimul S. Coll. Average	0.7875	0.8026	0.8822	1			
Range A to C	0.7405	0.8606	0.8230	0.9780	1		
Relief First Week	-0.5313	-0.0859	0.0971	-0.2439	-0.2443	1	
Relief Second Week	0.1171	0.3654	0.1448	0.2470	0.3041	-0.4071	1

It was noteworthy that if the patient produced a considerable salivary flow before the start of the study it was likely that he or she had less Relief at the end of the First Week. When patients had advanced salivary hypofunction with poor unstimulated salivation before the start of the first treatment it was likely that they experienced more Relief at the end of the

First Week (only significant at the 10% level). For the treatment order AB the implication of the negative correlation between the Relief of the First and Second Treatment was that if the patient received a long Relief in the First Week the Relief of the Second Treatment Period was shorter, and when patients had short Relief in the First Week they experienced longer Relief in the Second Week.

Table 3.10b
Pearson Correlation Matrix of the BA Group of seven measurements including two derived measurements, Unstimulated Salivary Collection Average (from three collections) as well as the Range thereof

BA	Unstimul Salivary Coll. A)	Unstimul Salivary Coll. B)	Unstimul Salivary Coll. C)	Unstimul S. Coll. Average	Range A to C	Relief First Week	Relief Second Week
Unstimul Salivary Coll. A	1						
Unstimul Salivary Coll. B	0.8980	1					
Unstimul Salivary Coll. C	0.8493	0.8431	1				
Unstimul S. Coll. Average	0.9562	0.9541	0.9490	1			
Range A to C	0.9272	0.8861	0.9678	0.9757	1		
Relief First Week	0.1260	-0.2301	-0.0675	-0.0614	0.0312	1	
Relief Second Week	-0.2287	-0.2993	-0.4184	-0.3384	-0.3715	0.4066	1

In the AB Group it is worthwhile to observe that the correlation between the Relief experienced from the First Treatment was negatively related to the Relief experienced from the following Second Treatment (Pearson Correlation = -0.4071; Spearman Rank Correlation = -0.4231), compared to the corresponding positive correlation for the BA Group (Pearson Correlation = 0.4066; Spearman Rank Correlation = 0.4688). For the BA Group the relationship between the Relief obtained from the respective products was positive, in comparison with the AB Group, which was negative. The Relief obtained from B offered positive predictability for Relief from A. When changing the order of usage to AB the expected Relief from B could not be positively predicted (in fact, it was negative).

Table 3.11
Four tables combining Treatment Order as well as the Final Preference of the participants; the subjective choice after using the relevant test substance is shown within each of the two-by-two sub-tables

Treatment order	**AB**
Gender	(All)
Prefer Prod **at end**	A

Count of Name	Go on using B		
Go on using sub A	**No**	**Yes**	**Total**
No	0	0	0
Yes	5	2	7
Total	5	2	7

Treatment order	**AB**
Gender	(All)
Prefer Prod **at end**	B

Count of Name	Go on using B		
Go on using sub A	**No**	**Yes**	**Total**
No	0	3	3
Yes	0	3	3
Total	0	6	6

Treatment order	**BA**
Gender	(All)
Prefer Prod **at end**	A

Count of Name	Go on using A		
Go on using sub B	**No**	**Yes**	**Total**
No	0	6	6
Yes	0	3	3
Total	0	9	9

Treatment order	**BA**
Gender	(All)
Prefer Prod **at end**	B

Count of Name	Go on using A		
Go on using sub B	**No**	**Yes**	**Total**
No	0	0	0
Yes	1	2	3
Total	1	2	3

The discussion of the four sub-tables will be performed by concentrating on the top two tables where the treatments order was AB (summing the table totals resulted in 13 subjects). It was found that of the 13 subjects using the AB sequence seven preferred Product A after both test periods and six (in the right-hand table) preferred Product B at the end of both periods. All seven of these subjects would continue with Product A and of the other six (in the right-hand table); only three would prefer to continue with Product A.

