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A split mouth, double blind, placebo controlled trial to assess the impact of a lidocaine / prilocaine 2.5% / 2.5% anaesthetic gel when carrying out probing in a group of advanced periodontitis patients.

A Thesis submitted to the University of Dublin in partial fulfilment of the degree of Doctorate in Dental Surgery D.Ch.Dent. (Periodontology)

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2010

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at any other university. It consists of my own work, except where due acknowledgement has been made in the text.

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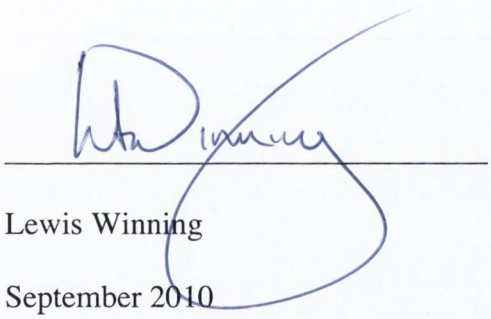

Lewis Winning

September 2010

Summary

The aim of the study was to evaluate the efficacy of an intra-pocket anaesthetic gel (Oraqix®, Dentsply Pharmaceutical, York, Pennsylvania, USA) in the reduction of pain on periodontal probing in a group of untreated generalised chronic periodontitis subjects.

The study was a randomised, double-blinded, split-mouth, placebo controlled trial. Thirty consecutive patients meeting the inclusion criteria had full mouth periodontal probing carried out. Prior to probing each quadrant was isolated and had a randomised gel (either placebo or test gel) placed in the periodontal pockets for 30 seconds, which was subsequently washed out following completion of probing in that quadrant. Pain was measured using two ungraded 100mm horizontal Visual Analogue Scale (VAS) representing right and left sides of the mouth.

The mean VAS for the test gel was 23.5mm(SD±16.8), and 51.6mm(SD±14.6) for the placebo gel. The mean reduction in VAS was 28.11mm in favour of the anaesthetic gel. A wilcoxon signed rank test was performed which showed the difference to be highly statistically significant; $p<0.0001$ (95% confidence interval: 24.00 - 38.50).

The VAS pain scores showed the favourable anaesthetic efficacy of the test gel compared to a placebo gel in reducing patient's pain on periodontal probing in a group of untreated, generalised, severe, chronic periodontitis patients. Furthermore the results suggest that the number of patients experiencing significant pain was less for the test sides compared to placebo sides. Such a gel may be used for those patients who find the

full mouth periodontal probing experience particularly painful in view of few tested alternatives.

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Chapter 1

Introduction

Introduction

The gathering of baseline information for the purposes of full mouth periodontal examination, if indicated, involves periodontal probing at six sites per tooth on all teeth. Not only is this gathering of information employed at baseline, but subsequently at re-evaluation, and thereafter as a tool for monitoring stability or progression of periodontal disease long term. If we examine the literature for the last number of decades, from the early periodontal studies to the more recent studies, evaluation of any response to therapy is measured most of all through the surrogate variable periodontal probing depth, and its derivatives loss of attachment and clinical attachment level.

In particular, the baseline periodontal examination has been reported, as one of the most painful dental procedures as patient's periodontal tissues are in their most inflamed state (van Steenberghe et al. 2004a). Periodontal probing has been reported to be a significantly painful experience for as many as 77% of patients with untreated periodontal disease (Magnusson et al. 2003, Al-Ajmi et al. 2005). Fowler et al. (1982) demonstrated on a histological level, that in an untreated, inflamed periodontal site, the periodontal probe penetrates the epithelium at the base of a periodontal pocket into the surrounding connective tissue, which is heavily infiltrated with inflammatory cells. Whereas in a treated, non-inflamed site, the periodontal probe dose not penetrate through the epithelium at the base of the pocket.

Quantification of pain as a measurement is inherently difficult, as it has both physical and psychological aspects. A common method utilised in pain studies is the Visual Analogue Scale (VAS). This scale has previously been shown to be simple to administer, reliable, and valid (Scott & Huskisson 1976, Bennett et al. 1991).

Heft et al. (1991) investigated the relationship between pain on periodontal probing and inflammation of the gingival tissues through studying the degree of painfulness on periodontal probing before and after initial periodontal therapy. They observed that as visual signs of inflammation and bleeding on probing decreased so too did the VAS for pain score, suggesting that there is a positive correlation between the degree of periodontal inflammation and the pain and discomfort associated with periodontal probing.

Currently, there are limited practical techniques to reduce pain on periodontal probing. Injection anaesthesia has been used, but for the purposes of full mouth periodontal probing, the unwanted side effects of prolonged anaesthesia, anaesthesia of adjacent structures such as the lips and tongue, and the psychological trauma of receiving multiple invasive 'injections', render it of limited use. Topical anaesthetics (jellies, ointments or sprays) may be preferred because they produce less post-procedure numbness (van Steenberghe et al. 2004b), but problems relating to lack of efficacy due to inadequate depth of penetration, uncontrolled spreading, too short duration of action, and difficulties of administration have limited their use (Milgrom et al. 1997).

More recently an intra-pocket anaesthetic gel (Oraqix®, Dentsply Pharmaceutical, York, Pennsylvania, USA) has been evaluated for scaling and root planing procedures in a variety of patients (Friskopp et al. 2001, Friskopp and Huledal 2001, Jeffcoat et al. 2001, Donaldson et al. 2003, Magnusson et al. 2003, van Steenberghe et al. 2004b). Oraqix® contains the active ingredients lidocaine 25mg/g and prilocaine 25mg/g and a thermosetting agent. At room temperature it exists as a low viscosity fluid, whereas when applied into a periodontal pocket, it transforms to an elastic gel. This feature

allows it to remain at the application site providing controlled anaesthesia. As yet the use of Oraqix® has not been evaluated for purposes of anaesthesia in full mouth probing procedures.

The aim of this study, therefore, is to evaluate the efficacy of an intra-pocket anaesthetic gel (Oraqix®) in the reduction of pain on periodontal probing in a group of untreated periodontal subjects.

Chapter 2

Literature Review

2.1 Pain

According to Melzack (1973), 19th century physiologists perceived pain to be a purely sensory experience, while others held that pain was solely an emotional response; Sherrington in 1900 was among the first to propose that pain involved both sensory and affective aspects.

The International Association for the Study of Pain (IASP) has defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Merskey et al. 1994). It is clear from this definition that tissue damage and pain perception are not necessarily correlated, and that the patient's account of pain should be accepted as his or her own perception of the problem. Moreover, pain perception is the sum of complex sensory, emotional and cognitive processes, represented by the biopsychosocial model of pain (Engel 1977, Engel 1980).

2.2 Measurement of Pain

As pain is a subjective experience, its objective measurement is quite difficult. Various methods have been developed in an attempt to quantify a patient's pain experience. There are a large number of pain measurement instruments that have been developed for use. They can be broadly described as unidimensional or multidimensional. Two of the most commonly used scales in pain studies within the dental literature are the verbal rating scale (VRS) and the visual analogue scale (VAS), both of which are of the unidimensional type.

A verbal rating scale (VRS) consists of a list of adjectives describing different levels of pain intensity or pain affect, ordered from least to most intense. The patient has to read the list and then choose the one word that best describes the intensity of their pain experience at a particular time point. Many different VRS lists (with variations in pain intensity levels) have been created.

The strengths of VRSs include the ease by which they can be administered and scored. Because they are generally easy to understand, compliance rates for VRSs are as good or better than those for other measures of pain intensity under most conditions (Jensen et al. 1986). Also, VRSs have consistently demonstrated their validity as indicants of pain intensity (Jensen et al. 1986, Jensen et al. 1989). They are related positively to other measures of pain intensity (Turk & Melzack 2001).

A limitation of this rank scoring method is that it assumes equal intervals between the adjectives, even though it is unlikely that equal intervals exist. That is, the interval between no pain and mild pain may be much smaller than that between moderate pain and severe pain, yet each interval is scored as if these differences were the same. A second problem is that VRSs represent ordinal scaling data. Verbal rating scale scores are often treated as if they were interval or ratio data, and subsequently analyzed using parametric statistical procedures rather than the appropriate nonparametric procedures. A third problem is that VRSs lacks sensitivity and does not allow for finer grade pain assessments. The small number of descriptors may force the patient to choose a particular category that may not describe the pain satisfactorily, and that the actual adjective used doesn't accurately express the intensity of the pain experience (Ong & Seymour 2004).

