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Master's thesis

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Local anaesthesia of a new bupivacaine lozenge compared to lidocaine injection in scaling and root planning of periodontitis patients

A randomised, split-mouth crossover study

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PREFACE

This Master's thesis was conducted at the Clinical Research Centre at Hvidovre University Hospital from November 2012 to May 2013. Patient enrolment took place from January 2013 to May 2013 at three dental clinics; Frederiksberg Tandlægerne, Dental Clinic by Jonna Bork and Dental Clinic by Søren Barsted.

Prior to patient enrolment I was involved in protocol writing and application to the Regional Ethics Committee and the Danish Health and Medicines Agency. While the authorities processed the application, I drafted the Case Report Form (CRF) and Trial Master Files. During patient enrolment, I created the electronic CRF database, participated in monitoring visits and administrative affairs. Due to slow patient recruitment two amendments were submitted to the authorities in December 2012 and January 2013 respectively involving new study centres to facilitate patient enrolment.

I would like to give a warm thank you to several people for their involvement in this project. Firstly I would like to thank my external supervisors Charlotte Treldal and Stine Mogensen at the Clinical Research Centre, Hvidovre University Hospital for their everyday support and indispensable guidance throughout the process.

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ABSTRACT

Background: Periodontitis patients regularly undergo scaling and root planning (SRP) in order to limit disease progression. SRP may be painful and uncomfortable for patients, and therefore local anaesthetics are often applied. A new bupivacaine lozenge has recently been developed offering a new method of local anaesthesia of the oral cavity.

Study aim: The aim of the study was to compare the anaesthetic effect of a bupivacaine lozenge to standard treatment by injection of a lidocaine-adrenalin solution before SRP of patients with periodontitis. Patient acceptance of the two pharmaceutical formulations was also evaluated.

Methods: The study was conducted using a randomised, split-mouth, two period crossover design, including periodontitis patients undergoing two individual SRPs. Pain and discomfort was measured using Visual Analogue Scale (VAS) before, during and after SRP. Pain was also evaluated using McGill Pain Questionnaire. Patients evaluated the two pharmaceutical formulations using a questionnaire.

Results: Nine patients were included in the study. This was a lower number than the power calculation, and the analysis is therefore underpowered. VAS pain scores during SRP were significantly higher when treated with the lozenge compared to injections *(p=0.03)*. The VAS scores for discomfort were also higher during treatment with the lozenge with borderline significance *(p=0.05)*. After SRP there was no significant difference between the lozenge and injections in VAS pain scores *(p=0.14)*. VAS discomfort scores after SRP were significantly lower for treatment with the lozenge compared to injection *(p=0.04)*. McGill Pain Questionnaire showed similar evaluations of pain when treated with the lozenge and injections.

Conclusion: The results show a trend towards a better anaesthetic effect of injection anaesthesia compared to the lozenge. The lozenge may reduce post-procedure discomfort compared to injections.

RESUME

Baggrund: Parodontosepatienter får jævnligt udført tandrensninger for at begrænse udviklingen af sygdommen. Tandrensningerne kan være smertefulde og ubehagelige for patienterne og derfor anvendes ofte lokalbedøvelse. En ny bupivacain sugetablet, som tilbyder en ny metode til lokalbedøvelse af mundhulen, er blevet udviklet.

Formål: Studiets formål var at sammenligne den lokalbedøvende effekt af en bupivacain sugetablet med standardbehandling med injektion af en lidokain-adrenalin opløsning ved tandrensning af parodontosepatienter. Patientaccept af de to formuleringer blev også evalueret.

Metode: Dette var et randomiseret, split-mouth, to-periode crossover forsøg, som inkluderede parodontosepatienter, der skulle have udført to seperate tandrensninger. Smerte og ubehag blev målt ved hjælp af Visual Analogue Scale (VAS) før, under og efter tandrensningen. Smerte blev også evalueret ved McGill Pain Questionnaire. Patienterne evaluerede de to formuleringer ved hjælp af et spørgeskema.

