THE EFFECT OF A TOPICAL COMBINED ANTI-INFLAMMATORY ANTIBIOTIC PREPARATION ON THE OUTCOME OF THIRD MOLAR SURGERY

by

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GLOSSARY OF TERMS

Dry socket is a post extraction complication characterised by:

i) constant radiating pain beginning 2 - 4 days postoperatively which is not relieved by analgesics,
ii) partial or total absence of a blood clot,
iii) tenderness on palpation,
iv) pain relieved by the placement of eugenol iodoform dressing, and
v) malodour.

Dry socket is also known as:

i) alveolar osteitis,
ii) fibrinolytic alveolitis,
iii) localised osteitis,
iv) alveolitis sicca dolorosa.
v) alveolar osteomyelitis
vi) extracortical focal supparative osteomyelitis

SUMMARY

Third molar surgery may be associated with a number of complications the most common of which are postoperative pain, swelling and trismus, and dry socket formation. The appearance of these post-operative sequelae is intimately related to the manifestations of inflammation in response to tissue injury. There is significant post-operative morbidity associated with these complications and it was thus the objective of this study to investigate the effect of a combined antibiotic/anti-inflammatory intrasocket medication on post-operative pain, swelling and dry socket formation. The medication chosen for the study was Covomycin D®. Covomycin D® is a commercially prepared opthalmological preparation - each 1 millilitre contains 2 mg chloramphenicol, 5 mg neomycin sulphate and 0,5 mg dexamethasone.

Nineteen subjects were included in the study after fullfilling certain criteria. All subjects were operated under general anaesthesia by the same surgeon. The patients were blinded to the side of the medication and were asked to complete a pain visual analogue scale and note the side of the worst swelling in the post-operative period. All patients were followed up in the first week following surgery by an independent oral and maxillofacial surgeon who was also blinded to the side on which the medication was placed.

The results showed a significant difference ($p< 0.6$) in the pain experienced on the non-medicated compared to the medicated side on day one in eleven of the nineteen patients (57.9%). When the data was analysed over the six day postoperative period sixteen of the nineteen patients (84.2%) had significantly less pain on the medicated side compared to the non-medicated side ($p < 0.6$). The swelling was reported as being worse on the non-medicated side in fourteen out of the nineteen patients (73.7%). Dry socket occurred in three out of nineteen patients or three out of thirty eight surgical extraction sites; an overall incidence of 7.9% or an incidence of 0% for the medicated side and an incidence of 15.8% on the non-medicated side i.e. all the dry sockets occurred on the non-medicated side.

In conclusion, this double-blinded prospectve study, showed that the use of a combined antibiotic/anti-inflammatory intrasocket medication favourably influences the common adverse post-operative sequelae following the removal of lower third molars.

OPSOMMING

Derde molaar chirurgie is met sekere komplikasies geassosieer. Die mees algemene komplikasies is postoperatiewe pyn, swelling, trismus en droë tandkas. Die voorkoms van hierdie komplikasies hou nou verband met die manifestasies van inflammasie in respons op weefselskade. Daar is noemenswaardige post-operatiewe morbiditeit gekoppel aan hierdie komplikasies. Die doel van hierdie navorsingsprojek was dus om te kyk of die gebruik van 'n gekombineerde antimikrobiale/anti-inflammatoriese medikasie binne in die tandkas enige effek op post-operatiewe pyn, swelling en droë tankas formasie het. Covomycin D®, 'n oftalmologiese preparaat, is vir die projek gebruik. Elke 1 ml bevat 2mg chlooramfenikol, 5 mg neomisien, en 0.5 mg deksametasoon.

Negentien pasiënte is volgens sekere kriteria in die projek ingesluit. Al die pasiënte is onder algemene narkose deur dieselfde chirurg opereer. Die pasiënte was onbewus ten opsigte van die kant keuse met betrekking tot medikasie plasing en hulle is in die post-operatiewe periode gevra om 'n pyn visuële analoog skaal uit te vul en die kant van die ergste swelling optemerk. Al die pasiënte is in die eerste post-operatiewe week deur 'n onafhanklike kaak-gesig en mond chirurg opgevolg; dié chirurg was ook onbewus ten opsigte van die kant keuse met betrekking tot medikasie plasing.

Die resultate het 'n noemenswaardige verskil in die pyn ervaring ($p < 0.6$) tussen die medikasie en die nie-medikasie kant getoon op dag een in elf van die negentien pasiënte (57.9%). Analise van die data oor ses dae post-operatief het gewys dat daar 'n noemenswaardige vermindering van pyn ($p< 0.6$) op die kant van die medikasie in sestien uit die negentien pasiënte was. Die swelling was erger op die nie-medikasie kant in veertien van die die negentien pasiënte (73.7%). Droë tandkas het in drie van die negentien pasiënte of drie van die ag-en-dertig taandkaste ontwikkel en al die droë tandkaste het op die nie-medikasie kant ontwikkel; dit wil sê 'n insidensie van 7.9% van alle ekstraksies of 'n insidensie van 0% op die medikasie kant en 15.8% op die nie-medikasie kant.

Opsommend hierdie dubbel blinde prospektiewe proef bewys dat die gebruik van 'n gekombineerde antimikrobiale/anti-inflammatoriese tandkas medikasie 'n gunstige uitwerking op die algemeenste post-operatiewe komplikasies na onder derde molaar verwydering het.

CHAPTER ONE

Introduction and Literature study

1.1 Introduction and Statement of Problem

Third molar surgery may be associated with a number of complications the most common of which are postoperative pain, swelling and trismus, and dry socket formation.[1] The appearance of these post-operative sequelae is intimately related to the manifestations of inflammation in response to tissue injury and it is thus not surprising then that modalities that serve to reduce or dampen the inflammatory response such as corticosteroids have a favourable effect on these complications.[2,3] Furthermore the effect of antimicrobial therapies on the incidence of dry socket formation and to a lesser extent on swelling and trismus is also well known.[1]
Much research has been conducted into the factors that may influence the incidence of the abovementioned complications and the search still continues for treatment modalities that minimise these complications while protecting the patient from the unwanted side effects of the treatment concerned.

1.2 Literature Study

When evaluating the common complications associated with third molar removal the following factors have been shown to be of importance: operator experience; the degree of difficulty of the extraction/surgical removal and thus the extent of bone removal and tooth sectioning; the length of the operative procedure;[4] the use of perioperative antibiotics (topical and systemic); the use of perioperative steroids[2] and anti- inflammatory agents;[3] the patients age and the patients inclination to swell.[1,4]
Dry socket most commonly follows the removal of impacted lower third molars and is characterised by: i) constant radiating pain beginning 2 - 4 days postoperatively which is not relieved by analgesics, ii) partial or total absence of a blood clot, iii) tenderness on palpation, iv) pain relieved by the placement of eugenol iodoform dressing and, v) malodour.[5] The aetiology of dry socket is still not fully understood but fibrinolysis albeit bacterial or as a result of the release of local acute inflammatory mediators is thought to play a major role in dry socket formation.[5,6] Risk factors that have been shown to predispose to the formation of dry socket include gender (females > males), patients on oral contraceptives, smoking, the difficulty of the extraction, age (most common in the third and fourth decades) and experience of the surgeon.[5,6] The morbidity associated with dry socket formation has led to a concerted effort in the literature to delineate treatment modalities that aid in the prevention of this complication which include intra-operative irrigation,[6] placement of clot stabilising factors,[7] antifibrinolytics,[6]

topical antibiotics within the socket, antimicrobial rinses[8] and systemic antibiotics.[6] Of these, the best methods of prophylaxis appear to be intraoperative lavage, topical antibiotic placed within the socket or perioperative 0,12 % chlorhexidine rinses.[9]

Removal of impacted lower molars invariably causes some degree of pain, swelling and trismus;[10] the incidence of excessive pain, swelling and trismus is reported as 12,3%, 8,6% and 5,7% respectively.[1] Pain has been correlated to surgical extractions, suturing, bony impactions and the duration of surgery;[1] pain following third molar removal has in fact been used as a useful clinical model for the evaluation of analgesics.[10] Swelling is correlated to surgical extractions, reflection of the mucoperiosteum and the duration of surgery. Trismus is correlated to surgical extractions, the duration of extraction and tooth sectioning.[1] Swelling and trismus have been shown to be reduced with the use of corticosteroids (local and systemic),[2] non steroidal anti- inflammatory agents[3] and systemic antibiotics[1,11] although the risk benefit ratio when using systemic antibiotics does not justify their use for the reduction of swelling and trismus on a routine basis.[1] Pain is influenced favourably by the perioperative administration of corticosteroids and non-steroidal anti- inflammatory agents but is unaffected by the perioperative administration of sytemic antibiotics.[1]

The surgical outcome of third molar surgery can, using the data obtained from the literature, be influenced in the patients favour; postoperative sequelae are however still common and thus the search for treatment modalities that may serve to decrease the incidence of these sequelae still further should be investigated.

The appearance of these post-operative sequelae is intimately related to the manifestations of inflammation in response to tissue injury orchestrated by the mediators of the acute inflammatory response.[2,3] It is thus not surprising then that modalities that serve to reduce or dampen the inflammatory response such as corticosteroids have a favourable effect on these complications. Furthermore the effect of antimicrobial therapies on the incidence of dry socket formation and to a lesser extent on swelling and trismus is also well known.[1,6,9] The use then of an agent that combines anti-inflammatory and antimicrobial activities should, bearing in mind the discussion above, serve to reduce the common postoperative sequelae of third molar removal on two fronts.

The use of intrasocket medication is well reported in the literature - tetracycline, sulfa drugs,[12] lincomycin[13] and clindamycin[5] are some of the antimicrobials that have proven effective; corticosteroids either alone or combined with tetracycline have also been investigated showing that corticosteroids used alone decrease postoperative complications but have no effect on the incidence of dry socket formation;[5] when used in combination with tetracycline as TerraCortril® a reduction in the incidence and severity of dry socket was demonstrated (28.% incidence on non-medicared side compared to 6.6% on th medicared side);[14] this

reduction in incidence is, however, very similar too that experienced by Hall and associates[15] with a tetracycline dressing (7%) which suggests that nothing is to be gained by adding a topical steroid.