The visual analogue scale (VAS) consists of a line, usually 10 cm long, whose ends are labeled as the extremes of pain (e.g., no pain to unbearable pain). A VAS may also have specific points along the line that are labeled with numbers or intensity-denoting adjectives. Such scales are called graphic-rating scales. Patients are asked to indicate which point along the line best represents their pain intensity. The distance from the no pain end to the mark made by the patient is that patient's pain intensity score.

The VAS is widely used and has the advantage of simplicity. It is easily understood by most patients and can be readily reproduced on successive presentations. Children from age seven can understand it (Ashburn & Rice 1998). It is sensitive to pharmacological and nonpharmacological procedures, which alter the experience of pain (Seymour 1982, Joyce et al. 1975). A major advantage of the VAS is its ratio scale properties and so may be treated as such statistically (Price et al. 1994). In contrast to many other pain measurement tools, equality of ratios is implied, making it appropriate to speak meaningfully about percentage differences between VAS measurement s obtained either at multiple points in time, or from independent samples of subjects (Ong & Seymour 2004). The scale also has a high number of response categories. This makes the VAS potentially more sensitive to changes in pain intensity than measures with limited numbers of response categories. Research indicates that the VAS of pain intensity is usually more sensitive and more reliable to treatment changes than VRS (Seymour 1982, Joyce et al. 1975, Downie et al. 1978, Max et al. 1988).

2.3 Pain experienced during dental procedures

There have been various studies reporting on the magnitude of pain reported by patients during and following dental procedures. The majority of the available literature use pain VAS as the primary outcome measure. A representative sample of mean pain values has been reproduced (Maguire 2007) and is schematically presented in Fig 2.1.

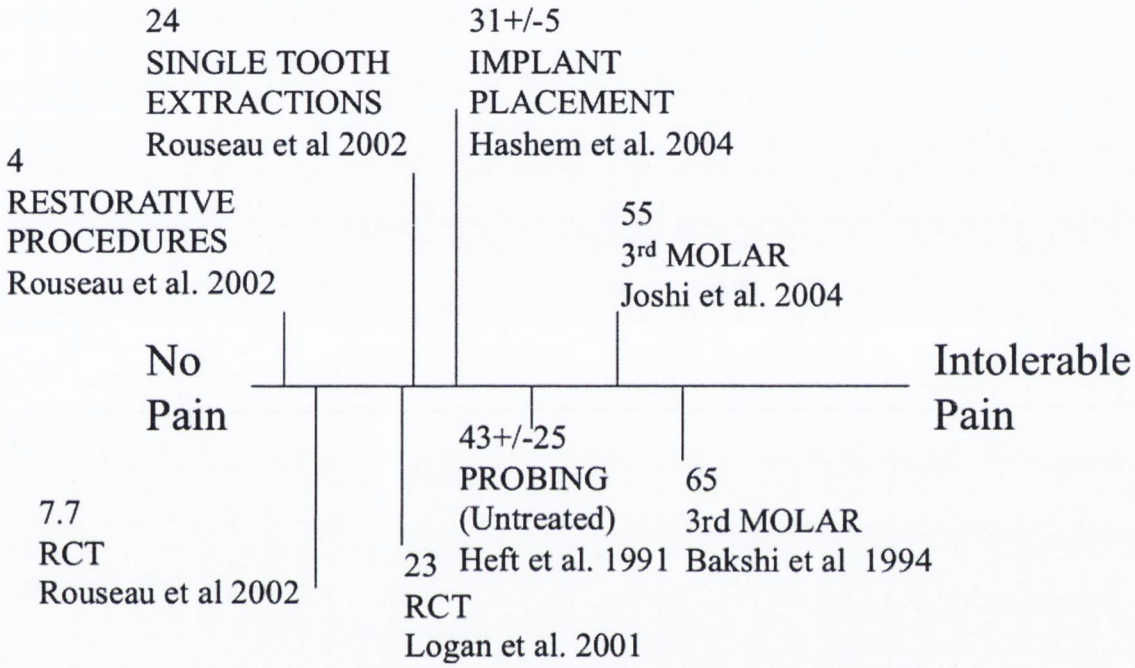

Figure 2.1
Pain values represented as mean VAS (mm) +/- standard deviation for various dental procedures (Maguire 2007).

The above mentioned studies were all pain studies focusing on various dental procedures. Rousseau et al. (2002) carried out a study on 250 patients regarding their pain levels prior to treatment and their pain levels during the different dental procedures. Of the total number of patients, 150 had a pulpectomy, 50 patients had a single extraction, and 50 patients had a single restoration. Experienced clinicians undergoing specialist training carried out all procedures. The results showed extraction caused more pain than RCT or restoration.

Hashem et al. (2006) investigated pain experience and anxiety following dental implant placement using questionnaires and salivary cortisol measurements. Eighteen patients having thirty implants placed were included in the study. The authors concluded 'patient self-assessment indicates that implant placement is a mild to moderately painful and anxiety-provoking procedure'. Heft et al. (1991) performed a periodontal probing study to analyses was the degree of inflammation related to pain score. (This study is discussed in detail in section 2.4). The literature seems to deem 3rd molar surgery as being the most painful with Joshi et al. (2004) and Bakshi et al. (1994) reporting high VAS scores in comparison to the other studies.

It is clear from the literature review that periodontal probing in untreated patients is a significantly painful procedure in relation to other procedures such as RCT, single tooth extraction or implant placement. It should also be noted that periodontal probing is usually carried out without local anaesthesia.

2.4 Periodontal Probing and Pain

Periodontal probing in patients with untreated periodontal disease often results in the probe penetrating through the inflamed pocket epithelium, into the underlying connective tissues. Fowler et al. (1982) demonstrated on a histological level, that in an untreated, inflamed periodontal site, the periodontal probe penetrates the epithelium at the base of a periodontal pocket into the surrounding connective tissue which is heavily infiltrated with inflammatory cells. Whereas, in a treated, non-inflamed site, the periodontal probe dose not penetrate through the epithelium at the base of the pocket.

Despite being one of the most frequently performed oral procedures, pain upon periodontal probing has received little attention from the literature.

Heft et al. (1991) studied the relationship of gingival inflammation to the pain associated with periodontal probing. 46 patients were assessed at baseline, 1 month, and 3 months. At each of the 3 sessions, clinical measures of gingival inflammation included an observational gingival index and bleeding score. In addition, periodontal probing of all existing teeth was performed with a constant force probe (25 g). Following completion of the probing at each session, subjects rated the painfulness of the probing using a visual analogue scale for pain. Results of this study showed that judged painfulness of probing was related to clinical inflammation (bleeding score) at baseline and 1 month and suggest that the degree of periodontal inflammation is related to the pain and discomfort associated with periodontal probing, (See figure 2.2). However it may not be excluded that patients became more accustomed to periodontal treatment and thus experienced less anxiety and therefore less pain.

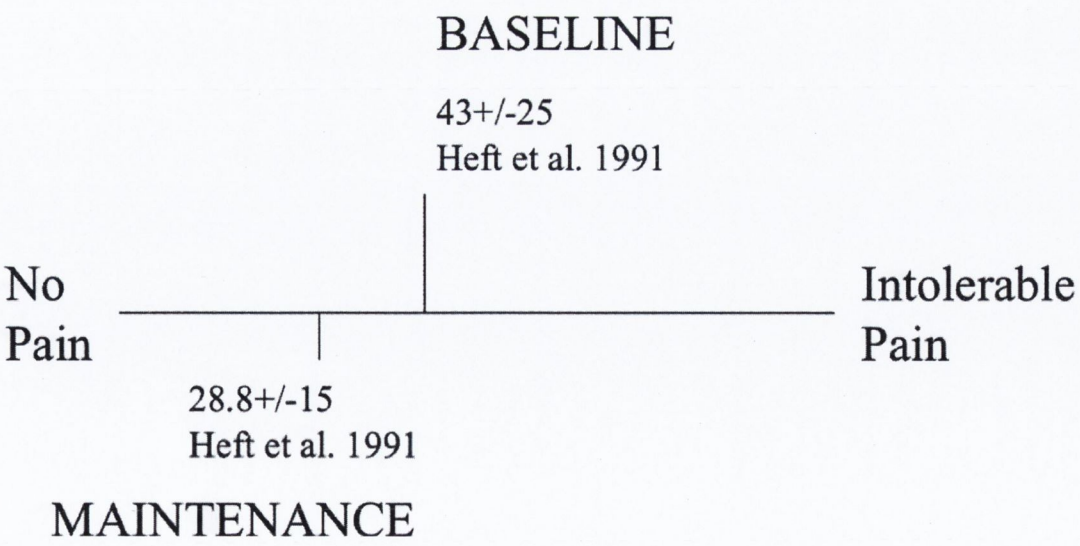

Figure 2.2
Pain values represented as mean VAS (mm) +/- standard deviation for pain on probing at baseline and during maintenance (Heft et al. 1991).