Resultater: Ni patienter blev inkluderet i studiet. Dette var et lavere antal end udregnet ved styrkeberegningen, og analysen har derfor ikke tilstrækkelig styrke til at kunne drage endegyldige konklusioner. VAS smerte score under tandrensning var signifikant højere ved behandling med sugetabletten sammenlignet med injektioner *(p=0.03)*. VAS score for ubehag var også højere ved behandling med sugetabletten med grænsende signifikans *(p=0.05)*. Efter tandrensning var der ikke signifikant forskel mellem de to behandlinger i VAS smerte score *(p=0.14)*. VAS score for ubehag efter tandrensning var signifikant lavere ved behandling med sugetabletten sammenlignet med injektioner *(p=0.04)*. McGill Pain Questionnaire gav lignende evalueringer af smerten ved behandling med sugetabletten og injektioner.

Konklusion: Resultaterne viste en tendens mod en bedre lokalbedøvende effekt af injektioner sammenlignet med sugetabletten. Sugetabletten kan derimod muligvis nedsætte ubehaget efter tandrensninger i forhold til injektioner.

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LIST OF ABBREVIATIONS

CAL – Clinical Attachment Level

CNS – Central Nervous System

CRF – Case Report Form

MPQ – McGill Pain Questionnaire

NWC – Number of Words Chosen

PPD – Probing Pocket Depth

PRI(R) – Pain Rating Index for Rank values

PRI(S) – Pain Rating Index for Scale values

SRP – Scaling and Root Planning

UGE – Upper Gastrointestinal Endoscopy

VAS – Visual Analogue Scale

LIST OF TERMS

Gingival Sulcus – The shallow groove between the teeth and the gingiva that extends around the circumference of the tooth

Maxilla – Upper jaw

Mandible – Lower jaw

Subgingival – Below the gingival margin, i.e. in the gingival sulcus

Supragingival – Above the gingival margin, i.e. on the crown of the tooth

1. BACKGROUND

Periodontitis is a common inflammatory disease affecting between 5% and 15% of the population in industrialised countries in its severe form [1]. The condition is characterised by a progressive destruction of the periodontal tissue, which may lead to increased tooth mobility and ultimately tooth loss. The tissue destruction is caused by oral bacteria and their complex interaction with the immune system, which causes disruption of tissue homeostasis [2]. Research indicates that disease progression is also linked to genetic disposition, lifestyle and a number of medical conditions. Dental hygiene, however, remains the cornerstone in the treatment of periodontitis [3].

In periodontitis oral bacteria accumulate to form a biofilm on the surface of the teeth. This may spread into the gingival sulcus and pockets in the periodontal tissue formed as a result of tissue destruction. The complex composition of the biofilm makes antibiotic treatment alone inadequate for complete removal [2]. Scaling and root planning (SRP) is therefore a necessary treatment to remove pathogenic bacteria and obtain infection control. During SRP bacterial plaque and calculus is removed from the surface of the teeth using hand or power driven instruments [3]. The procedure may be painful and uncomfortable for patients and local anaesthetics are therefore often applied [4].

Injection of a local anaesthetic solution is often used for SRP. This method of anaesthesia, however, has a number of disadvantages. Injections are invasive, associated with patient discomfort and a risk of nerve damage [5, 6]. In clinical practice, anaesthesia is only desired in the area around the teeth subject to SRP. This may be difficult to accomplish by injections, as the affected teeth often are scattered throughout the oral cavity. It is thus often necessary to anaesthetise large sections of the oral cavity using injection, which may be inappropriate. Moreover the duration of anaesthesia is often longer than required, which may be inconvenient for the patient [7].

It is evident that there is scope for developing a safer, more convenient alternative to local anaesthesia by injection in dentistry. One alternative is administering a lozenge containing the local anaesthetic bupivacaine. This method of anaesthesia has been investigated for use before upper gastrointestinal endoscopy (UGE) with promising results. A single-blinded randomised controlled trial included 100 patients undergoing UGE. The bupivacaine lozenge significantly improved patient acceptance of UGE and gag reflexes compared to the standard method of anaesthesia by a lidocaine pharyngeal spray.