It thus seems from the literature that the use of an antimicrobial agent combined with a corticosteroid would serve to reduce the postoperative complications of swelling, pain, and dry socket.

It is important to note however that the use of intrasocket medication is not without complications. The use of sulfa drugs resulted in delayed healing;[12] the use of TerraCortril® has been associated with myospherulosis[16,17] and the use of tetracycline cones and tablets leaves a tarry precipitate in tissue that provokes a foreign body reaction and retards healing.[18]

The type of antimicrobial selected should possess a spectrum of activity that is appropriate for the local bacterial population. Extraction sites are routinely contaminated with microorganisms. Those most commonly found are *Streptococcus viridans, Corynebacterium xerosis, Staphylococcus lactis, Vibros fusobacteria, Bacteroides melanogenicus, Neisseria pharyngis* and *Staphylococcus aureus*. Although the pattern of aerobic organisms found in extraction sockets are similar to that found in saliva the anaerobic bacteria namely Bacteroides, Vibros and Fusiforms are significantly higher within the socket than within the saliva. Treponema denticola has also been suggested as a possible aetiologic agent in the genesis of dry socket.[19] Based on this knowledge an appropriate antibiotic choice would be a broad spectrum antibiotic aimed at gram negative anaerobes; clindamycin is such an antibiotic and studies using clindamycin as an intrasocket medication did result in a significant reduction in the incidence of dry socket formation.[5]

Chloramphenicol is also a broad spectrum antibiotic with gram positive, gram negative and anaerobic activity; most gram positive bacteria are inhibited in concentrations of 1 - 10 µg/ml and many gram negative bacteria are inhibited in concentrations of 0,2 - 5 µg/ml of chloramphenicol.[20] Chloramphenicol, because of its potential toxicity (i.e. gastrointestinal disturbances and bone marrow disturbances including disturbances in red cell maturation and aplastic anaemials[21,22]) and the availability of other effective drugs, it's systemic use is indicated only in certain life threatening infections.[20,22,23] It is however used topically in the treatment of eye infections because of it's wide antimicrobial activity and its penetration of ocular tissues and aqueous humor.[20,24] The gastrointestinal side effects and the interference with red cell maturation are both related to high systemic dosing; the former associated with 1,5 - 2,5 grams daily and the latter associated with the regular use of systemic chloramphenicol in excess of 50 mg/kg/day.[20,22] Aplastic anaemia is a rare complication of chloramphenicol use via any route - it probably develops once in 25000 - 40000 patients who have taken chloramphenicol. It probably represents an idiosyncratic

genetically determined reaction within the individual and is not related to the dose or time of intake but[20,21,22] does occur more often with prolonged use.

Neomycin, together with bacitracin, is another antibiotic that has been successfully used as an intrasocket topical agent and effectively reduced the incidence of postoperative infection and associated pain.[25] Neomycin is an aminoglycoside antibiotic active against gram negative organisms including Escherichia coli, Proteus, Klebsiella and Enterobacter. Parenteral administration results in toxicity but topical use rarely results in detectable serum concentrations.[26] The addition of this agent thus improves the gram negative spectrum of any preparation without significantly compromising the safety of the preparation.

The use of topical and systemic corticosteroids in preventing swelling and trismus following the removal of third molar teeth has been well documented.[2] This anti-inflammatory response occurs as a result of interference with capillary dilatation, oedema formation, fibrin deposition, leucocyte migration and phagocytosis. The systemic side effects of corticosteroid administration are many but it has been shown that short term administration of corticosteroids does not pose a threat to or interfere with wound healing in healthy individuals.[2]

The use of a combination antibiotic-anti-inflammatory agent should serve to decrease the common adverse effects experienced in the postoperative period following third molar surgery namely swelling, pain, and dry socket.

1.3 Objective

The object of this study was to evaluate the effect of a combination corticosteroid-antibiotic agent on the postoperative incidence of pain, swelling, and dry socket following the removal of impacted lower third molars.

CHAPTER TWO

Experimental Procedure (Materials and Methods)

2.1 Selection of the model

The study population was drawn from patients attending the maxillofacial and oral surgery outpatients clinic at 1 military hospital. The patients selected for the study fulfilled the following criteria:

2.1.1 No pericoronal infection preceding the surgery.

2.1.2 No antibiotics in the period leading up to the surgery.

2.1.3 No anti-inflammatory medication leading up to the surgery.

2.1.4 Similar impactions bilaterally as determined from clinical and radiological examination (see Fig. 1).

2.1.5 No associated co-morbidity.

Written consent was obtained following prescribed procedures and each patient received a written post-operative instruction pamphlet (Appendix I, II and III).

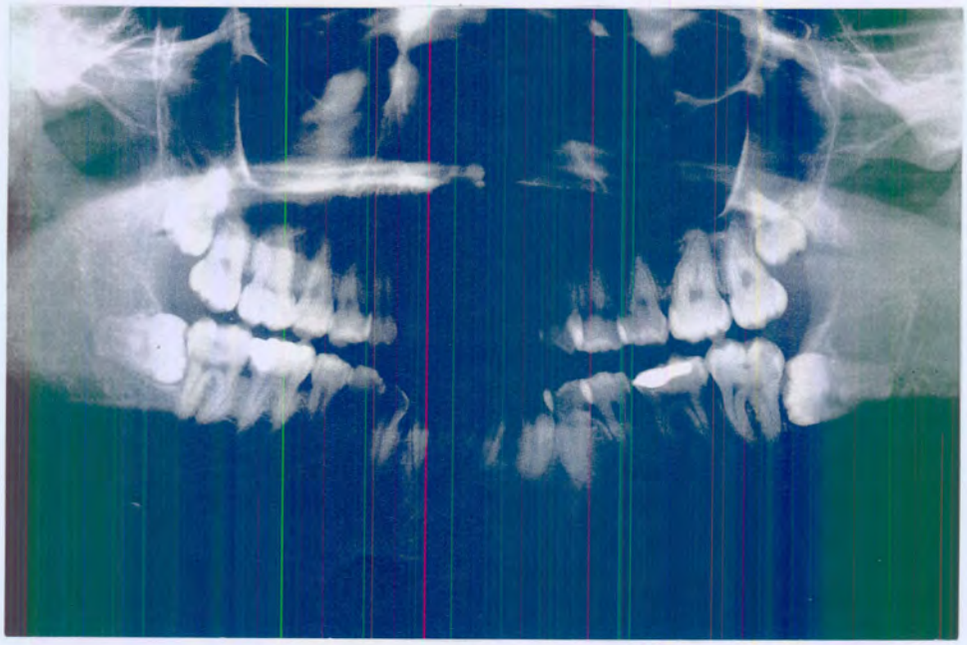

Figure 1. Panoramic radiograph demonstrating similar impactions on each side.

2.2 Experimental Design

2.2.1. Study Design.

The study was a prospective randomised double blind study with the patients serving as their own control. The medication was placed into the surgical site on one side - the side being determined randomly - and on the contralateral side no medication was added to the surgical site. The surgery was carried out by the same surgeon.

2.2.2. Peri-operative patient management.

The patients selected for the study were examined clinically during the week preceding the surgery to ensure that the operation site was not infected. The position of the impacted teeth to be removed were recorded from the orthopantomogram and were classified according to the tooth's angulation relative to the adjacent molar, the space between the adjacent molar and the ascending ramus of the mandible and the degree of bony impaction.

The surgery was carried out under general anaesthesia and adherence to standard sterile procedure was observed: the operative field including the nose, lips, chin and buccal regions was cleaned using a chlorhexidine in water solution; the surgical field was then isolated by draping the paient with surgical drapes in the standard manner. Where indicated a standard mucoperiosteal envelope flap was raised and the neccessary bone removal and/or tooth sectioning carried out (see Fig. 2).

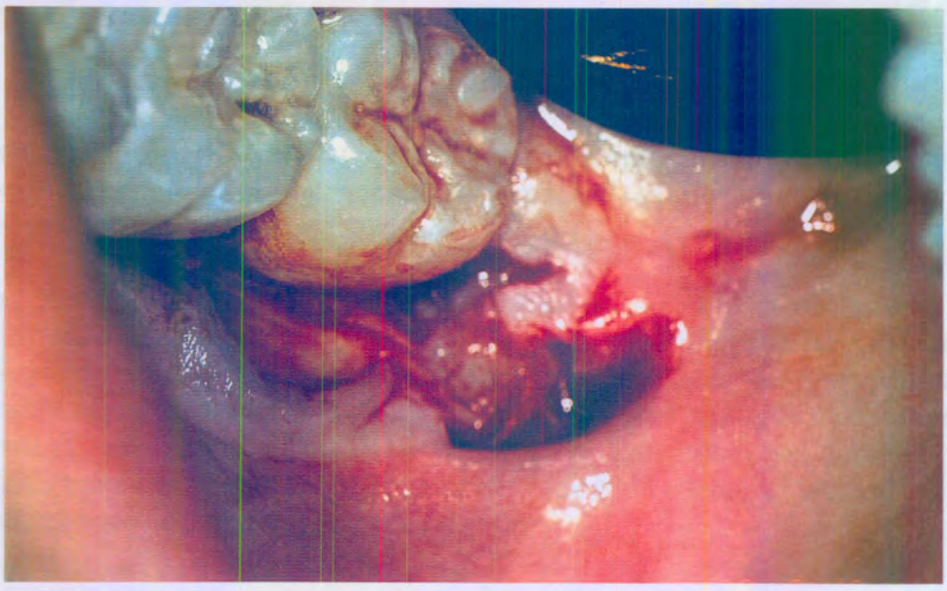

Figure 2. Standard mucoperiosteal flap raised for access to an impacted lower third molar tooth.