The information (opinions) contained in the second row of two-by-two tables would now be discussed. The treatment order was BA (summing of the table totals resulted in 12 subjects). Of the 12 subjects using the BA sequence, nine preferred to use product B after the first treatment period, but after the second treatment period three of these patients had a preference for product A. This could be due to the fact that it was a while since they experienced the characteristics of product B. The preference for the respective products was not of statistically significant importance.

Table 3.12a
Frequency table of Preferences of subjects after experiencing both products (Treatment order AB)

Treatment order	***AB***

Count	Gender		
Prefer Product	Female	Male	Total
A	3	4	7
B	3	3	6
Total	6	7	13

For the AB Group seven patients preferred Product A and the remainder of the 13 in this group preferred Product B. It is necessary to keep in mind that they have stopped using Product A at least seven days before they expressed their preference. It was possible that they could not clearly remember the effect of Product A at that stage. For this particular group there was no clear-cut preference for Product A or B.

Table 3.12b
Frequency table of Preferences of subjects after experiencing both products (Treatment order BA)

Treatment order	***BA***

Count	Gender		
Prefer Product	Female	Male	Total
A	3	6	9
B	0	3	3
Total	3	9	12

Nine patients in the BA Group preferred Product A and the remainder (three) of the 12 in this group preferred Product B. It is necessary to keep in mind that they have stopped using Product B at least seven days before they expressed their preference. It was possible that they could not clearly remember the effect of Product B at that stage. Under the assumption (null hypothesis) of equal preferences for the two products the probability of such an outcome (nine for A and three for B) was 0.146 (two-sided). This could result in patients reporting on their desired preference when the BA sequence was used in either way (B) or (A) and was not of statistical significance.

Not one of the test substances A or B was found to be statistically significantly superior in comparison to the other.

Chapter Four

Discussion and Conclusions

4.1 Discussion of results

During the data collection period three individuals exercised their right to withdraw from the study. All of these individuals provided whole unstimulated saliva samples at baseline, questionnaires were completed and patients were provided with their first test substance. At the second visit all three individuals withdrew from the study. They had not used any of the substitutes. One patient withdrew because she was not prepared to complete a log of when the test substance was used. Another patient said she was confused with the whole process and was not prepared to participate. The third patient was worried that the test substance would aggravate his radiation induced mucositis and was not prepared to risk using our test substance to alleviate his xerostomia. Patients who withdrew from the study were replaced by individuals that fulfilled the inclusion and exclusion criteria and were prepared to participate in the study according to methodology of this study. Radiotherapy was provided with three different radiotherapy units. During our study period maintenance work was carried out on one machine and another machine was shut down to carry out essential repairs. Therefore only 25 patients who satisfied the inclusion and exclusion criteria, and who were prepared to participate in the study, could be recruited in the data collection period.

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The average age of the test group approached 60 years of age. The youngest patient was 48 and the oldest patient 78 years of age. The males in our test population were on average three years older than the females, but this was not statistically significant. In this study population the females showed a tendency to develop cancer earlier than the males, although this was not statistically significant.

The mouth was the most common tumour site with 11 patients affected. The larynx was the second most common affected area with six patients affected followed by the hypopharynx affected in three patients, oropharynx in two patients and the maxillary sinus in one patient. Of the 25 patients, 21 were diagnosed histologically with squamous cell carcinomas. There were also single subjects with adenocarcinoma, acinic cell adenocarcinoma, lymphoepithelioma and a schwannoma.

The participants in our test group have all completed a radiation treatment program of four weeks in the Tygerberg Radiotherapy Department. Patients receive a daily dose of 2 Gy and by the time they have completed a four week course of radiotherapy they would have received a cumulative dose of at least 32 Gy. The average radiation dose received in this group was 36,35 Gy with a maximum of 44,26 Gy and a minimum of 32 Gy. Radiation doses of this magnitude are responsible for irreversible salivary hypofunction and the stimulated as well as unstimulated salivary flow rates are affected (Porter *et al,* 2004; Regelink *et al,* 1998)

Not all patients approached to join the study had subjective xerostomia related symptoms and so they were not included in our study group. All the patients in our test group had radiotherapy related complications by the end of the fourth week of radiotherapy which included pain, mucositis, loss of taste, xerostomia, oral discomfort and they felt generally unwell. Patients received palliative medications to limit pain and discomfort. Where fungal and bacterial infections were diagnosed, they were managed appropriately.