Moreover, the lozenge was evaluated to have a palatable taste and texture and it was well accepted among patients [8].

1.1 STUDY AIM

The aim of this study was to compare the anaesthetic effect of a bupivacaine lozenge to standard treatment by injection of a lidocaine-adrenalin solution before SRP of patients with periodontitis. Patient acceptance of the two pharmaceutical formulations was also evaluated.

The main hypotheses were:

- The anaesthetic effect of a bupivacaine lozenge is no worse than that of lidocaine-adrenalin injections *during* SRP of periodontitis patients.
- The anaesthetic effect of a bupivacaine lozenge is no worse than that of lidocaine-adrenalin injections *after* SRP of periodontitis patients.
- The majority of patients will prefer anaesthetic treatment with a bupivacaine lozenge to lidocaine-adrenalin injections for SRP.

2. INTRODUCTION

2.1 ANATOMY OF THE PERIODONTIUM

The periodontium is the supporting tissue of the teeth. Its main function is to connect the teeth to the bone tissue of the jaws and to maintain the integrity of the surface of the oral mucous membrane. The main components of the periodontium include gingiva, periodontal ligament, cementum and alveolar bone, see figure 1 [1, 9].

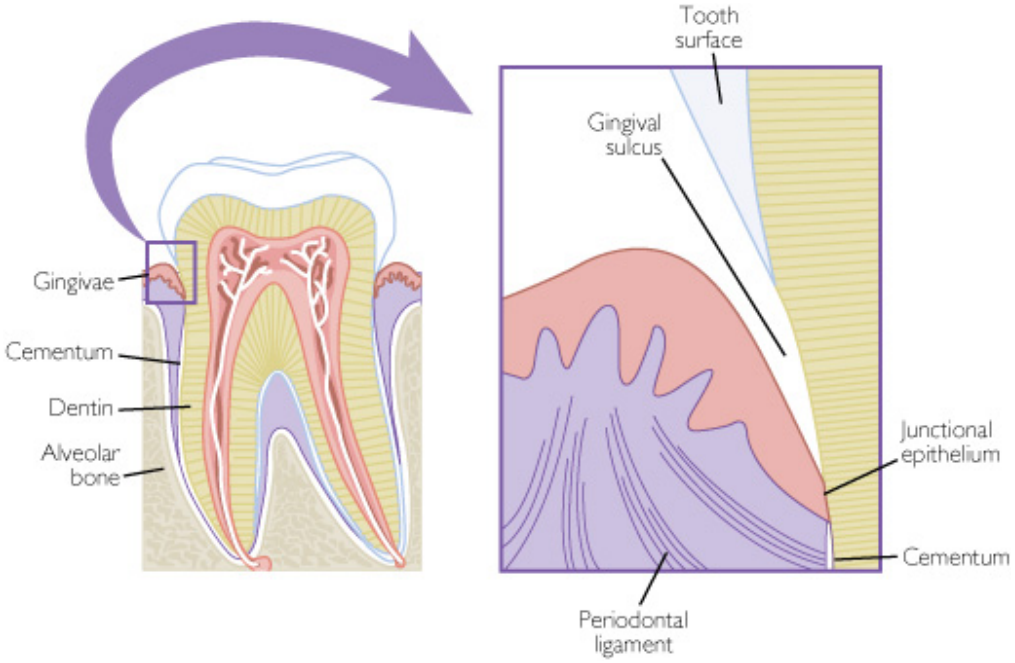


Figure 1 - Main anatomical components of the periodontium [10]

Gingiva is the part of the oral mucous membrane that covers the alveolar bone and surrounds the cervical portion of the teeth. In healthy individuals, the gingiva is the only clinically observable periodontal tissue with a pale pink colour and a sharp edge scalloped around the teeth [1, 11]. The gingival sulcus is the shallow groove between the teeth and the gingiva that extends around the circumference of the tooth. For a healthy fully erupted tooth, the gingival sulcus may be between 0.5 and 4.5 mm in depth depending on the site and individual [11, 12].