Once the tooth had been removed the surgical field was well irrigated with sterile normal saline solution and any surgical debris removed. The one side was then closed in the standard manner using 3-0 chromic cat gut resorbable sutures following the insertion of an inert gelfoam carrier moistened with normal saline in the surgical site; on the contralateral side (preselected on a random basis by the flip of a coin) the combined antibiotic/anti-inflammatory preparation was introduced into the surgical site on an inert gelfoam carrier before standard closure was affected (see Fig. 3).

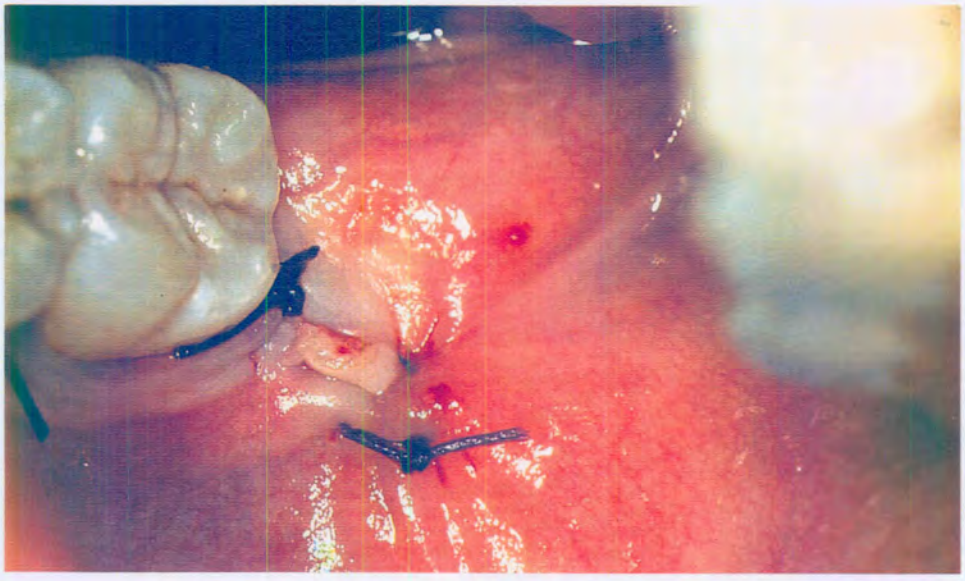

Figure 3. Mucoperiosteal flap sutured closed using chromic catgut sutures following irrigation of the socket with normal saline and placement of intrasocket medication.

In the post-operative phase the patients were asked to record the following: the time of onset and the disapearance of post-operative swelling and the time when the swelling reached the maximum for each side. The post-operative pain was evaluated by the post-operative pain scores using a visual analogue scale for each side with 0 indicating no pain and 10 the worst pain imaginable (see appendix II). The pain scores were recorded at six hour intervals from the day of surgery and on subsequent postoperative days up until day six.

The patients were examined clinically on day six by an independent surgeon - the patients were assessed for postoperative complications including dry socket and postoperative infection. Dry socket was diagnosed if the following criteria were met: i) constant radiating pain beginning 2 - 4 days postoperatively which was not relieved by analgesics, ii) partial or total absence of a blood clot, iii) tenderness on

palpation and iv) pain relieved by the placement of eugenol iodoform dressing. Post-operative infection was assessed using the following criteria: i) presence of cellulitis; ii) presence of fluctuance; iii) presence of purulent or non-purulent drainage from the socket; iv) pain and swelling that failed to improve 48 hours after surgery; v) hyperpyrexia > 37,8°C, 48 or more hours after surgery without local signs or symptoms if no other source of infection can be found.

2.3 Choice of medication

2.3.1 Intrasocket medication.

Covomycin D®, which is an opthalmolgical combination medication, was chosen for the purposes of this study. It fulfils the criteria of a combined antibiotic/anti-inflammatory medication, that is, it contains 2mg chloramphenicol, 5mg neomycin sulphate and 0,5mg dexamethasone per millilitre of preparation and it is commercially prepared. Dexamethasone is a powerful corticosteroid 0,75mg of which is equivalent to 20mg hydrocortisone.

2.3.2 Post-operative medication.

All patients were prescribed postoperative medication in the standard manner: that is analgesic/anti-inflammatory medication six hourly when neccessary (Myprodol®), oral antibiotic medication (amoxicillin five hundred milligrams eight hourly or in penicillin allergic patients erythromycin five hundred milligrams six hourly) for five days and a 0,2% chlorhexidine gluconate mouthrinse six hourly for five days.

2.4 Staff facilities and equipment

2.4.1 Personnel.

Personnel needed for the study included one maxillofacial and oral surgical registrar, one maxillofacial and oral surgical specialist, one project leader and one secretary.

2.4.2 Equipment.

Equipment needed for the study included the following: a fully equipped dental surgery including access to a panoramic X-ray machine; a fully equipped operating theatre with the necessary anaesthetic, surgical and resuscitation equipment; adequate supply of Covomycin D® medication.

CHAPTER 3

Results

3.1 Statisical analysis

The data was analysed using the Wilcoxons matched pairs signed ranks test. This is an appropriate statistical test for the analysis of non-parametric numbers (as in the visual analogue scale).

3.2 Results (see Appendix 4, table 1)

19 patients were selected for the study using the criteria mentioned above and all patients underwent surgery within a six week time period.

3.2.1 Pain results.

3.2.1.1 Day one.

There was a significant difference ($p< 0.6$) in the pain experienced on the non-medicated compared to the medicated side on day one in eleven of the 19 patients (57.9%). A further two patients had less pain on the medicated side although the difference between the medicated and non-medicated sides was not significant ($p > 0.6$). Four patients (21.1%) had significantly more pain on the medicated side on day one ($p < 0.6$) and a further one had more pain on the medicated side although the difference between the medicated and non-medicated sides was not significant ($p > 0.6$). In one patient the sample size was to small to ever reach statistical significance.

3.2.1.2 Days one to six.

When the data was analysed over the six day period sixteen out of the 19 patients (84.2%) had significantly less pain on the medicated side compared to the non-medicated side ($p < 0.6$). One patient had less pain on the medicated side although the difference pain between the medicated and non-medicated sides was not significant ($p = 0.882$). One patient experienced more pain on the medicated side over this period although the difference in pain between the medicated and non-medicated sides was not significant ($p = 0.107$).

3.2.2 Swelling results.

The swelling was reported as being the worst on day two in all but four patients (see table 1). Two of the four experienced the worst swelling on day one, one on day three and one on day four. The swelling was reported as being worse on the non-medicated side in 14 out of the 19 patients (73.7%).

3.2.3 Dry socket results.

Dry socket occurred in three out of 19 patients or three out of 38 surgical extraction sites; an overall incidence of 7.9% or an incidence of 0% for the medicated side and an incidence of 15.8% on the non-medicated side i.e. all the dry sockets occurred on the non-medicated side and all patients in which dry socket developed were smokers. Three out of the nine females included in the study were on the contraceptive pill and one of them developed the complication of dry socket. The other two patients who developed the complication of dry socket were males. All three patients were in the third decade and older than the mean age for the study of 21.4 years.

3.2.4 Other findings.

The mean time taken for each surgical removal from the time of the incision to placement of the last suture was eight minutes. There was no significant difference for the time taken on the medicated and the non-medicated sides. Furthermore there was no significant increase in complications in cases where the procedure took longer than the mean. No cases of surgical infection occurred. Of the 19 patients chosen for the study seven smoked on a regular daily basis and, as mentioned above, all the dry sockets that occurred did so in this population group.

CHAPTER FOUR

Discussion and Conclusion

4.1 Introduction

Removal of impacted lower molars invariably causes some degree of pain, swelling and trismus;[10] the incidence of excessive pain, swelling and trismus is reported as 12,3%, 8,6% and 5,7% respectively.[1] Pain has been correlated to surgical extractions, suturing, bony impactions and the duration of surgery;[1] pain following third molar removal has in fact been used as a useful clinical model for the evaluation of analgesics.[10] Swelling is correlated to surgical extractions, reflection of the mucoperiosteum and the duration of surgery. Trismus is correlated to surgical extractions, the duration of extraction and tooth sectioning.[1] Swelling and trismus have been shown to be reduced with the use of corticosteroids (local and systemic),[2] non steroidal anti- inflammatory agents[3] and systemic antibiotics[1,11] although the risk benefit ratio when using systemic antibiotics does not justify their use for the reduction of swelling and trismus on a routine basis.[1] Pain is influenced favourably by the perioperative administration of corticosteroids and non-steroidal anti- inflammatory agents but is unaffected by the perioperative administration of systemic antibiotics.[1]

4.2 Inflammation and inflammatory mediators

The appearance of these post-operative sequelae, although affected favourably or unfavourably by surgical technique, mucoperiosteal flap reflection etc. are ultimately related to the manifestations of inflammation in response to tissue injury orchestrated by the mediators of the acute inflammatory response.[2,3] Inflammation maybe defined as the reaction of vascularised tissue to local injury.[27] Factors instrumental in the causation of inflammation are intimately associated with factors that cause cell injury and include microbial infections, physical agents (such as burns, radiation and trauma), chemicals (toxins and caustic substances), necrotic tissue and all types of imunnologic reactions. Acute inflammation is of relatively short duration, lasting for a few minutes, several hours, or one or two days, and its main characteristics are exudation of fluid and plasma proteins (oedema) and the emigration of leucocytes, predominantly neutrophils. Regardless of the nature of the injurious agent acute inflammation is more of less stereotypic. Many of the vascular and cellular responses of inflammation are mediated by chemical factors derived from the action of the inflammatory stimulus on plasma or cells. A series of such chemical mediators acting together or in a sequence then influence the evolution of the inflammatory response. It is important to note that certain stimuli, such as toxins, bacteria, and

ischaemia, cause cell necrosis directly, and that necrotic tissue, in turn, can trigger the elaboration of inflammatory mediators. The arena of the inflammatory response is the vascularised connective tissue including plasma, circulating cells, blood vessels, and cellular and extracellular constituents of connective tissue. The local signs of acute inflammation are heat, redness, swelling, pain and loss of function. These signs of the inflammatory response are induced by changes in vascular flow and diameter (haemodynamic changes), changes in vascular permeability, and leucocyte exudation. These three mechanisms may overlap and share common mediator mechanisms.[27]