Most of the measurements used to evaluate the responses to the artificial saliva were subjective to a more or lesser extent. It was interesting to note that the females in our study population had average unstimulated salivary collections which were lower than those found in the males. The average unstimulated salivary collections were still at a level higher than that accepted for an objective diagnosis of xerostomia. It is accepted that the unstimulated salivary flow rate should be no more than 0,2 ml/min for such a diagnosis (Navazesh *et al,* 1992). It also showed that the males had subjective complaints of xerostomia with even higher unstimulated salivary secretions. In the test group about 70% of patients did not have objective unstimulated salivary flow rates diagnostic of xerostomia. 70% of patients had unstimulated salivary flow rates of greater than 0,2 ml/min. This proportion of patients without concrete measurements implicating xerostomia was much higher than reported by Frost *et al,* (2000) where 35% of patients were reported to have no objective evidence of xerostomia. Females had consistently lower average unstimulated salivary flow rates than males in our test population regardless of which test substance they used first, (A) or (B). Nine females were included in our study group and of these only four had objective unstimulated salivary flow rates of less than 0,2 ml/min. On average these females were of older age, but this was not statistically significant. Of the 16 males only four had objective unstimulated salivary flow rates of less than 0,2 ml/min. Males tended to complain of xerostomia in the presence of higher unstimulated salivary flow rates compared to the females, but this was not statistically significant. It might have been worthwhile to have taken unstimulated salivary collections of patients before they commenced radiation therapy. This would have been useful to determine whether patient's salivation decreased from the radiation. Frost *et al* (2002) & Ghezzi *et al* (2000) suggested that an unstimulated whole salivary flow rate of 50% of the usual flow rate could be used to make an objective diagnosis of xerostomia rather than a measurement of the differences between individuals.

During the collection of samples it was often possible to identify those patients who produced significant amounts of saliva although they complained of xerostomia related symptoms. The consistency of this saliva was often very watery and sometimes very viscous. This suggested that it is not always the amount, but often the consistency and composition of saliva which gives rise to subjective complaints of xerostomia (Thomson *et al,* 1998; Samarawickrama, 2002).

There were no significant differences between unstimulated salivary collections taken at baseline, after the first test period and after the second test period. It was expected that further radiation therapy during the first and second treatment periods would further reduce salivation, but this was not the case. It was also hypothesized that the use of a salivary substitute might increase unstimulated salivary secretions as seen in a study by McMillan *et al* (2006), but this was not seen in our study population.

The subjective complaints of xerostomia were evaluated by asking questions with relation to “dry mouth”, “difficulty speaking”, “difficulty chewing”, “difficulty swallowing”, “dry mouth when sleeping”, “taste disturbance” and “pain or burning sensation”. Al of these were graded by the patients according to severity “none”, “minor”, “moderate” and “severe”. From the statistical evaluation it was found that the only xerostomia related question which showed some relevance was that of “dry mouth”.

After data capturing, the code to which was test substance (A) and which test substance (B), held by our independent person, was revealed. Substance A was identified as Sinspeek and substance B was Xerostom®.

In the test population using the AB sequence, six patients experienced improvements for “dry mouth” over the first week, five reported no changes and in two patients the dry sensation increased. In this AB group, five patients improved, six remained the same and two deteriorated during the

second test period. There was no statistical significance in these findings with regard to which test substance gave superior relief for “dry mouth”.

For the BA sequence group there were three patients with improvements, six with no change and three deteriorated with regard to “dry mouth” during the first test week. During the second test week, for this group, six patients showed improvements, five with no change and one deteriorated with regard to “dry mouth”. Again there was no statistically significant difference between the two products for the relief of “dry mouth”.