Heins et al. (1998) assessed the probing pain thresholds of 10 periodontally healthy individuals. A higher threshold for maxillary molar sites than maxillary incisor sites was observed. This corresponds to a greater density of free nerve endings in the anterior areas of the gingiva (Tolman et al. 1965). Heins et al. (1998) also suggested that there was an inter-subject variability and classified individuals as least pain sensitive individuals and most pain sensitive individuals.

Karadottir et al. (2002) investigated the degree of pain experienced by patients during probing and debridement procedures utilizing pain VAS and a pain frequency-tallying device. They determined whether these responses could be predicated by the patient's age, gender, percentage of sites ≥4mm deep, and responses to a questionnaire on dental anxiety. The results showed that when using arbitrary thresholds of pain frequency ≥50% and VAS ≥40mm, approximately 15% of the patients had a significantly painful experience. Stepwise multiple regression analysis disclosed that significant proportions of the pain levels could be predicted by gender and the patient's answers to two of the dental anxiety questions.

Chung et al. (2003) carried out a study in which 2 dental hygienists recorded VAS's for their perception of the pain experienced by patients during both probing and debridement procedures. This was then correlated with the actual VAS recorded by the patient for both these procedures. Patients also completed an anxiety questionnaire. Using the arbitrary threshold of VAS ≥40mm, 20% to 33% of patients had a significant pain experience. The operators were quite accurate in their relative predictions of patient's pain experiences. Regression analysis disclosed that significant portions of the

pain responses could be predicted by the patient's answers to one of the dental anxiety questions.

In a similar study, Al-Ajmi et al. (2005) investigated the pain reported using a VAS during probing on three groups of 20 patients presenting for periodontal assessment. Three periodontists carried out full mouth probing and independently rated the pain level they perceived that each patient experienced also using a VAS. Again, using the arbitrary threshold of VAS ≥40mm to indicate significant pain, 9 of the 20 patients had a significant painful experience. Differences were observed between the pain levels expressed by the three groups of patients. While two of the three periodontists were able to appraise the pain experienced by their patients, the third was not.

Hassan et al. (2005) carried out a study on three groups of twenty patients, each examined by three different therapists, using two probe tip diameters, (0.40mm and 0.63mm). The pain levels expressed by the three groups of patients varied, confirming the previously mentioned studies, which also observed differences in patient's pain experiences following probing by different therapists. Lower median pain responses following probing with the 0.63mm probe compared to the 0.40mm were reported for patients of one of the therapists, and for the quartile of all 60 patients that showed the highest VAS scores. For the other 2 therapists no differences were observed.

Kim et al. (2007) conducted a study to determine whether periodontal residents could enhance their ability to assess the pain levels experienced by their patients during probing using VAS to record pain. For each of three periodontal residents, forty consecutive patients with periodontal disease were asked to express the degree of pain

they experienced during probing. Independently the residents rated the pain levels they perceived that the patients had experienced. The two recordings were compared, and then discussed between the residents and their patients. Over time the differences between patient and examiner's VAS were observed to gradually become smaller. The authors summarised that 'the training program improved the resident's ability to estimate the pain experiences of their patients', and 'this training program, using periodontal probing as a model, could serve as an educational tool for students and practitioners who want to improve their sensitivity to their patient's pain experiences'.

2.5 Probing force and probing pressure

Periodontal probing should be accurate and technically simple (Hefti 1997). The current probing methods are subject to various errors. Amongst other errors, there appears to be a relationship between probing force and pocket penetration (Hassell et al. 1973, Van der Velden 1979, Mombelli et al. 1992).

As discussed in the previous section, the degree of probe tip penetration into the pocket is also influenced by the presence of inflammation of the periodontal tissues (Armitage et al. 1977, Van der Velden 1980, Fowler et al. 1982, Bulthuis et al. 1998). Even with relatively high forces, the probe tip usually fails to reach the connective tissue attachment in healthy sites (Fowler et al. 1982). In inflamed sites the probe tip generally stops, already with minimal probing pressures, at the level of intact connective tissue fibres or may even penetrate beyond (Bulthuis et al. 1998).

To be able to enter the pocket with a periodontal probe, a certain force is needed to overcome the resistance (tonus) of the gingival tissues; not only the force applied but also the dimensions of the probe tip should be considered (Garnick & Silverstein 2000). Probing force as such has been recognised as an important factor in measuring pocket probing depth but little attention has been paid to the issue of probing pressure.

Probing pressure is a product of the probing force (N) relative to the tip diameter (mm). The pressure exerted by the probe is directly proportional to the force on the probe and inversely proportional to the surface area at the probe tip (Garnick & Silverstein 2000).

It has been described that with increasing probing force i.e. probing pressure, the recorded probing depth will increase (Robinson & Vitek 1979, Van der Velden 1979, Barendregt et al. 1996). The histological locations of the probe tip considered to be the most relevant in periodontal diagnostics, are the base of the periodontal pocket and the most coronal connective tissue attachment (Aguero et al. 1995). Bulthuis et al. (1998) showed that in diseased sites, the tapered probe (tip diameter 0.5 mm) with a 0.25N force was on average located at this level. In healthy/treated sites in humans, even pressures up to 400 N/cm2 left the probe tip coronal to this landmark by a mean of 0.73mm (Fowler et al. 1982). This means, an over or underestimation of the true attachment level will still occur when assessing the pocket probing depth (Listgarten 1980, Kalkwarf et al. 1986).

Periodontal probing registers resistance of the tissue to the pressure applied by the probe: the greater the pressure, the greater the advancement of the probe into the tissues. However, the advancement depends on the resistance of the tissue at the site being

measured (Garnick & Silverstein 2000). With a specific pressure, the probe will proceed until a reaction pressure develops from deformation of tissues (Aguero et al. 1995). Tissue pressure that resists probe displacement depends on the tissue morphology including loss of connective tissue attachment and the severity of tissue inflammation. Accordingly, this tissue pressure will vary (Aguero et al. 1995). With treatment, inflammation is reduced and/or tissue attachment is increased, the resistance to probing pressure is increased and the displacement of the probe will be less. The difference in probing depth therefore reflects a reduction of inflammation and the response to treatment (Garnick & Silverstein 2000).

From the search of the literature, no studies were identified that have investigated the relationship between probing force or pressure and pain on periodontal probing.

2.6 Neurophysiology of local anaesthetics

It has been established that the primary effects of local anaesthetics occur during the depolarization phase of the action potential (Dejong & Wagman 1963). The nerve membrane is the site at which local anaesthetics exert their pharmacological actions. There have been various theories proposed explaining the mechanism of action of local anaesthetics, these include; the acetylcholine theory (Dettbarn & Bartels 1968); the calcium displacement theory (Goldman & Blaustein 1966); the surface charge (repulsion) theory (Wei 1969); the membrane expansion theory (Lee 1976); and the specific receptor theory (Arthur & Strichartz 1987).

The specific receptor theory is the most favoured today. This theory proposes that local anaesthetics act by binding to specific receptors on the sodium channel. The action of the drug is direct, not mediated by some change in the general properties of the cell membrane. Both biochemical and electrophysiological studies have indicated that a specific receptor site for local anaesthetic agents exists in the sodium channel either on its external surface or on the internal axoplasmic surface (Butterworth & Strichartz 1990, Ritchie 1975). Once the local anaesthetic has gained access to the receptors, permeability to sodium ions is decreased or eliminated and nerve conduction is interrupted.

The primary action of local anaesthetics in producing a conduction block is to decrease the permeability of the ion channels to sodium ions (Na^+). Local anaesthetics selectively inhibit the peak permeability of sodium. The following sequence is the proposed mechanism of action of local anaesthetics:

1. Displacement of calcium ions from the sodium channel receptor site,
2. Binding of local anaesthetic molecules to this receptor site,
3. Blockade of the sodium channels,
4. Decrease in sodium conductance,
5. Depression of the rate of electrical depolarization,
6. Failure to achieve the threshold potential level,
7. Lack of development of propagated action potentials,
8. Conduction blockade.