A surgical trauma, or any other tissue damage due to mechanical, chemical or immunological insult to the body activates the inflammatory response. This is a complex series of biochemical and cellular events involving a variety of inflammatory mediators and algogenic substances.[27] These mediators are able either to activate the primary afferent nerves or sensitise these nerves and thus enhance nociception. Hyperalgesia due to the sensitisation of the afferent nerves is an important factor in the continued sensation of pain after tissue damage; when the nerve endings are sensitised by proinflammatory substances, their threshold to activation is lowered and the response to noxious stimuli increases. The eiconosoids, which consist of the prostaglandins and the leukotrienes, are instrumental in promoting the inflammatory response. They are synthesised from arachadonic acid which is found normally esterified in membrane phospholipids and becomes available for eiconosoid synthesis through the activation of cellular phospholipases by mechanical, chemical and physical stimuli or by other mediators (eg. C5a). Following activation, biosynthesis of the metabolites of arachdonic acid occurs by one of two major pathways namely the cyclooxygenase and lipoxygenase pathways. Cycloxygenase transforms arachadonic acid to prostaglandins, prostacyclins and thromboxans. Lipoxygenase converts arachadonic acid into hydroperoxy derivatives (hydroperoxyeicosatetraenoic acid [HPETE]; 5-HPTE may undergo peroxidation to hydroxyeicosatetraenoic acid (HETE) which is a potent chemotactic stimulus for neutrophils. 5-HPETE also gives rise to the leukotrienes leukotriene A_4, leukotriene B_4, leukotriene C_4, leukotriene D_4, and leukotriene E_4.[27]

Prostoglandins elicit different biological effects that contribute to the inflammatory response and it is thought that prostaglandin E and prostacyclin are the most important mediators of inflammatory vasodilation. They also markedly potentiate the permeability by increasing the chemotactic effects of other mediators.[27] Prostaglandin E_2 is detected in most acute inflammatory conditions and is considered to be the most predominant eiconosoid and is one of the most potent proinflammatory mediators among the substances induced by the cyclooxygenase pathway and although it does not activate nociceptors directly it sensitises the receptors on the primary nerve endings to the actions of bradykinin and histamine.[28] Other cyclo-oxygenase derivatives are found at sites of inflammation although in concentrations less than a quarter of the concentration

of prostaglandin E_2 and of these it is thought that prostacyclin (PGI_2) is the most important.[28] Prostacyclin has, as mentioned above, important vasodilatory effects, and is more hyperalgesic than PGE_2.

The leukotrienes consistently found in inflammation are leukotriene B_4 and 12-HETE; the former causes aggregation and adhesion of leucocytes to venular endothelium and both are powerful chemotactic agents and effect the release of a hyperalgesic substance, 8(R),15(S)-diHETE which sensitises nociceptors. [28]

The kinins are another group of inflammatory mediators that play an important role in the inflammatory cascade. They are one of three mediator systems directly triggered by surface activation of Hageman factor which ultimately results in the release of the vasoactive nonapeptide bradykinin. Bradykinin is synthesized in plasma whenever blood vessels are damaged as it is a by product of the coagulation system; the enzyme prekallikrein is converted to kallikrein, which then acts on kininogen resulting on the release of bradykinin into the tissues. The action of bradykinin is short lived because it is quickly inactivated by the enzyme kininase. Kallikrein, however is a potent activator of Hageman factor allowing for autocatalytic amplification of the initial stimulus; it also has chemotactic activity and causes aggregation of neutrophils in vivo.[27] Bradykinin is a potent agent that increases vascular permeability, causes smooth muscle contraction, is a potent activator of nociceptors, and promotes vasodilation. It is thought to have a role in chemotaxis by some[29] and not by others.[27]

The vasoactive amines involved in the immune response are histamine and serotonin and they are believed to be mediators in the immediate active phase of increased permeability. Histamine is mainly present in the tissues stored in the secretory granules of mast cells, basophils and in platelets. Serotonin is also found in mast cells and may also be released from activated platelets and is found in high concentrations in inflammatory exudates. Many agents release amines from mast cells. Principal among these are physical agents such as trauma or cold; immunologic reactions through a mechanism involving receptors on the mast cell surface that bind with IgE; C3a and C5a fragments of complement that induce increased vascular permeability; histamine releasing factors from neutrophils, monocytes and platelets; and interleukin-1. The release of histamine may also be stimulated by the effect of the neuropeptide substance P. Histamine is important mainly in early inflammatory responses and in immediate IgE mediated hypersensitivty reactions and its biological effects include itching, the activation of nociceptors, and increased capillary permeability. Serotonin is able to acctivate nociceptors and potentiates the effect of other inflammatory mediators such as bradykinin.[27]

ADP and potassium ions are present in all cells and when released following cell damage are also able to activate nociceptors. Central to the patients experience of the acute inflammatory response are the physical manifestations mentioned above

i.e. pain, swelling, loss of function, redness,and warmth. Of these pain and swelling feature commonly following the removal of third molar teeth.

4.3 Pain transmission, modulation and post-operative sequelae

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[30] The sensory component of pain is termed nociception. This complex electrochemical mechanism has been characterised as consisting of four distinct physiologic processes.

1. **Transduction** describes the conversion of noxious stimuli into electrical signals by peripheral nerve endings.
2. **Transmission** is the propagation of the electrical signals along the nociceptive pathways.
3. **Modulation** describes the alteration of the nociceptive signals within the dorsal horn of the spinal cord. Here nerve endings of various types intersect and release neurotransmitters, which inhibit, amplify or alter the sensory signal.
3. **Perception** is the process whereby the nociceptive input is integrated with cognitive and emotional factors to create the subjective experience of pain.

A pain state is normally generated secondary to activation of unencapsulated nerve endings that fire in response to stimuli that threaten or actually produce tissue damage; firing frequency is directly related to stimulus intensity.[31] Some receptors respond to only one modality and others are sensitive to several types of noxious stimulation (polymodal nociceptors). Virtually all are supplied by a subpopulation of small diameter myelinated (Aδ) and unmyelinated (C) nerved fibres. Long (100 to 400 μm) bare axonal endings are juxtaposed with small blood vessels and mast cells. Antidromic activation of these peripheral terminals releases neurotransmitters in the periphery. The local release of these agents, including substance P and other tachkinins (bradykinin, histamine, protons, prostaglandins, leukotrienes, interleukins and TNF-α), causes vasodilation and plasma extravasation and in enough quantity can result in oedema. Following vasodilation, histamine and bradykinin are released locally from the blood cells; both can sensitise nociceptors to future stimulation (hyperalgesia). Tissue damage and substance P can activate mast cells, releasing additional histamine as well as arachadonic acid metabolites and cytokines (interleukins and tumour necrosis factor). These substances produce additional receptor sensitisation as well as ongoing activity in afferent nerve fibres. Thus, free nerve endings use other cells and their chemical products, rather than encapsulated receptors, to transduce environmental factors into action potentials. Thus nociceptive activity in the afferent nerves is responsible for the perception of pain and furthermore induces the synthesis and release of neuropeptides from the peripheral terminals of sensory nerves, a phenomenon known as neurogenic inlflammation. One kind of

C nociceptor is referred to as a silent nociceptor; it is activated only in the presence of tisssue damage or inflammation. Following the release of injury products, these previously silent receptors are activated by a wide range of thermal and mechanical stimuli and may also have a background discharge. Pain sensation appears to be dependent on the particular afferent fibres being activated and not on the pattern of stimulation. Activation of Aδ nociceptors produces a short lasting pricking sensation (first pain), whereas activation of C fibres results in poorly localised burning sensation (second pain). Only stimulation of fibres connected to nociceptors results in reports of pain. Stimulation of other fibres at the same or higher frequencies never results in pain sensations. In the absence of tissue damage, afferent nociceptive fibres display little to no background activity.[32]

Substance P acts centrally as a neurotransmitter, which in the spinal cord signals pain, and in the periphery is involved in the inflammation causing vasodilation, extravasation and mast cell degranulation.

The hyperalgesia induced by tissue injury is present both in the area of direct injury (primary hyperalgesia) and in the surrounding undamaged tissues (secondary hyperalgesia). Primary hyperalggesia comprises a decreased threshold to mechanical andd thermal stimuli and an increased response to painful stimuli; secondary hyperalgesia is mainly provoked by mechanical rather than thermal stimuli.[29] Secondary hyperalgesia is partly due to peripherally directed impulses in the sensory C-fibres, affecting the blood vessels and releasing substance P into an area extending beyond the traumatised region. As mentioned above many of the nociceptors in healthy tissues are inactive or silent, and thus function as an alarm system that can be activated to warn the body when the nerve terminals are sensitised in the case of continuous or repeated damage to the tissues. The spreading of extracellular fluid with an increased content of histamine and serotonin contributes to secondary hyperalgesia by sensitising nociceptors.[29]

Thus the inflammatory response after tissue trauma is a highly complex interaction between substances released from damaged tissues, the blood, the sensory nerves and the immunological cells in the tissue. The changes within the tissues cause the typical symptoms of inflammation, and usually the aim of treatment is to alleviate pain induced by inflammation; this can be achieved by pharmacologic intervention at different levels.