Patients also reported on the duration of relief from the salivary substitutes, in a subjective manner. Time intervals reported by the subjects ranged in compartments of five and ten minutes. There were two males who reported prolonged time of relief, completely outside the range reported by other patients. Neither test substance was found to be superior to the other with relation to the time of relief obtained. There was not statistically significant proof that any of the test substances was superior to the other with regard to “relief”.

When patients had unstimulated whole salivary flow rates above that accepted for a diagnosis of xerostomia, there was less relief from the test substances. Those subjects who had salivary gland hypofunction clearly reported more “relief” from their xerostomia when using a salivary substitute. Patients in the AB group had more relief from Sinspeek when they had salivary gland hypofunction, but only at a significance level of 10%. Subjects in the AB group also reported poor relief from Xerostom® after they had long periods of relief from Sinspeek during the first week. Patients in his group who reported short relief from Sinspeek in the first week had a tendency to report longer relief from Xerostom® in the second test week. Relief in the first treatment period was thus negatively correlated to that of the second treatment period.

In the BA group the correlation was found to be positive, so patients who experienced relief from the test substance in the first period could be

positively predicted to have relief from the second test substance too. Both the Pearson Correlation Test and the Spearman Rank Correlation Test confirmed these tendencies.

When patients indicated that they would like to continue using a specific test compound, the sequence in which the substances were used played a role. This might be owing to the fact that by the time they had used the second test substance, they had forgotten the effect of the first substance. This could have influenced their favoring of the last test substance.

All the patients in this study group suffered from other radiation induced oral complications, the most common being mucositis and pain. Some patients with mucositis reported that Xerostom® caused a burning sensation, which influenced them to use this product less. This finding was not significant. Similarly some patients disliked Sinspeek because it made their saliva more viscous and they also disliked the consistency and taste. Again there was no statistical significance. Sixteen patients preferred Sinspeek and this was the preferred saliva substitute at the end of both test periods; but there was no statistical significance in the manner in which patients reported their preferences. All patients reported that they would like to carry on using a salivary substitute to relieve xerostomia-related complaints.

The Null Hypothesis was proven to be correct for this study. It was concluded that both test products were found to be equally useful in the management of xerostomia, with no statistically significant difference between Sinspeek and Xerostom®.

4.2 Conclusions

Correct management strategies for patients with cancer of the head and neck are helpful in limiting oral disease and discomfort. Management therefore be before, during and after radiotherapy to limit the complications of radiation induced xerostomia (Meyerov & Touyz, 1987).

Every individual should be able to enjoy everyday life, to do everyday tasks, and to interact with other people. When persons manage to do this, they are in a state of well-being and is referred to as “quality of life”.

Perceptions of quality of life (QOL) vary between individuals and the evaluation of this should be based on these individual perceptions (Epstein, Robertson, Emerton, Phillips and Stevenson-Moore, 2001). Cancer alone will affect the QOL of patients, and treatment of head and neck cancer has numerous adverse effects so that QOL will certainly be affected in different ways for each individual. The older the patient the more their QOL is affected and the QOL in patients, who suffered from therapy related complications like pain, dysphagia and speech impediments occurring after radiotherapy of the head and neck will adversely affect QOL. In certain patients the complaints of post treatment pain will not subside for as long as 6 months after radiation. Mucosal sensitivity and dysphagia will affect the food patients prefer and could lead to malnutrition and loss of the enjoyment of eating. Xerostomia was a complaint of 95% of patients of whom almost three quarters complained of severe xerostomia (Epstein *et al,* 2001).

The longer a patient survives after cancer the more satisfied with life he or she becomes.

Products alleviating the symptoms of xerostomia are an important part in the management of these patients. The range of products available in South Africa has improved in recent years. Prescribing of medicaments for

pathological conditions would seem to be a simple matter, but this is often not the case where QOL is important and patients have financial limitations. Almost all salivary substitutes are classified as toiletries and some as food substitutes. For these reasons health care funders are reluctant to cover the cost of these preparations (Price, 2003).