(Covino & Vassallo 1976, Malamed 2004)

An impulse that arrives at a blocked nerve segment is stopped because it is not able to release the necessary energy for propagation. Nerve block produced by local anaesthetics is called a nondepolarizing nerve block. Local anaesthetics are classified as either amine esters or amino amides according to their chemical linkages. The nature of this linkage is important in defining several properties of the local anaesthetic.

2.7 Topical anaesthetics

Local anaesthetics for topical application can be incorporated into a number of different preparations. The type of preparation can affect efficacy. It has been shown (Giddon et al. 1968) that lower concentrations of lignocaine were needed in film strips compared to the concentration in sprays to achieve the same level of analgesia. The different methods by which topical anaesthetics may be applied intra-orally include:

1. as water soluble salts,
2. dissolved in organic solvents,
3. as oil-water emulsions;
4. as eutectic mixtures;
5. incorporated into patches and controlled release devices;
6. using iontophoresis and phonophoresis;
7. incorporated into liposomes.

(Meechan 2000)

Conventional dental topical anaesthetics are unable to penetrate intact skin but do diffuse through abraded skin (eg. that occurring with sunburn) or any mucous membrane. The concentration of a local anaesthetic applied topically is typically

greater than the same local anaesthetic administered by injection. The higher concentration facilitates diffusion of the drug through the mucous membrane. Many local anaesthetics used effectively via injection prove to be ineffective when applied topically (eg. articaine, mepivacaine, prilocaine, and procaine) because the concentrations necessary to produce anaesthesia via topical application are high, with significantly increased overdose and local tissue toxicity potential (Malamed 2004).

Two of the common dental topical anaesthetics are benzocaine and lidocaine. Benzocaine is an ester, while lidocaine is an amide. These topical anaesthetics are insoluble in water, but soluble in alcohol, propylene glycol, polyethylene glycol, and other vehicles for surface application.

2.8 EMLA® (Eutectic Mixture of Local Anaesthesia)

EMLA® cream (EMLA® cream; AstraZeneca International, Södertälje, Sweden) composed of lidocaine 2.5% and prilocaine 2.5%, is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. It was designed as a topical anaesthetic able to provide surface anaesthesia of intact skin (other topical anaesthetics do not produce a clinical action on intact skin, only abraded skin), and as such is used primarily before procedures such as venipuncture, and other needle insertions (Malamed 2004).

EMLA® use has become almost routine during leg ulcer debridement (Vanscheidt et al. 2001), circumcision (Taddio 2001), and in gynaecological procedures (Wright 2001).

EMLA® is contraindicated for use in patients with congenital or idiopathic methemoglobinemia, infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents, or patients with a known sensitivity to amide-type local anaesthetics or any other component of the product (AstraZeneca 2000).

Due to EMLA® being effective in penetrating intact skin, its ability to produce effective topical anaesthesia intra-orally would seem likely. EMLA® cream for intra-oral use has been investigated in several studies:

Donaldson & Meechan (1995) carried out an investigation comparing the use of EMLA® cream to a 'standard' intraoral topical anaesthetic (5% lidocaine) as a means of anaesthetising the gingival sulcus. 14 individuals were recruited in a double blind, split-mouth study. A 5-minute application of EMLA® in a customised intra-oral splint resulted in a significant increase in depth of probing of the gingival sulcus without discomfort compared to a similar application of 5% lidocaine. The authors concluded 'EMLA® may be advantageous in providing periodontal anaesthesia where manipulation of the gingiva is necessary'.

Svensson et al. (1994) studied the efficacy of EMLA® on pain and unpleasantness provoked by scaling of periodontal pockets. 20 patients with mild chronic periodontitis were selected to take part in a balanced, randomized, double-blind, split-mouth design. EMLA® or a placebo cream was applied and occluded by Orahesive Oral Bandages. Pain intensity and unpleasantness were evaluated on 100 mm visual analogue scales (VAS). Mean reductions in VAS pain intensity in favour of the EMLA® bandage were

58.9% and 61.9% for the maxilla and mandible respectively. Corresponding reductions in unpleasantness were 31.9% and 25.6% respectively. The authors concluded that study demonstrated the efficacy of EMLA® in a clinical situation and stated that it 'may be recommended as a simple pharmacologic strategy to reduce pain and unpleasantness during scaling procedures'.

Vickers & Punnia-Moorthy (1992) compared the 2 min application of 5% lignocaine, 15% benzocaine with 1.7% amethocaine, and EMLA® on the discomfort produced by insertion of a 27 gauge needle to a depth of 5 mm in the maxillary premolar buccal sulcus in a double-blind splitmouth investigation. They found that their volunteers reported significantly less pain with all active agents compared to placebo and concluded that EMLA® was the most effective of the topical preparations.

Meechan & Winter (1996) compared the efficacy of placebo, transcutaneous electronic nerve stimulation (TENS) and a 5 min application of EMLA® on palatal mucosa. They found that EMLA® was significantly more effective than either placebo or TENS in reducing the discomfort of palatal injections of 2% lignocaine with 1:80,000 adrenaline in adult patients having maxillary teeth extracted.

Meechan & Thomason (1999) compared different topical preparations as treatments to reduce the discomfort of periodontal ligament injections. They found that injection discomfort was less following a 5 min application of EMLA® compared to a similar application of 5% lignocaine in a double-blind split-mouth study in volunteers.

2.9 Oraqix®

Oraqix® (Dentsply Pharmaceutical, York, Pennsylvania, USA) lidocaine and prilocaine periodontal gel 2.5%/2.5%, is a microemulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature; therefore both local anaesthetics exist as liquid oils rather than crystals. Oraqix® contains poloxamer excipients, which show reversible temperature-dependent gelation. Together with the lidocaine-prilocaine 1:1 mixture, the poloxamers form a low-viscosity fluid system at room temperature and an elastic gel in the periodontal pocket. Geletation occurs at body temperature, followed by the release of the local anaesthetics, lidocaine and prilocaine. Prilocaine base and lidocaine bases are both relatively hydrophilic amino-amides. They both block sodium ion channels required for the initiation and conduction of neuronal impulses, resulting in local anaesthesia. The onset of local anaesthesia after application occurs after 30 seconds and a longer waiting time does not enhance the anaesthetic effect. Anaesthetic effect lasts for about 20 minutes (Denstply 2005).

2.10 Oraqix® studies

There have been several studies evaluating the efficacy of Oraqix® gel, (Friskopp & Huledal 2001, Friskopp et al. 2001, Jeffcoat et al. 2001, Donaldson et al. 2003, Magnusson et al. 2003, van Steenberghe et al. 2004b).

Friskopp et al. (2001) in a randomised, parallel-group, open-labelled study examined the onset and duration of Oraqix® in a group of thirty people having scaling and root planing (SRP). Patients were randomised to 3 groups with durations of 30 seconds, 2

min, or 5 min of treatment with the gel prior to SRP of a tooth. On completion of SRP of each tooth (2-3 teeth were treated per patient), the patients rated their pain on a 100mm visual analogue scale (VAS). Mean duration of anaesthesia was also measured as pain on probing. The authors observed that Oraqix® provided effective anaesthesia after an application time of 30 seconds, with a mean duration of effectiveness of 17 to 20 minutes.

Friskopp & Huledal (2001) in a second study investigated the plasma levels of lidocaine, prilocaine, and two of their metabolites following a single dose of Oraqix® in a group of 10 patients with severe periodontal disease. Peak plasma concentration of lidocaine (96-266 ng/ml) and prilocaine (26-118 ng/ml) occurred 20-40 minutes after the start of application. These levels were low compared to those reported to cause initial signs of CNS toxicity (5000-6000 ng/ml). Side-effects were reported as being few and of mild local effects of short duration. The authors concluded, that there was a large safety margin with respects to systemic effects following the application of up to 3.5 grams Oraqix® in periodontal pockets.