Minimizing pain is in keeping with the physicians primary goal of relieving suffering. Moreover, effective treatment of perioperative and postoperative pain also represents an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential for decrease in perioperative morbidity.[33] Noxious stimuli, such as surgical trauma and subsequent postoperative pain, result in a broad range of endocrinologic, immunologic, antinflammatory responses, including increased release of catabolic

hormones and inhibited secretion of anabolic mediators. This group of responses is known collectively as the neuroendocrine stress response to injury. The stress response results in catabolism, arrhythmogenesis, hypercoagulability, and immunosuppression. Pain causes reflexive activation of cardiac sympathetic fibres with increased cardiac work and an increase in myocardial oxygen demand. These changes may be maladaptive after an operation. Minimizing the afferent drive and accordingly the stress response may enhance recovery.[33] The provision of adequate post-operative analgesia alone does not guarantee an amelioration of the stress response. The systemic administration of opioids only has a modest effect in this regard even though it can provide excellent postoperative analgesia. Maximal suppression of the stress response can only be obtained with complete sensory blockade of the operative site.[33]

The nervous system does not modulate sensory stimuli in a fixed and unchanging manner. Animal experiments have shown that in response to intense or repeated stimulation, the nociceptive pathways of the dorsal horn develop persistent reflex hyperexcitability that represents a central sensitisation. Persistent C afferent fibre excitation results in the facilitation of the discharge of dorsal horn wide dynamic-range neurons in a process known as wind up. This heightened reactivity results in dramatic increases in the frequency of discharge in response to subsequent afferent stimuli, and this condition is thought to be accompanied by an increase in the perception of pain. If the nociceptive pathways are pharmacologically blocked before the intense stimulation occurs, these changes are diminished or prevented.[33]

In most cases post-operative pain has a clear causal relationship to surgical trauma. Therefore most efforts in post-operative pain management are focused directly on inhibiting nociception, with relatively less emphasis placed on the emotional components of pain. Because no agent has yet been identified that specifically inhibits nociception without associated side effects, it has become common practice to employ a polypharmacologic approach to the treatment of postoperative pain. The use of multiple agents in reduced doses to intervene at various points along the nociceptive pathway allows additive or synergistic analgesic effects while minimising side effects. This notion of balanced analgesia forms the conceptual basis for the effective treatment of acute pain.[33] As mentioned above the mechanism of pain has been characterised as consisting of four distinct physiologic processes, namely, transduction, transmission, modulation, and perception. For the purposes of this discussion it is appropriate to consider the therapeutic modalities which affect transduction as it is at this station along the pain pathway that the topical application of dexamethasone is effective.

4.4 Influence of glucocorticoids on pain and inflammation

Noxious stimuli in the periphery are converted into electrical signals and then transmitted to the spinal cord by primary nociceptive fibres. Agents which serve

to alter peripheral transduction include the glucocorticoids and the non-steroidal anti-inflammatory agents. The glucocorticoids have the capacity to dramatically reduce the manifestations of inflammation and exert their effects in the periphery by a number of different mechanisms. They have profound effects on the concentration, distribution and the function of peripheral leucocytes and to their inhibition of phospholipase A_2 activity. After a single dose of short acting glucocorticoid the concentration of neutrophils increases while the lymphocytes (T and B cells), monocytes, eosinophils, and basophils in the circulation decrease in number. The changes are maximal at six hours and are dissipated in 24 hours. The increase in neutrophils is due both to an increase influx from the bone marrow and decreased migration from the blood vessels, leading to a reduction in the number of cells at the site of inflammation. The reduction in circulating lymphocytes, monocytes, eosinophils and basophils is the result of their movement from the vascular bed to lymphoid tissue.[34]

Glucocorticoids inhibit the functions of leukocytes and tissue macrophages. The ability of these cells to respond to antigens and mitogens is reduced. The effect on macrophages is particularly marked and limits their ablity to phagocytose and kill microorganisms and to produce interleukin-1, pyrogen, collagenase, elastase, tumour necrosis factor, and plasminogen activator. Lymphocytes produce less interleukin-2. Large doses of glucocorticoids have also been reported to stabilise lysosymal membranes, thereby reducing the concentration of proteolytic enzymes at the site of inflammation.[34] The effect of glucocorticoids on leucocytes is significant as it is currently believed that the attraction of these cells to tissues is essential for inflammation; furthermore by influencing the secretion of the abovementioned cytokines glucocorticoids modulate the inflammatory response further by interfering with the directional cues for the movement of leucocytes in inflammation .[35]

In addition to their effects on leucocyte function, glucocorticoids may influence the inflammatory response by reducing the prostoglandin and leukotriene synthesis. Corticosteroids may also increase the concentration of proteins called lipocortins, who are said to bind the phospholipid substrates of phospholipase A_2 . This action would also reduce the formation of prostaglandins and leukotrienes. Finally, glucocorticoids may reduce the expression of cyclo-oxygenase, thus reducing the amount of enzyme available to produce prostaglandins.[34] Glucocorticoids also cause vasoconstriction when applied directly to vessels, and they decrease capillary permeability by inhibiting the action of kinins and bacterial endotoxins and by reducing the amount histamine released by basophils.[34]

The use of local glucocorticoid therapy such as topical preparations for skin disease, opthalmic forms for eye disease, intra-articular injections for joint disease provides means of delivering large amounts of steroid to the diseased tissue with reduced systemic effects. The therapeutic efficacy of topical corticosteroids is

based primarily on their anti-inflammatory activity. Corticosteroids are only minimally absorbed following application to normal skin. There is a marked regional anatomic variation in corticosteroid penetration. Compared to the absorption from the forearm, hydrocortisone is absorbed threee and a half times as well through the scalp, six times as well through the forehead, nine times as well through the vulvar skin and 42 times as well through the scrotal skin. Penetration is increased severalfold in the inflammed skin of atopic deramatitis; and in severe exfoliative diseases there appears to be little barrier to penetration;[24] application as an intrasocket medication probably poses little resistance to penetration.

All absorbable corticosteroids possess the potential to suppress the pituitary-adrenal axis. Iatrogenic Cushings syndrome may occur as a result of protracted use of topical corticosteroids in large quantities.[24] However, in a review of the literature of the use of corticosteroids in oral surgery Gersema and Baker reported that no adverse reactions were attributable to corticosteroid use in any of the previously mentioned studies; their review included studies in which corticosteroids were used in both topical and systemic forms.[2] Furthermore a study by Williamson et al. which looked at suppression of the pituitary-adrenal axis following the intravenous administration of 8mg dexamethasone in 10 patients undergoing oral surgery by measuring the concentrations of 11-deoxycortisol on day three and day seven post-operatively found that the short term administration of corticosteroids is a relatively safe procedure.

Retarded wound healing is another complication which has raised concerns with regard to corticosteroid use in oral surgery; Gersema and Baker, after their review of the literature, came to the conclusion that humans do not appear to be at risk for delayed wound healing when corticosteroids were administered for less than three days. Indeed their did not appear to be any difference in the rate of healing of the extraction sites in which the Covomycin D® was placed and no adverse effects that could be attributable to the use of dexamethasone were reported by the patients involved in this clinical trial.

In the periphery, injury is known to increase the release of prostanoids; these lipidic acids, by a local action, can enhance the spontaneous activity and increase the excitability of peripheral afferent terminals. Additional information has emerged that suggests that persistent nociceptive afferent activation may increase the spinal release of prostanoids. Within the spinal dorsal horn these prostanoids can enhance the release of excitatory transmitters. The glucocorticoids can thus exert a central effect in the spinal cord. Mechanistically it can be seen then that the glucocorticoids exert their action by reducing the enhanced excitability of the system are thus in effect antihyperalgesic agents.[33]

4.5 Dry socket

Dry socket is another commonly reported complication of third molar removal. Dry socket most commonly follows the removal of impacted lower third molars and is characterised by: i) constant radiating pain beginning 2 - 4 days postoperatively which is not relieved by analgesics, ii) partial or total absence of a blood clot, iii) tenderness on palpation iv) pain relieved by the placement of eugenol iodoform dressing and v) malodour.[5] The aetiology of dry socket is still not fully understood but fibrinolysis albeit bacterial or as a result of the release of local acute inflammatory mediators is thought to play a major role in dry socket formation.

Normal healing of an extraction socket passes through a number of phases which can be divided in to (i) the immediate reaction following extraction, (ii) the first week wound, (iii) the second week wound, (iv) the third week wound, (v) and the fourth week wound. For the purposes of this study the first two phases will be discussed as it is during this period that the common complication of dry socket occurs. Immediately following the removal of a tooth the blood filling the socket coagulates, red cells become trapped in a fibrin network and the ends of the torn blood vessels in the periodontal ligament become sealed off. Within the first 24-48 hours after the extraction the acute inflammatory response is responsible for alterations in the vascular bed and recruitment of leucocytes. Vasodilation and engorgement of the blood vessels in the remnants of the periodontal ligament occurs and mobilisation of leucocytes to the immediate area surrounding the clot occurs. The surface of the blood clot is then covered by a thick layer of fibrin and the clot shows areas of contraction. The collapse of the unsupported gingival tissue into the opening of the fresh extraction wound is a great aid in maintaining the clot in position. Within the first week after tooth extraction, proliferation of fibroblasts from connective tissue cells in the remnants of the periodontal ligament is evident and these fibroblasts begin to grow into the clot around the periphery. The clot forms the scaffold upon which cells associated with the healing process may migrate; it is however only a temporary structure and is gradually replaced by granulation tissue but remains a crucial element in the healing of an extraction socket[37]. In fact many believe that an increase in fibrinolysis with resultant clot dissolution is responsible for the development of dry socket. Birn hypothesised that partial or complete lysis and destruction of the blood clot was caused by tissue kinases liberated during inflammation resulting in the transformation of plasminogen into plasmin with subsequent lysis of fibrin within the clot and the formation of kinins with the final result being clinical dry socket.[38] The role of an overexuberant inflammatory response was thus considered to be important in the formation of dry socket and the findings that dry socket occurs more commonly following difficult extractions and the use of a dental bur for tooth removal would seem to support this theory.[5,12] The use of modalities that might serve to modify this response were thus investigated. The use of antifibrinolytic agents have shown mixed results.[39,40,41,42]

Since it has been shown that glucocorticoids stabilise cellular lysosomal membranes (see discussion above) with subsequent prevention of the release of vasoactive kinins and destructive enzymes it was inevitable that the efficacy of steroids in the prevention of dry socket would be tested. Julius and his co-workers were unable to demonstrate any benefit by the addition of a topical corticosteroid to an antibiotic dressing in the incidence of dry socket formation.[14] Furthermore Chapnick et al. in their review of dry socket report that although steroids decrease immediate post-operative complications they fail to reduce the occurrence of dry socket after extractions.[5]

These results call into question then the sole role of inflammatory mediators in the activation of the fibrinolytic system and the subsequent formation of dry socket. It has also been shown that activation of the fibrinolytic system may also be brought about by the action of bacterial pyrogens.[5] Focus thus shifted to the role of bacteria in dry socket formation. The results of studies conducted on the microbiology of intraoral wounds suggest that persons with high preoperative streptococci counts at the wound site have a higher probability of development of dry socket than patients with relatively low counts.[43] Studies have thus been conducted which have looked at modifying the bacterial response at all possible stations of influence.