The benefit of salivary substitutes to ameliorate the effects of xerostomia is well established and proper advice and access to relevant preparations is essential. There are variations in preference for certain substances between individuals. It could help to use samples of different salivary substitutes so that patients could decide which substitute they prefer. Favorable characteristics which improve xerostomia alone will not guarantee that patients will prefer such a product and factors such as taste and cost could be more important (Epstein & Stevenson-Moore, 1992).

It is encouraging to see that some pharmaceutical companies are now importing different salivary substitutes into South Africa, which will lead to a bigger range of products from which the patients could choose.

4.3 Future extensions

Potential future extensions of this project would be to test some of the other salivary substitutes locally available, as well as to compare the efficacy of different types of preparations like gels, toothpastes or sprays.

4.4 Limitations

In a study by Momm *et al* (2005) a period of four weeks after radiotherapy was allowed for the early and late effects of the radiotherapy to manifest. Patients undergoing radiotherapy are generally unwell and it might be advantageous to consider postponing testing for some longer period after radiotherapy to allow for general healing of radiation induced complications, before testing saliva substitutes.

Owing to social and economic factors relevant to this study group it was not possible to expect patients to return at regular intervals merely to complete a questionnaire. Many of the participants of this study were illiterate and supervision was necessary with the filling in of questionnaires. These were the main reasons why a healing period was not allowed after radiation treatment, because they would not be under treatment for a period which would coincide with the study period.

During the planning of this study it was calculated that more than 15 patients were needed to make the conclusions statistically meaningful than the study by Momm *et al* (2005). On the advice of an independent statistician it was decided to use a study population of 30 patients. When the results were evaluated it became clear that owing to the subjective nature of the reporting on levels of xerostomia in fact it would be necessary to use an even larger study population to arrive at statistically significant conclusions. The test group of only 25 subjects is thus an acknowledged shortcoming of the study.

Only preparations available as rinses were used here to make it possible to design the study as a double blind retrospective study. It was not feasible to include all saliva substitutes available in South Africa in this study.

4.5 Appendix 1:

Patient information document

Title of project: A comparison of two salivary substitutes in the management of xerostomia during radiotherapy for cancer of the head and neck.

Reference number: 06/9/16

Principal investigator: Dr Johann Lochner

Address: Department of Oral medicine and Periodontology
Faculty of Dentistry
University of the Western Cape
Private Bag XI
Tygerberg 7505

Aim:
The aim of this study is to compare the palliative efficacy of two locally available salivary substitutes in patients during radiotherapy for head and neck cancer.

Procedures:
Patients who complain of a dry mouth will be asked to join the study. Dr Lochner will fill in a questionnaire after questioning patients. All patients will receive a dental examination and be referred for dental treatment if necessary. A test will be done to establish how dry the patient's mouth is by collecting saliva expectorated into a bottle after four and five weeks of radiotherapy. Patients will receive two saliva substitutes for a week each and after each test week questions will be asked again and the questionnaire completed by Dr Lochner. After both saliva substitutes are tested the questionnaire will be finalized.

Possible advantages:
Patients receiving radiotherapy often complain of a dry mouth. They usually drink fluids to alleviate the symptoms of the dry mouth. Some patients could benefit from using a saliva substitute for the symptoms of a dry mouth.

The substances used as saliva substitutes have all been tested before and are safe to use. Very few adverse reactions have been reported.

After completion of the study, patients will receive advice about the different substitutes used and where they could purchase them.

There would be no costs involved for the patients who participate in this study. There will not be any remuneration for patients participating in the study nor will they be given free saliva substitutes after completion of the study.

4.6 Appendix 2:

Informed consent document

Title of research project:

A comparison of two salivary substitutes in the management of xerostomia during radiotherapy for cancer of the head and neck.