Jeffcoat et al. (2001) conducted a double-blinded, multicentre trial using Oraqix®. 122 patients spread over 8 centres, all of which had moderate to severe periodontitis and required scaling and root planing (SRP) were enrolled. A test quadrant was selected, and patients had either a placebo or the active gel applied, followed by SRP. After all the teeth in the test quadrant had received SRP, the overall pain was assessed by the patient using a 100 mm horizontal, ungraded visual analogue scale in which the left side was marked 'no pain' and the right side marked 'worst pain imaginable'. Patients also assessed pain by using a 5-point verbal rating scale, from 'no pain' to 'very severe pain.'

The visual analogue scale showed significant reductions in reported pain, favouring the active gel over the placebo (mean reduction, 8mm; $P<0.0005$). The verbal rating scale revealed that 90% of patients treated with active gel reported no pain or mild pain compared to 64% of placebo-treated patients ($P<0.001$). The authors conclude that Oraqix® may offer an alternative to infiltration anaesthesia for SRP procedures.

In another multi-centre trial in six Canadian dental schools a similar design was used (Donaldson et al. 2003). The study consisted of 130 patients and either the test gel or a placebo gel was applied in a test quadrant of the mouth in a randomized, double-blind fashion, before SRP was carried out. Patients again completed a Visual Analogue Scale (VAS) and a Verbal Rating Scale (VRS). The median VAS pain score for the patients treated with the anaesthetic gel was 5mm (range 0-85) as opposed to 13mm (range 0-79mm) in the placebo treated patients ($P=0.015$). There was no significant difference in the percentage of patients reporting no or mild pain; 78% and 76% for the anaesthetic gel and placebo, respectively. The authors concluded that VAS pain scores showed that Oraqix® was statistically more effective than the placebo in reducing pain during periodontal debridement.

Magnusson et al. (2003) suggested that the anaesthetic gel is more effective in 'pain sensitive patients'. 113 patients with severe periodontitis were screened for pain sensitivity on probing. Eighty-five reported VAS ≥30mm on probing and were included in the treatment phase; 43 in the anaesthetic group and 42 in the placebo gel group. In the same way as the previous studies, one quadrant was selected for testing with either the placebo or test gel, followed by scaling and/or root planing, with VAS and VRS being the outcome measures. The median VAS pain score was 11mm in the

anaesthetic group and 27mm in the placebo group. The Hodges-Lehmann point estimate of the treatment difference was 10 mm (P=0.004). No pain or only mild pain was reported by 70% in the anaesthetic group and by 48% in the placebo group (P=0.003). The authors concluded that the study demonstrated the favourable efficacy of the active gel over a placebo gel in selected pain-sensitive patients.

Van Steenberghe et al. (2004b) carried out a multicentre, crossover, randomized open study, in which patients were asked to evaluate the test gel versus conventional anaesthesia during scaling and or root planing. In addition the adequacy of anaesthesia and occurrence of post-procedure problems were assessed. The patients were also asked about their willingness to return if they were offered anaesthetic gel at their next visit. 157 patients completed the study; 70% preferred the anaesthetic gel to injection anaesthesia 22%. The most common reason was less post-procedure numbness. 80% of patients expressed satisfactory anaesthesia with the gel and 96% with injection anaesthesia. Post procedure problems were significantly less with the gel than with injection (P<0.001). The anaesthetic gel would make almost every second patient more willing to return for the next treatment. The authors concluded that a somewhat less profound anaesthesia with the gel was clearly preferred by the patients because of the low incidence of post-procedure problems as compared to conventional anaesthesia.

As yet, there have been no clinical trials assessing the use of Oraqix® for purposes of full mouth periodontal probing. Although the studies mentioned have shown a small but statistically significant benefit in using the anaesthetic gel over a placebo gel for scaling and root planing procedures, it should not be presumed that this effect would still be observed when carrying out probing in untreated periodontal subjects.

2.11 Aims of study

The aim was to evaluate the efficacy of an intra-pocket anaesthetic gel (Oraqix®) compared with a placebo gel in the reduction of pain on periodontal probing in a group of untreated generalised chronic periodontitis subjects.

Chapter 3

Materials and Methods

3.1 Overview

This study was a randomized, double blinded, split mouth, clinical trial comparing the action of the anaesthetic gel Oraqix® against that of a placebo gel in a group of untreated periodontal patients.

3.2 Investigators

Two investigators were required; Examiner A and Examiner B. Examiner A carried out the initial screening of the patients at the 'Screening Visit', while examiner B carried out the periodontal probing of the patient's at the 'Test visit'.

3.3 Examiner Standardization and calibration

Examiner B was an experienced periodontal researcher and as part of previous studies (Loos et al. 1989, Nylund & Egelberg 1990, Claffey et al. 1990) utilising probing depth and loss of attachment as primary outcomes, had examiner standardization and calibration procedures performed. Intra-examiner agreement procedures had been performed with both patient based scores and with site-based analysis; On a small group of patients, two examinations had been performed, where at the first pass a set of representative teeth were chosen and examined, and then at the second pass their contralateral counterparts were examined as the other set of representative teeth for the dentition. Mean values for pocket depth and loss of attachment were generated with the representative teeth and their contralateral counterparts and a Student's *t*-test performed to verify that both groups of teeth would be representative of the whole dentition.

In the present study one examiner (Examiner B), performed all examinations, therefore only intra examiner variability was important as a calbration factor (as apposed to inter).

3.4 Ethical Approval

The study gained ethical approval from the Faculty of Health Sciences, Research Ethics Committee, Trinity College Dublin in October 2008.

3.5 Study Population

Subjects were recruited from patients that were referred to the Department of Periodontology and Restorative Dentistry, Dublin Dental School and Hospital, in relation to their periodontal conditions. Patients screened included both patients who had previously been seen in the Dublin Dental School and Hospital, and those attending for the first time, referred by either dentists within the hospital or dentists outside.

3.6 The Screening visit

Examiner A carried out the screening visit. This visit comprised of a routine dental history (including presenting complaint, medical history, dental history social history, oral hygiene practices, etc.) and examination (including extra- and intra- oral examinations, examination of dental hard tissues, and where indicated radiographic tests and vitality testing).

A Periodontal Screening Recording (PSR) was carried out. The PSR index divides the mouth into 6 segments (sextants) and the greatest probe depth in each sextant of the mouth is determined and recorded. This entails a PSR probe being walked around the

gingival crevice or periodontal pocket and the presence of plaque or calculus, bleeding and/or pocketing noted, and a score assigned accordingly. Codes range from 0-4 where code 0 indicates that there is probing depth that is less than 3.5mm in the deepest crevice in the sextant with no calculus or defective margins or bleeding on probing detected;

- Code 1 only differs from Code 0 in that bleeding is present.
- Code 2 only differs from Code 0 in that there is supra- or subgingival calculus and/or defected margins present.
- Code 3 indicates that the probing depth is greater than 3.5mm but less than 5.5mm.
- Code 4 indicates that the probing depth is greater than 5.5mm.

3.7 Inclusion and Exclusion Criteria

Subjects entered into the study met the following requirements:

- Aged 18-65
- Periodontal Disease Status: Only patients with four or more sextants with a PSR of 4 (ie. denoting the presence of one or more teeth with pocket depths greater than 5.5mm in that sextant) were included.
- Teeth Present: Patients needed to have a minimum of two incisors, one canine, one pre-molar and one molar in all four maxillary quadrants to be considered acceptable to this study.
- Patient's should not have undergone SRP / detailed periodontal treatment in the previous 12 months
- Signed the informed consent form approved by the ethics committee of the Faculty Research Ethics Group – Faculty of Health Sciences.

Subjects were excluded from the study if they:

- Required prophylactic antibiotics prior to periodontal probing
- Suffered from any psychiatric disorders, or patient's suffering with chronic pain problems
- Had coagulation disorders, or where on anticoagulation therapy
- Were female patients that were pregnant or lactating
- Were patients with congenital or idiopathic methemoglobinemia or patients receiving treatment with methemoglobin-inducing agents
- Reported allergies to dental anaesthetics
- Were taking NSAIDs in the three days prior to participation in the study.
- Patients having acute periodontal pain, pulpitis, abscesses, or other acute infections.

Those patients who met the entry requirements at the screening visit were subsequently invited to partake in the study, and an information sheet was issued, (Appendix 7.1). The patient was then invited to a second, 'Test Visit'.