The use of pre-operative chlorhexidine mouthrinses and plaque control to prior to surgery have shown a decrease in the incidence of dry socket formation.[44] Thorough irrigation of the extraction socket using 175mls of sterile normal saline compared to sockets irrigated with only 25mls of the same solution showed that the sockets receiving the higher volume lavage had a dry socket incidence of 5.7% compared to 10.9% incidence of dry socket in sockets receiving the minimal volume lavage. It was concluded that simple lavage could reduce the incidence of dry socket by 50%.[45]

The influence of systemic and topical antimicrobials on the incidence of dry socket formation had been extensively studied. Systemic administration of antibiotics has shown mixed results. Curran and co-workers in a double blind study using pre- and post-operative systemic penicillin therapy were unable to demonstrate any difference in dry socket incidence between the therapeutic and placebo groups.[46] Krekmanov, however, in his study using only a single dose of 800mg of phenoxymethyl penicillin orally pre-operatively, demonstrated a marked decrease in dry socket formation compared to the group receiving no medication.[47] Similarly Bystedt et al. using four different antibiotics pre- and post-operatively (for seven days) found a 50% decrease in the incidence of dry socket when systemic antibiotics were used compared with the controls.[48] Despite the success in the reduction of dry socket incidence using systemic antibiotics (as demonstrated in these studies) many feel that the administration of systemic antibiotics for the prevention of dry socket is not justified.[5]

The effectiveness of topical medicaments in the prevention of dry sockets has been extensively investigated and it has been shown that the use of tetracycline,[15,49,50,51,52] sulfa drugs,[12] lincomycin[13] and clindamycin[5] are effective in reducing the incidence of dry socket formation.

As mentioned above the rationale for the use of bacterial modifying therapies is to reduce the level of bacterial pyrogens which are believed to be the stimulus for fibrinolytic activity and thus clot breakdown and dry socket formation. The type of antimicrobial selected should possess a spectrum of activity that is appropriate for the local bacterial population i.e. based on the microorganisms most commonly found in extraction sites.[5] Extraction sites are routinely contaminated with microorganisms which commonly include *Streptococcus viridans, Corynebacterium xerosis, Staphylococcus lactis, Vibros fusobacteria, Bacteroides melanogenicus, Neisseria pharyngis* and *Staphylococcus aureus*. Although the pattern of aerobic organisms found in extraction sockets are similar to that found in saliva the anaerobic bacteria namely Bacteroides, Vibros and Fusiforms are significantly higher within the socket than within the saliva.[5] *Treponema denticola* has also been suggested as a possible aetiologic agent in the genesis of dry socket.[19] Based on this knowledge an appropriate antibiotic choice would be a broad spectrum antibiotic aimed at gram negative anaerobes eg. clindamycin, and studies using clindamycin as an intrasocket medication did result in a significant reduction in the incidence of dry socket formation.[5]

Chloramphenicol is also a broad spectrum antibiotic with a single aromatic ring and short side chain that binds reversibly to the 50S portion of the bacterial ribosome and in so doing inhibits peptide bond formation. Chloramphenicol has gram positive, gram negative and anaerobic activity; most gram positive bacteria are inhibited in concentrations of 1 - 10 µg/ml and many gram negative bacteria are inhibited in concentrations of 0,2 - 5 µg/ml of chloramphenicol.[20] The systemic use of chloramphenicol is indicated only in certain life threatening infections,[20,22,23] because of its potential toxicity (i.e. gastrointestinal disturbances and bone marrow disturbances including disturbances in red cell maturation and aplastic anaemias[21,22]) and the availability of other effective drugs. It is however used topically in the treatment of eye infections because of it's wide antimicrobial activity and its penetration of ocular tissues and aqueous humor.[20,24] The gastrointestinal side effects are related to high systemic dosing associated with 1,5 - 2,5 grams of chloramphenicol daily. Chloramphenicol causes two types of bone marrow suppression; a dose related, reversible suppression of all elements, which occurs during therapy at the maximal recommended doses (4g/day in adults), and an irreversible aplastic anaemia, which occurs approximately one in every 25000 - 40000 exposures. The reversible form has been reported to follow all forms of chloramphenicol treatment, including ocular administration and develops months after therapy is discontinued.[22] This irreversible aplastic anaemic reaction probably represents an idiosyncratic genetically determined reaction within the

individual and is not related to the dose or time of intake[20,21,22] but does occur more often with prolonged use. The probable incidence of an adverse reaction in the patients chosen for this study was very low as the dosage used was low (1 ml per socket: 1ml contains 2mg chloramphenicol); furthermore it is a one off dosage not to be repeated. Indeed no adverse reactions occurred in the postoperative period in any of the patients that participated in the study.

Cones, containing a combination of neomycin and bacitracin were tested against a placebo following the removal of impacted third molars and were found to effectively reduce the incidence of postoperative infection and associated pain.[25] When tested separately neither neomycin or bacitracin proved to be as effective as tetracycline in reducing the incidence of dry socket formation.[50] Neomycin is an aminoglycoside antibiotic active against gram negative organisms *including Escherichia coli, Proteus, Klebsiella* and *Enterobacter*. Parenteral administration results in toxicity but topical use rarely results in detectable serum concentrations.[26] The addition of this agent thus improves the gram-negative spectrum of any preparation without significantly compromising the safety of the preparation.

Risk factors that predispose to the formation of dry socket include gender (females > males), patients on oral contraceptives, smoking, the difficulty of the extraction, age (most common in the third and fourth decades) and experience of the surgeon.[5,9] The results from this study indicate an overall dry socket incidence of 7.9% (three out of 38 extraction sites). All the dry sockets occurred on the non-medicated side. Computed differently, the dry socket incidence on the medicated side was 0% (zero out of 19 extraction sites) and that on the non-medicated side was 15.8% (three out of 19 extraction sites). The reported incidence of dry socket formation varies greatly from one study to another which is probably due to the criteria used for making the diagnosis, the teeth involved; and the incidental treatment of the socket at the time of surgery.[9] When studies include the removal of all 32 teeth the incidence of dry socket is in the range of 2% to 5%. The reported incidence of dry socket following mandibular third molar removal with no accompanying extractions and no therapeutic intervention is in the range of 9.3% - 38%.[9,12,14,15,40,42-45,47-53] The incidence of dry socket formation on the non-medicated side in this study thus compares favourably with that reported in the literature. Improvement of the dry socket incidence from 15.8% on the non-medicated side to 0% on the medicated side demonstrates the favourable effect of the combined antibiotic/anti-inflammatory medication on the formation of dry socket in this study. It is difficult to determine which of the ingredients in the combined intrasocket medication is responsible for the improvement in the dry socket incidence but if the literature is accurate it would seem as though the primary effect resides with the antimicrobial. This is based on previous studies where the addition of a corticosteroid to intrasocket medicaments has not shown any significant reduction in dry socket incidence[14,50] and there is no reason to believe that it would in this study; it would thus seem that the wide spectrum of

chloramphenicol with the reinforced gram negative cover of neomycin effectively reduces or alters the microbial environment within the extraction socket in such a way so as to reduce the incidence of dry socket formation.

When controlling for the other risk factors traditionally associated with an increased incidence of dry socket formation such as gender (females > males), patients on oral contraceptives, smoking, the time taken for the extraction, and age (most common in the third and fourth decades),[5] the only factors that adversely affected the dry socket incidence in this study were smoking and the patients age.

All three dry sockets occurred in patients that smoked. The incidence of dry socket formation is said to be increased in smokers by some[54] and is said not to play a significant role by others.[55] Those claiming an influential role for smoking cite contamination of the surgical site, systemic effects on the clotting mechanism, heat or the disturbance of the existing clot, and the act of smoking by dislodging the clot by suction, as possible mechanisms for the increase in the incidence of dry socket. The reasons however for the effects seen with smoking have not been positively established.[5]

The age of the patients included in this study varied from 16-32 years with a mean age of 21.4 years. The patients who developed the complication of dry socket were 23 ,25 and 27 years of age and were thus in the third decade which correlates with findings in other studies.[5]

The male to female ratio of dry socket development was two to one in this study i.e male > female. The one female that did develop the complication of dry socket was taking oral contraceptive medication (as well as being a smoker); the other two females taking oral contraceptive medication had an uneventful post-operative course. The increased incidence of dry socket in female patients[56] has been explained as resulting from oral contraceptive use in this population. Studies prior to 1960 failed to demonstrate any gender differences in the incidence of dry socket formation and this is thought to correlate with the lack of oral contraceptive use at this time.[9] With the increase in oral contraceptive use in later years a positive correlation between the use of oral contraceptives and dry socket formation has been demonstrated. This is thought to be due to the effect of oestrogen on the coagulation and fibrinolytic system with increased fibrinolytic activity and subsequent clot lysis. [57,58] The results of this study, which failed to demonstrate any correlation between oral contraceptive use and dry socket formation, correlate with the findings of others,[9] and is most likely due to the small sample of patients using oral contraceptives in this study. Furthermore it is also possible that previous studies, most done several years ago, looked at females who were using oral contraceptives with higher oestrogen levels than those used currently;[9] the new oral contraceptive pills have lower oestrogen levels than ever before and thus their influence on the fibrinolytic system may be negligible.