Reference number: 06/9/16

Principal investigator: Dr Johann Lochner

Address: Department of Oral Medicine and Periodontology
Faculty of Dentistry
University of the Western Cape
Private Bag XI
Tygerberg 7505

DECLARATION BY OR ON BEHALF OF THE PATIENT/PARTICIPANT

I, the undersigned, ……., ID number,……., the patient/participant or in my capacity as ……..of the patient/participant, ID number……..…., of ……(address),

A. CONFIRM THE FOLLOWING:

1. I, the patient/participant, was invited to take part in abovementioned research project which took place at: The Tygerberg Hospital
2. The following aspects were explained to me, the patient/participant:

2.1 Aim

2.2 Procedures

2.3 Alternatives

2.4 Risks

Materials: No known risks.
Routine sterile protocols will be followed.
Possible advantages: Symptoms of xerostomia are likely to be improved.

2.5 Confidentiality

The identity of the patient/participant will not be disclosed nor will the identity be disclosed in any future publication.

2.6 Access to results

The patient/participant will have access to the results, once these have been analysed and published, by contacting the researchers.

2.7 Voluntary participation/refusal/termination

Participation in the project is voluntarily. The patient/participant or his/her representative can refuse participation or can terminate participation at any stage of the study. The termination of participation will have no detrimental effect on any further or future treatment of the patient/participant at this institution. The researcher can also terminate the participation of the patient/participant if this seems to be in the best interest of the patient/participant.

3. The information was supplied and explained by Dr Lochner in English/Afrikaans and I confirm that I understand the English/Afrikaans language. If I did not understand the explanation by Dr Lochner in these languages, an interpreter was engaged to translate the explanation in the language of my preference.
4. I was not forced to consent to participate and I understand that I can terminate participation at any time without any penalization whatsoever.
5. Participation to the project will have no additional costs for me, the patient/participant.

B. AGREE VOLUNTARILY TO PARTICIPATE IN THE ABOVEMENTIONED PROJECT/ALLOW THE PATIENT TO PARTICIPATE IN THE ABOVEMENTIONED PROJECT. GIVE MY CONSENT THAT INFORMATION GATHERED FROM THIS STUDY BE USED FOR FUTURE STUDIES AND PUBLICATIONS.

Signed/consent at The Tygerberg Hospital on……..2007.

Signature or right thumb print of patient or representative of patient/participant

Signature of witness

DECLARATION BY RESEARCHER

I, Johann Georg Lochner, declare that

- I explained the content of this document to ……..or her/his representative;
- I encouraged the patient/participant to ask questions and that enough time was allowed to ask questions;
- I communicated in the English language and that no translator/a translator was used.

Signed at the Tygerberg Hospital ……2007.

…… ……
Signature of researcher Signature of witness

DECLARATION BY TRANSLATOR

I, ……., confirm that I

- translated the content of this document from English to ……for the patient/participant or his/her representative;
- explained the content of this document to the patient/participant or his/her representative;
- translated the questions asked by the patient/participant or his/her representative as well as the answers provided by the researchers;
- gave a factual correct interpretation of all communicated information.

Signed at the Tygerberg Hospital …… 2007.

……..
……..
Signature translator Signature witness

IMPORTANT MESSAGE TO THE PATIENT/PARTICIPANT OR HIS/HER REPRESENTATIVE

Dear patient/representative of the patient

Thank you for your participation to this project. If you request any further information regarding this project or if any discomfort/emergency should arise as a result of this project you can contact me, Dr J G Lochner, at the following numbers:
021 9373168 during office hours
0724197792 outside office hours

4.7 Appendix 3:

Randomisation list

Subject#	Start treatment	Second treatment
1	**B**	**A**
2	**A**	**B**
3	**B**	**A**
4	**A**	**B**
5	**A**	**B**
6	**B**	**A**
7	**A**	**B**
8	**B**	**A**
9	**B**	**A**
10	**A**	**B**
11	**B**	**A**
12	**A**	**B**
13	**B**	**A**
14	**A**	**B**
15	**B**	**A**
16	**A**	**B**
17	**A**	**B**
18	**B**	**A**
19	**A**	**B**
20	**B**	**A**
21	**A**	**B**
22	**B**	**A**
23	**B**	**A**
24	**A**	**B**
25	**A**	**B**
26	**B**	**A**
27	**A**	**B**
28	**B**	**A**
29	**B**	**A**
30	**A**	**B**