3.8 'Test visit'

For those patients willing to partake in the study, written consent was taken (see Appendix 7.2). The patients were then asked to fill out a short dental anxiety questionnaire (see Appendix 7.3). This consisted of three questions from the Dental Anxiety Questionnaire (Kleinknecht et al. 1973, Kleinknecht & Bernstein 1978). Karadottir et al. (2002) investigated the Dental Anxiety Questionnaire and found these three questions were found to correlate with patients' responses to instrumentation.

Patients then began the test procedure. Examiner B carried out the test probing. The study was carried out in a split-mouth fashion, incorporating left and right sides. One side of the mouth would receive the 'test gel' (Oraqix®), and the other side would receive a 'placebo gel'. The placebo gel consisted of a supplied gel with the same physical / handling properties as the test gel, with the exception of having no anaesthetic action.

Prior to the patients attending, a third party, not involved in the study, randomized the side of the mouth to receive either the test or placebo gel. Gels were placed in 2mm graduated leur lock syringes with a blunt-ended, needle applicator (23 gauge, 0.6mm). They were then placed in sealed envelopes with either 'RIGHT' or 'LEFT' written on the envelope and also an identifier number, which was assigned to a patient. Neither the patients, nor investigators, were aware of which gel was in which envelope until after the study was completed.

The examiner began with the upper right quadrant, opening the first envelope marked 'RIGHT'. The quadrant was dried and then isolated with cotton rolls and a lingual aspirator used as tongue retraction. The active or placebo gel was then administered around each of the gingival margins of the test teeth and also into the periodontal pockets in accordance with the manufacturer's described use of Oraqix®, (Figure 3.1). Central incisors were excluded from gel application so as to avoid cross-side contamination with either test or placebo gels, these were then subsequently excluded from the actual periodontal probing also. The gel was left in-situ for a period of 30 seconds following application before probing began.

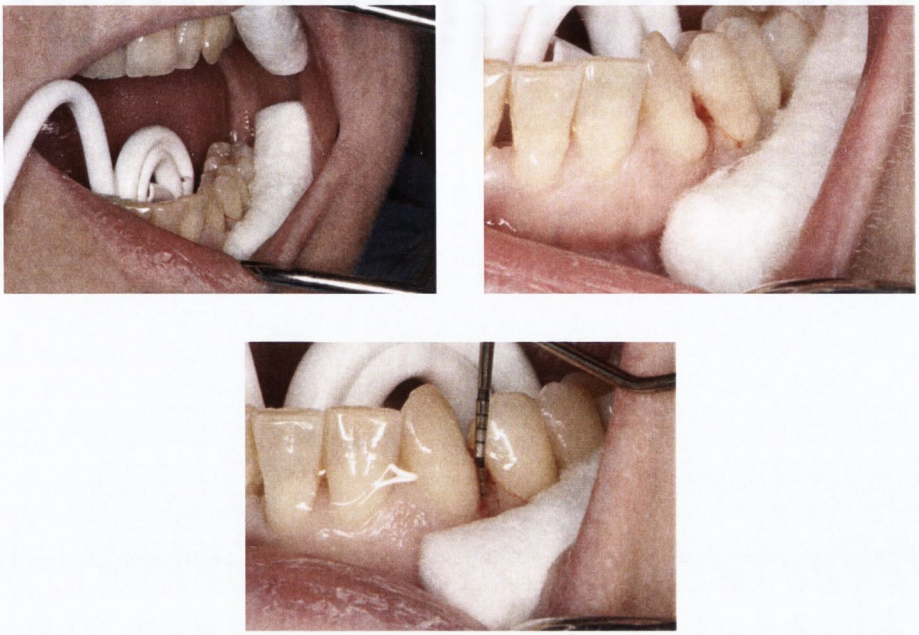

Figure 3.1
Isolation of quadrant and administration of test or placebo gel.

Periodontal pocket measurements were taken using utilizing a UNC (University of North Carolina) Pattern Probe with a probe tip diameter of 0.5mm and 1 mm increments as follows at six sites per tooth. The height of recession was also recorded, and also the presence of bleeding on probing and / or suppuration present. A note was made of the amount of gel used (ml) in that quadrant and the duration of time taken.

Following completion of recording of details in one quadrant, the gel was washed away with 30 seconds using a pressurised water spray. The examiner then proceeded to the lower right quadrant. This was dried, and isolated, the procedure was repeated with the same gel as for the upper right quadrant. After washing this quadrant, the patient was then asked to fill out a pain assessment for probing in the RIGHT side of their mouth using a 100-mm, ungraded VAS, with the left end-point marked 'no pain' and the right

end-point marked 'worst imaginable pain' as the primary efficacy parameter (Appendix 7.4).

The examiner then proceeded with the second envelope; 'LEFT'. The procedure was repeated in identical fashion; first the upper left quadrant, and then the lower left. The patient then filled in a second VAS corresponding to probing for the LEFT side of the mouth (Appendix 7.5).

By compiling results in this fashion, each patient was effectively acting as their own control, producing two separate VAS's for probing on both the right and left side's of their mouths. Following completion of the clinical component of the investigation the blinding of which gel (either test or placebo) was in which envelope was lifted and the envelope numbers matched to the patients. Data from the patient's profile, clinical periodontal examination data, dental anxiety score's and VAS data were compiled.

3.9 Statistical Analysis

Descriptive statistics and data analysis were performed using 'R' version 2.9.2. (Urbanek & Iacus 2009). Because the data were not normally distributed, statistical tests were performed using non-parametric techniques; a Wilcoxon signed rank test was used to establish the significance of difference between VAS measurements for test and placebo gels. The Spearman's *roe* rank correlation coefficient was used to test demographic data, clinical characteristics and Dental Anxiety Questionnaire results against the recoded VAS observed for placebo and test gels, and also the difference between them. Using the arbitrary threshold of VAS ratings ≥40mm as being clinically significantly painful, a Pearson Chi-squared test was used to test whether there was a

significant difference in patients experiencing clinical significant pain on the side of the mouth receiving the test gel versus the side receiving the placebo gel. Probability values ≤ 0.05 were considered statistically significant.

Chapter 4

Results

4.1 Demographics and Baseline Characteristics

A total of 30 eligible subjects were recruited. The patients included in the study were Caucasians males and females. Demographics (Table 4.1) and mean patient baseline characteristics (Table 4.2) are summarized.

Table 4.1 Patient Demographics

	Mean (±S.D)	Range
Patient Age	46.17 (±7.88)	33-66
Patient Gender	15:15 (M:F)	

Table 4.2 Mean Patient Baseline characteristics

	Mean (±S.D)	Range (Min-Max)	IQR (Q1)	IQR (Q2) Median	IQR (Q3)
Number of teeth probed	22.6 (± 2.17)	19-28	21	23	24
Mean Patient PPD* (mm)	4.54 (± 0.71)	2.93-5.64	4.08	4.50	5.11
Mean Patient CAL* (mm)	5.73(± 1.29)	3.09-8.37	4.83	5.52	6.47
% Sites BOP	79.15 (± 15.05)	35.12-100	71.80	80.00	89.13
% Sites Suppuration	1.37 (± 3.26)	0-15.94	0	0	0.78

* For each patient, mean PPD and mean CAL was calculated. The figures presented here are summaries of the individual mean data.

There were no significant differences in either the mean teeth probed in the test side of the mouth versus the placebo side, nor was there any significant difference in the amount of gel each tooth received in both test and placebo sides of the mouth. There was also no significant difference in the amount of time it took to probe placebo or test sides. All 30 patients who partook in the study completed the full probing examinations, with no adverse events reported.

4.2 Efficacy Results

A Box plot (Figure 4.3) demonstrates the Visual Analogue Scores (VAS) in mm for both the test and placebo gels. The bottom edge of the box is the 25th percentile, the top is the 75th, and the thickened centre line is the median. The median VAS pain score for the test gel was 20mm (range 1-61mm) as apposed to 52.5mm (range 29-79mm) for the placebo gel.