4.6 Conclusion

It thus seems from the literature and this study that the use of an antimicrobial agent combined with a corticosteroid would serve to reduce the postoperative complications of swelling, pain, and dry socket. The use of a combination agent is useful as the individual components work in different ways to bring about a decrease in the postoperative sequelae following third molar removal. From the discussion above it is clear that the corticosteroid is probably responsible for the decrease in pain and swelling; the antibiotic though probably has little effect in this regard. The antibiotic is however probably responsible for the decrease in the incidence of dry socket formation a post-operative complication probably minimally influenced by the corticosteroid.

The results of this study and a review of the literature indicate that the common post-operative complications of lower third molar removal of pain, swelling, and dry socket may be effectively minimised by intraoperative lavage,[9] placement of a combined topical antibiotic/anti-inflammatory medication in the socket, and perioperative 0,12 % chlorhexidine rinses.[9] Furthermore factors that influence the formation of dry socket include smoking and the age of the patient. Other factors commonly cited as influential in the formation of pain, swelling and dry socket such as time taken for the extraction, gender, and use of oral contraceptive medication appeared not to play a significant role in this study.

APPENDIX I

CONSENT FORM

INFORMATION and CONSENT FORM
INFORMASIE en TOESTEMMINGSVORM

Maxillo-Facial and Oral Surgery
Kaak-, Gesig- en Mond-Chirurgie

Konsultant/Dokter:
Consultant/Doctor: .....

Patient's surname/*Pasiënt se van:* .....
First name/*Voorname:* .....
Titel/*Titel:* .....
Address/*Adres:* .....

Profession and/or business/
Beroep en/of besigheid: .....
Work address/*Werksadres:* .....
.....
Tel (Home/*Huis):* ..... (Work/*Werk):* .....
ID number/*nommer :* .....

Date of birth/*Geboortedatum:* .....
Age/*Ouderdom:* .....
Sex/*Geslag:* .....

Patient a child/*Pasiënt 'n kind:*
Name of parent and title
Naam van ouer en titel: .....
Profession of father:
Beroep van vader: .....
Profession of mother:
Beroep van moeder: .....

Medical Aid/*Mediese Fonds:* .....
Number/*Nommer:* .....
Name & postal address, person respondible for account
Naam & posadres, persoon verantwoordelik vir rekening .....
.....
.....

Referring doctor (compulsory)/
Verwysende dokter (verpligtend): .....
Address/*Adres:* .....

House Medical Practitioner/
Huisgeneesheer: .....
Address/*Adres:* .....
House Dental Practitioner/
Huistandarts: .....
Address/*Adres:* .....

Other Specialist/*Ander Spesialiste:* .....

Medical History
Mediese Geskiedenis:

Angina Pectoris / *Pektoris*	☐	AIDS/VIGS	☐
Asthma/*Asma*	☐	Infective conditions / *Infektiewe toestande*	☐
Stroke/*Beroerte*	☐	Hypertension/*Hipertensie*	☐
Haemorrhage / *Bloedingsneigings*	☐	Liver problems/*Lewerprobleme*	☐
Diabetes/*Diabetes*	☐	Mocard. Infarct./*Hart Infark.*	☐
Epilepsy/*Epilepsie*	☐	Ear-Nose-Throat/*Oor-Neus-Keel*	☐
		Porphyria/*Porfirië*	☐
		Rheumatic Fever / *Rumatiekkoors*	☐
		Psychological treatment / *Sielkundige behandeling*	☐

Allergies/*Allergieë:* Antibiotika (cs) | Elastoplast | Scoline / *Skolien* | Other / *Ander*

Previous operations (all)/
Vorige operasies (almal): .....
Past 2 yrs to doctor/hospital/
Laaste 2 jr na dokter/hospitaal: .....
Serious illness/*Ernstige siekte:* .....

Pregnant/*Swanger:* Yes/*Ja* | No/*Nee*

Medicine: / *Medisyne:* Cortisone / *Kortisoon* | Insulin / *Insulien* | Blood pres / *Bloeddruk* | Other / *Ander*

Other problems/
Ander probleme: .....

Family history/
Familie geskiedenis: .....
.....

Main Complaint/
Hoofklagte: .....

Did an acquaintance/friend recommend me to you? / *Het 'n bekende/vriend my aanbeveel?* — Yes / *Ja* — No / *Nee*
Who/*Wie?* .....

CONSENT (Treatment and payment)
TOESTEMMING (Behandeling en betaling)

I herewith give the surgeon permission to examine me / my wife / my child and, on his recommendation and in consultation with me / my wife to proceed with the necessary treatment. I also undertake to pay the full amount of professional fees (which shall not be according to the scale of benefits), which result from consultation, examination material(s) and treatment(s), as soon as possible, and I accept that interest will be charged on outstanding accounts (+ 120 days).

Hiermee gee ek toestemming dat die chirurg myself/ my vrou / my kind mag ondersoek en op sy aanbeveling en toestemming deur myself / my vrou die nodige verdere behandeling mag voortsit. Hiermee aanvaar ek ook dat ek alle professionele gelde (wat nie volgens voordeleskaal is nie) wat ontstaan deur die konsultasie, ondersoekmateriale en behandeling/s so spoedig as moontlik ten volle sal vereffen en dat ek kennis daarvan neem dat rente gehef sal word op uitstaande bedrae (+ 120 dae).

....
Date/*Datum* Signature/*Handtekening*

CONSENT (Research)
TOESTEMMING (Navorsing)

I herewith give my consent for all examination materials (X-ray's, photos, models, etc) and examination reports of myself / my wife / my child, to be used for research and publication.

Hiermee gee ek toestemming dat alle ondersoekmateriale (Röntgenbeelde, foto's, modelle, ens) en ondersoekverslae van myself / my vrou / my kind gebruik mag word vir navorsing- en publikasiedoeleindes.

....
Date/*Datum* Signature/*Handtekening*

Date of admission: / *Datum van opname:* Date of discharge: / *Datum van ontslag:*

	Out patient / *Buitepasiënt*	In patient / *Binnepasiënt*	Out patient / *Buitepasiënt*	In patient / *Binnepasiën*
1.				
2.				

APPENDIX II

VISUAL ANALOGUE SCALE USED TO DETERMINE POSTOPERATIVE PAIN

NO PAIN |————————————————| WORST PAIN IMAGINABLE

SLIGHT MODERATE SEVERE

NO PAIN |————————————————| WORST PAIN IMAGINABLE

SLIGHT MODERATE SEVERE

NO PAIN |————————————————| WORST PAIN IMAGINABLE

SLIGHT MODERATE SEVERE

NO PAIN |————————————————| WORST PAIN IMAGINABLE

SLIGHT MODERATE SEVERE

NO PAIN |————————————————| WORST PAIN IMAGINABLE

SLIGHT MODERATE SEVERE

APPENDIX III

PATIENT INFORMATION
WOUND CARE FOLLOWING THIRD MOLAR SURGERY

Post operative instructions

1. Please ensure that your transport is arranged.

2. You may not drive on the day of the operation.

3. You may experience one or more of the following postoperatively:
   - sore throat
   - generalised body pain and muscle stiffness
   - pain in the region where the surgery was performed
   - inability to open the mouth widely
   - discolouration of the skin in the region of the surgery
   - swelling in the region of the surgery

Instructions to minimise discomfort

1. Take pain medication as prescribed when neccessary.

2. Take antibiotics as prescribed.

3. Rinse the mouth carefully following meals and before bedtime using the prescribed mouthrinse.

4. Apply lanoline, vaseline or nivea cream to the lips on a regular basis.

5.In the case of a bleed bite on a moist teabag (over the area of surgery) for one hour.

6. Sleep in the half sitting position for the first few days -this will limit the swelling.

7. For the first 24 hours take in only fluids and start thereafter with soft food.

8. If there are any problems please contact the surgeon on tel: 354-1000 page 3553.

APPENDIX IV

Table 1: Results Summary

Pat no. And age	Pain D 1-6 worst	Pain D 1 worst	Swelling worst side + day	Dry Socket + side	infectn	smoker	OC	gender	Ø time +	Ø time -
1. 17	NCS(sig)	NCS(sig)	D2 CS	None	none	no	no	female	5	5
2. 21	NCS(sig)	NCS(γs)	D2 NCS	None	none	no	no	male	5	5
3. 19	NCS(sig)	NCS(sig)	D2 NCS	None	none	no	no	male	9	7
4. 18	NCS(sig)	NCS(sig)	D4 NCS	None	none	no	no	female	5	7
5. 16	NCS(sig)	NCS(γs)	D2 NCS	None	none	no	no	female	12	9
6. 25	NCS(sig)	SS(γs)	D2 NCS	+ NCS	none	yes	no	male	8	8
7. 16	NCS(γs)	CS(sig)	D2 CS	None	none	no	no	male	7	7
8. 17	NCS(sig)	NCS(sig)	D1 NCS	None	none	no	no	female	9	9
9. 23	NCS(sig)	NCS(sig)	D2 NCS	None	none	no	yes	female	8	8
10. 27	NCS(sig)	CS(sig)	D2 NCS	+ NCS	none	yes	yes	female	8	8
11. 32	NCS(sig)	CS(sig)	D2 NCS	None	none	yes	no	male	12	12
12. 18	NCS(sig)	NCS(γs)	D2 NCS	None	none	yes	no	male	11	10
13. 20	NCS(sig)	NCS(sig)	D1 CS	None	none	no	no	male	5	3
14. 26	CS(γs)	NCS(sig)	D2 NCS	None	none	no	yes	female	10	10
15. 27	NCS(sig)	NCS(sig)	D2 CS	None	none	yes	no	male	5	10
16. 16	NCS(sig)	NCS(sig)	D2 NCS	None	none	no	no	female	9	9
17. 23	NCS(sig)	NCS(sig)	D2 NCS	+NCS	none	yes	no	male	10	10
18. 26	CS(sig)	CS(sig)	D2 CS	None	none	yes	no	male	7	7
19. 19	NCS(sig)	NCS(sig)	D3 NCS	None	none	no	no	female	8	8
Totals pts= 19	16/19 NCS(sig)	11/19 NCS(sig)	14/19 NCS	3/38 NCS	0/38	7/19 YES	3 YS	10/19 MALE		
Ø= 21.4			D2						8.1	8