4.8 Appendix 4:
Questionnaire

Salivary substitute study

1. Patient information

Patient no:
Name:
Address:

Tel no:
File no:

Gender: Male | Female

Age:
Today's date: d d m m y y

Commencement of radiation (date)
Radiation dose (Gy) received to date

2. Medication

3. Tumour Site (Tick appropriate box)

Oropharynx	Hypopharynx	Mouth	Larynx	Nose

Salivary glands	Thyroid	Cervical lymphatic nodes

Unknown primary

4. Histology

Squamous cell carcinoma	Adeno-carcinoma	Lymphoma

Other

5. Do you use anything for your dry mouth — Yes | No

6. If 'yes' what do you use?

7. Xerostomia related questions at baseline (Tick appropriate box)

Complaints

Dry mouth	None	Minor	Moderate	Severe
Difficulty speaking	None	Minor	Moderate	Severe
Difficulty chewing	None	Minor	Moderate	Severe
Difficulty swallowing	None	Minor	Moderate	Severe
Dry mouth when sleeping	None	Minor	Moderate	Severe
Taste disturbance	None	Minor	Moderate	Severe
Pain or burning sensation	None	Minor	Moderate	Severe

Unstimulated saliva collection _____ **g**

8. Product used in first treatment period

Product A	**Product B**

Amount dispensed _____ **g**

Commencement of saliva treatment (date)

d	d	m	m	y	y

Complaints after first treatment period

Dry mouth	None	Minor	Moderate	Severe
Difficulty speaking	None	Minor	Moderate	Severe
Difficulty chewing	None	Minor	Moderate	Severe
Difficulty swallowing	None	Minor	Moderate	Severe
Dry mouth when sleeping	None	Minor	Moderate	Severe
Taste disturbance	None	Minor	Moderate	Severe
Pain or burning sensation	None	Minor	Moderate	Severe

Unstimulated salivary collection _____ **g**

Additional questions after first treatment period

What was the effect of the saliva substitute on your mouth?

None	Minor	Moderate	Favourable

How long does the relief stay after an application? _____ Minutes

Amount of artificial saliva returned _____ **g**

How do you rate the tested compound?

(i)	In general	Very Bad	Bad	Acceptable	Pleasant
(ii)	In taste	Very Bad	Bad	Acceptable	Pleasant

Would you like to go on using the test substance?

Yes	No

9. Product used in second treatment period

Product A	Product B

Amount dispensed _____ **g**

Commencement of saliva treatment (date) d d m m y y

Complaints after second treatment period

Dry mouth	None	Minor	Moderate	Severe
Difficulty speaking	None	Minor	Moderate	Severe
Difficulty chewing	None	Minor	Moderate	Severe
Difficulty swallowing	None	Minor	Moderate	Severe
Dry mouth when sleeping	None	Minor	Moderate	Severe
Taste disturbance	None	Minor	Moderate	Severe
Pain or burning sensation	None	Minor	Moderate	Severe

Unstimulated saliva collection _____ **g**

Additional questions after second treatment period

What was the effect of the saliva substitute on your mouth?

None	Minor	Moderate	Favourable

How long does the relief stay after an application? _____ Minutes

Amount of artificial saliva returned _____ **g**

How do you rate the tested compound?

(i)	In general	Very Bad	Bad	Acceptable	Pleasant
(ii)	In taste	Very Bad	Bad	Acceptable	Pleasant

Would you like to go on using the test substance?

Yes	No

10. Question after both substances were tested

Which compound would you prefer to use?

Product A	Product B

4.9 Appendix 5:
Patient Log

Patient Name & Surname _____

Patient No

Product used during the First Week	**Product A**	**Product B**

Product used during the Second Week	**Product A**	**Product B**

Day One _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Two _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Three _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Four _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Five _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Six _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)

Day Seven _____ A tick for each occasion of usage

Morning (Before Twelve O'Clock) Afternoon (After Twelve O'Clock) Evening (After Six)