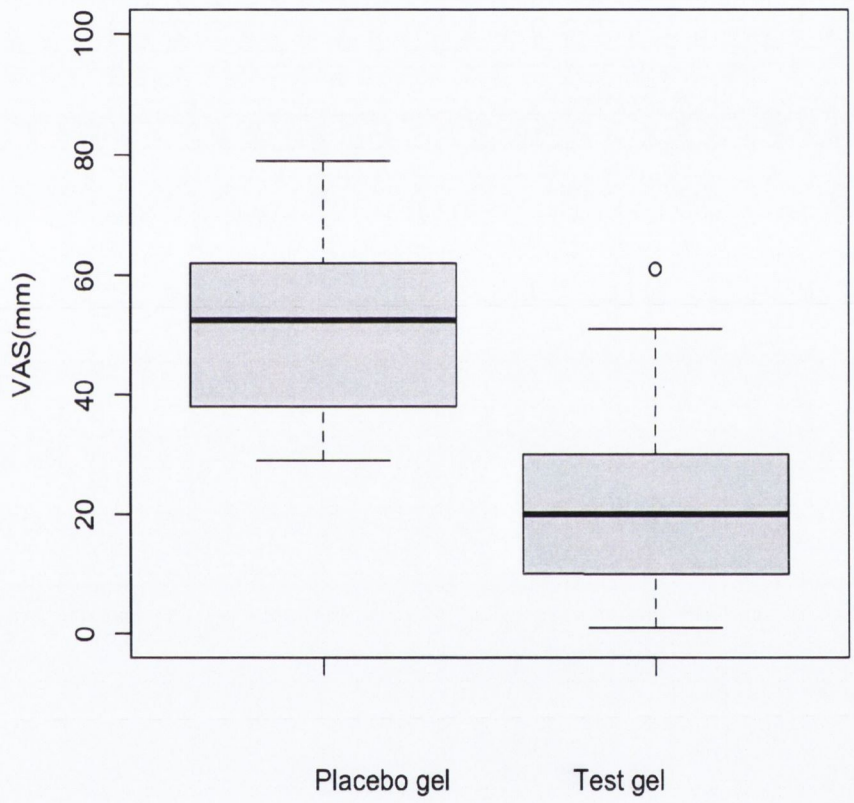

Figure 4.3
Box plots of placebo and test gels VAS(mm).

The mean VAS for the test gel was 23.5mm(SD±16.8), and 51.6mm(SD±14.6) for the placebo gel. The mean reduction in VAS was 28.11mm for the test gel side of mouth. A paired wilcoxon signed rank test was performed which showed the difference to be highly statistically significant; $p<0.0001$. (95% confidence interval: 24.00 - 38.50)

Empirical cumulative frequency distributions for both placebo and test gels are shown (Figure 4.4). A two-sample Kolmogorov-Smirnov test was used to examine the cumulative distributions, which showed a maximum difference of 0.67 ($p<0.00001$).

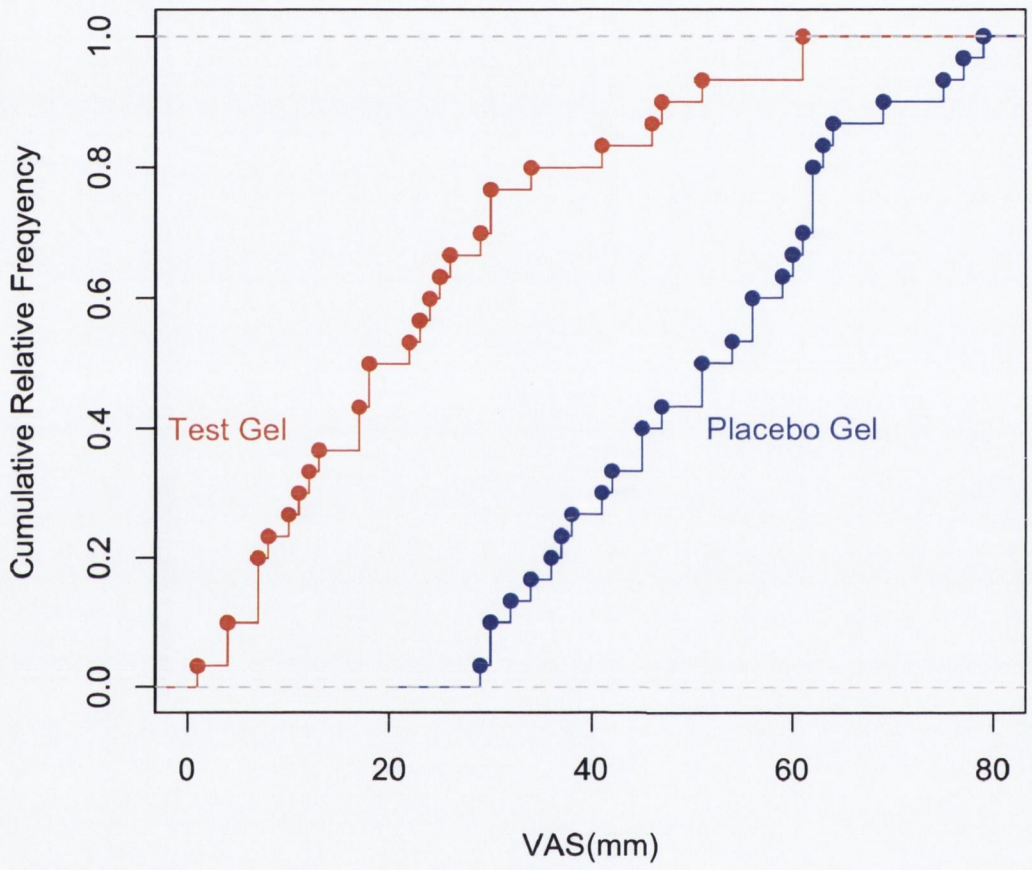

Figure 4.4
Empirical cumulative frequency distributions of placebo and test gels VAS(mm).

4.3 Correlation Results

Correlation testing was performed to see if factors such as age, gender, number of teeth/sites probed, results of the dental anxiety questionnaires, mean PPD, mean CAL, %BOP and %Suppuration was correlated to the patient's pain VAS for placebo or test gels and also for the difference between the scores.

Testing with Spearman's rank correlation (Table 4.5) showed only one significant correlation and that was that age seemed to correlate negatively for the VAS reported by patients on the side that had the test gel, ($r=-0.6$, $p<0.05$). That is, the older the patient the smaller the VAS reported on the active gel side.

The only other factor that approached significance, was that age nearly negatively correlated with the difference in VAS's observed ($r=0.32$, $p=0.09$). That is the older the patient got the less the reported difference in their two VAS's. All other variables failed to show any noteworthy statistical correlations, ($p>0.05$).

Table 4.5 Results correlation table

	SPEARMAN	
Characteristic (correlation with Placebo VAS)	***roe***	**p-value**
Pocket probing Depth	-0.02848145	0.8856
Bleeding on Probing	-0.05520548	0.7802
Suppuration	-0.03103547	0.8754
Total Number of teeth probed	0.04581494	0.817
DAQ.1	-0.05378927	0.7857
DAQ.2	-0.2823335	0.1455
DAQ.3	-0.1289421	0.5132
mDAQ	-0.1666253	0.3967
Age	-0.02359398	0.9051
Characteristic (correlation with Test gel VAS)	**Roe**	**p-value**
Pocket probing Depth	0.01041668	0.958
Bleeding on Probing	0.01055808	0.9575
Suppuration	0.2111778	0.2807
Total Number of teeth probed	0.06007662	0.7614
DAQ.1	0.01942557	0.9218
DAQ.2	0.1360373	0.49
DAQ.3	0.1066755	0.589
mDAQ	0.08401448	0.6708
Age	-0.6534395	0.0001631
Characteristic (correlation with Difference in VAS's)	**Roe**	**p-value**
Pocket probing Depth	-0.01259584	0.9493
Bleeding on Probing	-0.01547733	0.9377
Suppuration	0.2525413	0.1948
Total Number of teeth probed	0.1037309	0.5994
DAQ.1	0.001222316	0.995
DAQ.2	0.2252957	0.249
DAQ.3	0.149011	0.4492
mDAQ	0.1218807	0.5367
Age	-0.3227269	0.09393

4.4 Numbers of patients experiencing significant pain

Chung et al. (2003) suggested an arbitrary threshold of VAS ratings above 40mm as being clinically significantly painful. Applying this threshold to the present study, the number of patients falling into each category is shown in table 4.6.

Table 4.6
2x2 table for number of patient with VAS > and < 40mm for test and placebo gels

Outcome → Characteristic ↓	VAS >40mm, 'Significant pain'	VAS <40mm; 'non-significant pain'	Total
Test Gel	6	24	30
Placebo Gel	22	8	30
Total	28	32	60

Pearson's Chi-squared test with Yates' continuity correction; $\chi^2 = 15.06$; df = 1; p-value 0.0001. Fisher's Exact Test for Count Data; p-value = 7.293e-05

Thus the anaesthetic gel was found to have a clinically significant and statistically significant effect on the number of patients experiencing appreciable pain.