KEY: D1-6 = visual analogue pain scores in the postoperative period
D1 = visual analogue pain scores on the first postoperative day
OC = oral contraceptive use
Øtime = time taken from the execution of the incision to placement of the last suture
NCS = non-covomycin side;
CS = covomycin side
day = day of worst swelling
sig = statistically significant difference
γs = no statistically significant difference
ssγs = sample size to small to reach statistical significance
Ø = mean

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Curriculum vitae

PERSONAL DETAILS

NAME:	Simon Peter van Eeden
ADDRESS:	167 Sixth Avenue, Edenvale, South Africa, 1610
TELEPHONE:	0944 11 4525095 (h), 0944 82 4638724 (cell), 0944 12 3192232 (w)
AGE:	39
DATE OF BIRTH :	1960/08/28
FAMILY STATUS:	Married with 2 daughters aged 2 and 5 years.
WIFE'S OCCUPATION:	General Medical Practitioner/ Clinical Psychologist.

EDUCATION

1977	Matriculated at Michaelhouse with a first class matric exemption.
1981	Left dentistry for 1 year to major in Physiology and Histology. Attained a BSc. Degree, University of the Witwatersrand.
1985	Attained BDS degree. Passed with an average of 70% within the top 10% of the class, University of the Witwatersrand.
1990	Attained FFD(SA) Part 1.
1997	Attained MBCHB degree Cum Laude (with honours), University of Pretoria.
1993 - 2000	Postgraduate student and registrar in MChD (Chir. Max.-Fac.-Med) University of Pretoria.

AWARDS

1977 Awarded a scholarship to complete post-matric at Michaelhouse.

1990 Awarded a research grant by the Dental Development Foundation of the Dental Association of South Africa for the research project entitled: The influence of geometry and pore size of hydroxyapatite substrata on the initiation of bone formation.

1995 Awarded an academic bursary for academic excellence in the fourth year of study for the MBCHB degree.
Awarded the prize for the best fourth year medical student in Community Medicine.

1996 Awarded an academic bursary for academic excellence in the fifth year of study for the MBCHB degree.

1997 Attained the MBCHB degree Cum Laude and awarded academic honours.
Awarded the prize for the best final year medical student in Obsterics and Gynaecology.
Awarded the prize for the best final year medical student in Urology.

1999 Successfully passed the Intermediate exam attaining distinction (75%).

1999 Successfully passed the Oral Pathology exam attaining distinction (80%).

Continuing Education:

- Osseointegrated implant course Durban 1991.
- Annual meeting of the South African Society of Oral and Maxillofacial Surgeons, Wildcoast, 1991.
- An update on Orthognathic surgery, Johannesburg (Jhb) 1992 - Prof. Henderson.
- Emergency Medicine course parts 1-4, Jhb 1992.
- Towards greater acuity in orthognathic surgery, Jhb. 1993 - Prof. J Reyneke.
- Maxillo-Facial and Oral Surgery, Jhb. 1993 - Prof. H Sailer.
- Orthognathic surgery, Durban 1994 - Prof. T Turvey

- An update on Facial trauma, Jhb 1994.
- Annual meeting of the South African Society of Oral and Maxillofacial Surgeons, Cape Town, 1994.
- Triangular Maxillofacial and Oral surgeons Congress, Cape Town,1996.
- Controversies in Head and Neck cancer, Pretoria 1997- Prof. J Shar.
- ATLS course, American College of Surgeons, Pretoria 1998.
- Annual meeting of the South African Society of Oral and Maxillofacial Surgeons, Sun City, 1998.
- Basic Surgical Skills Course, Royal College of Surgeons, England; Pretoria 1998.
- Towards greater acuity in orthognathic surgery, Jhb. 2000 - Prof. J Reyneke.

SCIENTIFIC ARTICLES AND PRESENTATIONS

1991 Co-author of:
A comparative study of patients treated using two different implant systems. Presented at the annual scientific session of the South African Society of Maxillofacial and Oral Surgeons.

1992 Co-author of:
Bone morphogenesis in porous hydroxyapatite substrata: Influence of biochemical coating, porosity and geometric configuration on the expression of the osteogenic phenotype. Presented at the Sixth Bone and Mineral Metabolism congress at the Twenty-eighth SEMDSA Congress.

1993 Co-author of:
Skeletal and soft tissue changes following advancement genioplasty. Reyneke JP and van Eeden SP. J DASA 48 627-630 1993.

1994 First author of:
Bone differentiation in porous hydroxyapatite in baboons is regulated by the geometry of the substratum: implications for reconstructive craniofacial surgery. Van Eeden SP and Ripamonti U. PRS 93(5) 959-66, 1994.

1994 Author of:
The critical role of geometry in bone induction. Presented at the annual scientific session of the South African Society of Maxillofacial and Oral Surgeons.

1996 Author of:
Bilateral condylar fractures: The Wassmund splint therapy. Van Eeden SP. 8(1) Hands On 9-12, 1996.

First author of:
A questionaire examination for a comparison in the treatment of facial trauma. Van Eeden SP and Lefkowitz B. Presented at the Triangular Maxillofacial and Oral surgeons Congress, March 1996.

First author of:
Caudally based single layer septum vomer flap for cleft palate closure: a follow up report. Van Eeden SP, Bütow K-W and Jacobs F. Presented at the Triangular Maxillofacial and Oral surgeons Congress, March 1996.

First author of:
Nasal dome projection, columella lengthening in bilateral cleft lip-nose. Van Eeden SP and Bütow K-W. Presented at the Triangular Maxillofacial and Oral surgeons Congress, March 1996.

1999 First author of:
Topical combined anti-inflammation/antibiotic preparation effects on third molar surgery outcome. Van Eeden SP and Bütow K-W. Presented at the Thirty-third IADR Congress, August 1999.

EMPLOYMENT HISTORY

1985 Commenced compulsory military service in July 1985.

1986 Completed 4 months on the South West African border (now Namibia) in the Caprivi strip in charge of dental services for the sector.

1987 Transferred to the State hospital service where 6 months was spent in the Maxillofacial unit at King Edward VII hospital.

Finished compulsory military training in July 1987. Commenced work as an associate in a private dental practice in Durban. Left after 8 months to travel and work in London.

1988 Commenced work as a general dentist as an associate in London. Remained in London for a period of 2 years.

1990 Returned to South Africa and commenced work as an associate in a private practice in Johannesburg. Commenced work as an honorary member of staff in the Maxillofacial department of the University of the Witwatersrand.

1991 Joined the Maxillofacial department of the University of the Witwatersrand as a part-time member of staff doing seven sessions per week. Continued to work privately as an associate general dentist.

1992 Continued as a part time member of staff in the Maxillofacial department of the University of the Witwatersrand but increased the number of weekly sessions to 25 per week. Continued to work privately as an associate general dentist.

1993 Appointed as a full time registrar in Maxillo-Facial and Oral surgery in a fully accredited higher training post as a specialist registrar. Completed 9 months at Baragwanath hospital and 3 months at JG Strydom and University of the Witwatersrand Dental School hospital.

1994 Completed 3 months at JG Strydom and University of the Witwatersrand Dental school hospitals. Transferred to the Pretoria circuit affiliated with Pretoria University (in a fully accredited higher training post as a specialist registrar) and completed 4 months at Pretoria Academic hospital/Dental School hospital, 3 months at 1 military hospital and 3 months at Kalafong hospital.

1995 Completed 12 months at Pretoria Academic hospital/Dental School hospital.

1996 Completed 12 months at Pretoria Academic hospital/Dental School hospital.

1997 Completed 12 months at Pretoria Academic hospital/Dental School hospital.

1998 Completed 12 months at Pretoria Academic hospital as a

medical intern spending 2 months in paediatrics, 4 months in Internal medicine, 2 months in ENT and 4 months in General Surgery in the combined general surgery/head and neck unit.

1999 Spent 2 months as a registrar in Neurosurgery, 2 months in Plastic surgery and 2 months in Surgical Intensive Care. Spent 2 months at 1 military hospital and 4 months at Pretoria Academic hospital/Dental school hospital.

PROFESSIONAL AFFILIATIONS

1985 South African Medical and Dental Council registration: Dental Surgeon

1989 General Dental Council, UK, registration: Dental Practioner.

1995 Student member of the South African Society of Maxillo-Facial and Oral Surgeons.

1998 Health professions Council of South Africa registration as a General Medical Practitioner.

1998 Medical Association of South Africa.

1998 Trauma Society of South Africa.

1999 General Medical Council, UK, full registration: General Medical Practitioner.

HOBBIES AND INTERESTS

TRAVEL I have traveled extensively throughout Southern Africa; I have traveled through Europe, Israel and Turkey. While living in London I traveled the United Kingdom visiting Ireland, Wales, Scotland and much of England.

SPORT Colours awarded at school for hockey for 2 years. Represented the University of the Witwatersrand First XI and Southern Transvaal country districts XI in hockey. Represented the