Chapter 5

Discussion

Discussion

The primary aim of this study was to evaluate the efficacy of an intra-pocket anaesthetic gel (Oraqix®) in the reduction of pain on periodontal probing in a group of untreated periodontal subjects over a placebo gel. The design of the study was a randomised, double-blinded, split-mouth, placebo controlled trial. Thirty consecutive patients meeting the inclusion criteria had full mouth periodontal probing carried out. Prior to probing a side of the mouth, a randomised gel (either test or placebo), was placed in the periodontal pockets for 30 seconds. Probing of that side of the mouth was then completed in a quadrant fashion, with the gel being washed out at the end of each quadrant probing. The contra-lateral side probings were then taken in the same fashion. Patients were asked to complete a VAS after probing of each side of the mouth to describe their pain experience.

Inter-examiner variability has been shown to have a significant effect on the patient's reported experience of pain (Kim et al. 2007). This study utilised a single examiner to carry out periodontal probings at the test visit for all patients; intra-examiner reproducibility of probing has been shown to be accurate to 1mm in 95% of recordings (Isidor et al. 1984). It was decided to use a non-standardized probing force, to reflect the conditions applicable to private practice (Chung et al. 2003).

The results demonstrated a highly significant ($p<0.0001$) reduction in patient's perception of pain for the side of the mouth having the test gel compared to the side of the mouth having the placebo gel. In terms of the clinical significance of this result, Chung et al. (2003), suggested an arbitrary threshold of VAS ratings above 40mm as being clinically significantly painful. Applying that threshold to this study, the

percentage of patients having clinically significant pain on the placebo side of the mouth was 73%, compared to 20% on the anaesthetic gel side of the mouth ($p<0.0001$).

Three previous multi-centre, double blinded, randomized, placebo controlled clinical trials have studied the efficacy of the anaesthetic gel (Oraqix®) for purposes of scaling and/or root planing procedures, (Jeffcoat et al. 2001, Donaldson et al. 2003, Magnusson et al. 2003). The three studies included 337 subjects at 18 study centres. The studies used Hodges-Lehmann point estimate of treatment differences, and found the results to favour the anaesthetic gel by reducing VAS pain scores by magnitudes of 8mm (Jeffcoat et al. 2001), 10mm (Magnusson et al. 2003), and 4mm (Donaldson et al. 2003). There are perhaps several explanations why there is a smaller effect of the anaesthetic gel in these studies in comparison to the present study;

- In the three studies mentioned, the design utilised parallel group designs. In the present study, a single group, split mouth design was utilised. This has a significant effect in statistical testing as we are dealing with paired data. Also by having the same person report VAS pain scores for test and placebo gel, the patient is in effect acting as their own control. In a parallel group design, factors such as age, gender, ethnicity, previous pain experience, education, smoking status have all been shown to influence a patient's reporting of pain, and it is difficult to control for these across two groups unless the numbers are very large.
- The three studies mentioned, looked at procedural pain of scaling and or root planing, whereas as this study looked at pain experienced during periodontal probing. Pain experienced during scaling and or root planing is from two

sources; One is the manipulation of the gingival tissues; the second is the disturbing of the dentinal tubules which produces pain from the non-anesthetised nociceptive fibres in the tooth pulp itself. The test anaesthetic gel is not known to provide any form of pulpal anaesthesia, therefore for a procedure like periodontal probing, where the pain is purely from manipulation of periodontal tissues only, the test anaesthetic gel may be more effective, than compared with scaling and/or root planing procedures.

- Studies have show full mouth periodontal probing to potentially be a more painful experience in comparison to scaling and/or root planing procedures, when reporting using a VAS pain scoring system (Karadottir et al. 2002, Magnusson et al. 2003). The amount of pain during probing procedures is associated with the extent of periodontal inflammation (Heft et al. 1991). In the present study, only newly referred patients, with severe chronic periodontitis, who hadn't had any treatment for 12 months, made the inclusion criteria. By selecting patients with severe periodontitis, it was more likely that they would find the probing procedure painful, therefore there was a potential for a greater effect of the anaesthetic gel in this study.

Donaldson & Meehan (1995) investigated the use of a 5% eutectic mixture of local anaesthetics (EMLA®) cream to a standard 5% lidocaine intraoral topical anaesthetic for purposes of carrying out periodontal probing. 14 patients partook in the study; a 5-minute application of EMLA® cream in a customized intra-oral splint resulted in a significant increasing in the depth of probings recorded compared to the lidocaine gel. This demonstrates the efficacy of EMLA® being absorbed over conventional topical anaesthetics. Similar results in favour of EMLA® were also found in a study by

Svensson et al. (1994), where they compared the use of EMLA® versus a placebo cream for purposes of scaling. In this study they used topical adhesive bandages to place the EMLA®. The gel used in the present study is an evolution of EMLA® cream; essentially it has the same active anaesthetic ingredients (eutectic mixture of lidocaine 25mg/g plus prilocaine 25mg/f) with the addition of a thermosetting agent. This enables the gel to flow into the periodontal pocket, where it becomes an elastic gel at body temperature. The onset of anaesthesia has been shown to be 30 seconds after application, (Friskopp et al. 2001).

The present study relied on the use of the VAS for scoring pain and being the primary means of determining the anaesthetic gel's efficacy. Although the VAS is reliable, sensitive, reproducible, simple, quantifiable and amenable to statistical analysis (Hashem et al. 2006); it must also be recognised that the subjective nature of pain may lead to an over or underestimation of the efficacy of the test anaesthetic gel when using a VAS.

The split-mouth design is an example of a randomisation scheme on a site level where two treatments are randomly assigned to sites of one of the two halves of the mouth. The attractiveness of the split-mouth design is the removal of much of the inter-subject variability thereby increasing the power of the study compared to the whole-mouth design (a parallel group design).

Hujoel and colleagues (1990) reported the following problems with the design:

- The split-mouth design may lead to biased treatment efficacy estimates due to carry across effects.

- Recruitment of patients is hampered because of the need for symmetrical disease patterns among all segments of the dentition that are randomized in the split-mouth design. Restricting the recruitment to such patients seriously limits the external validity of the results.
- These authors point out that, in terms of measurements taken on each patient, the split-mouth design can only be more efficient than the parallel-group design when, the within patient correlation coefficient, is substantial.
- The statistical analysis of a split-mouth design is more complex than that of the whole-mouth design.

Correlation analysis resulted in only one significant correlation; age seemed to negatively correlate for the VAS reported by patients on the side that had the test gel applied ($r=-0.6$, $p<0.05$). That is, the older the patient the smaller the reported pain scores on the side of the mouth receiving the active gel. This is in agreement with previous results (Canakci & Canakci 2007). Age is one of the biological factors that have been discussed as important for pain experience (Fardal et al. 2002). A higher pain threshold in elderly subjects may be a consequence of tissue changes such as reduced vascularity and fatty degeneration of bone tissue (Holm-Pedersen & Löe 1986). However, the analysis did not show this relationship on that side of the mouth receiving the placebo gel (roe=-0.02, $p=0.91$). It is therefore difficult to interrupt age as being clear factor that predicts pain response in the present study.

The only other factor that approached significance was again age, which negatively correlated with the difference in VAS's observed within individuals for test and placebo

(r=0.32, p=0.09). It can therefore be speculated that the older the patient was the less the magnitude of the effect that that the active gel had compared to placebo gel.

All the other variables failed to show any noteworthy statistical correlations, ($p>0.05$), when compared to factors such as gender, number of teeth/sites probed, results of the dental anxiety questionnaires, mean PPD, mean CAL, %BOP and %Suppuration. This was probably due to the small sample size of 30 patients, and we can therefore not exclude the possibility that, in a larger, controlled sample size, correlations may be found with some of the above factors.

In conclusion, the anaesthetic gel; lidocaine 25mg/g plus prilocaine 25mg/g and thermosetting agents, provides a statistically significant reduction in patients reporting of pain on periodontal probing in untreated advanced periodontitis patients. It suggests the gel may be used for those patients who find the full mouth periodontal probing experience particularly painful in view of few tested alternatives. Further studies should be conducted to assess whether the use of an agent such as that investigated in the present study would result in decreasing patient discomfort with a subsequent better reproducibility of probing measurements.

Chapter 6

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