The periodontal ligament is the soft tissue surrounding the roots of the teeth, attaching the cementum to the alveolar bone [9]. The tissue is highly vascularised and innervated containing free nerve endings that record signals such as pain, touch and pressure [1, 9].

The periodontal ligament has a great adaptive capacity in response to mechanical stimuli, and the width, height and quality of the tissue determine the mobility of the tooth [1].

Cementum is the mineralized tissue covering the root surface and occasionally small portions of the crown of the teeth. The cementum forms the attachment between the periodontal ligament and the root of the tooth and contributes to the repair process after damage to the root surface [9].

The alveolar bone is the part of the maxilla (upper jaw) and mandible (lower jaw) that support and form the socket of the teeth [9]. The walls of the sockets are lined with a layer of dense bone called compact bone, whose thickness varies throughout the oral cavity [1]. The mandibular buccal compact bone has the greatest thickness, while it is thinner in the area of the mandibular canines and incisors. The compact bone of the maxillary is relatively thin compared to the compact bone of the mandible [6].

2.1.1 The oral mucous membrane

The oral mucous membrane acts as a barrier to external materials and to retain tissue fluids. It consists of an outermost layer of stratified squamous epithelium and a connective tissue component separated by a basement membrane, see figure 2 [13]. The connective tissue is primarily composed of fibroblasts, collagen and elastin fibres, vasculature and neural processes [11].

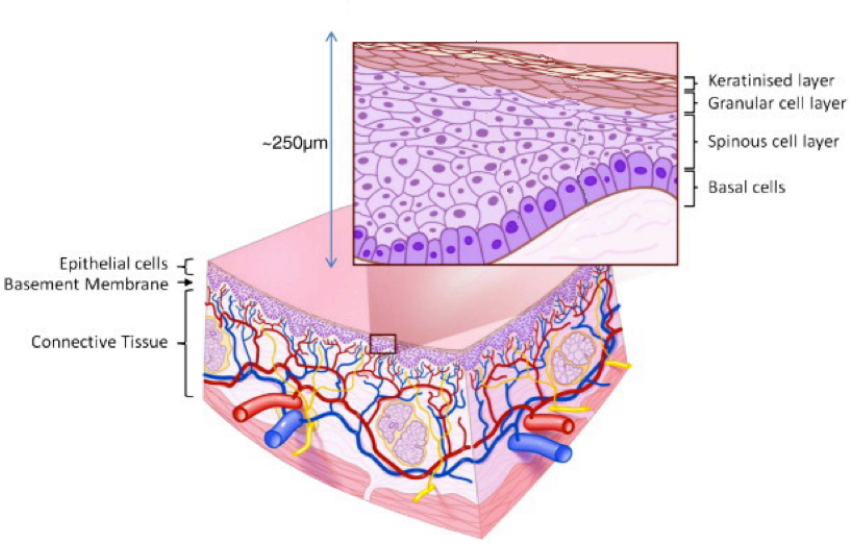


Figure 2 - Structure of the oral mucosa[14]

The oral mucosa includes the gingival, buccal, sublingual, palatal and labial mucosae; all of which have differing permeability [14, 15]. The varying permeability is due to differing thickness of the epithelium and degree of keratinisation at the different sites [14]. The thickness of the buccal mucosa is greatest measuring 500–800 μm compared to the thickness of the hard and soft palates, the sublingual and the gingival mucosa, which measures at about 100–200 μm. The mucosa of the areas subject to mechanical stress, i.e. the gingiva and hard palate are keratinised, while the mucosa of the soft palate, the sublingual, and the buccal regions are not [15]. The keratinised gingiva therefore has the lowest permeability, followed by the buccal mucosa while the most permeable area of the oral mucosa is the sublingual mucosa. In areas of damaged mucosa, the barrier may be impaired leading to an increased permeability [13].

2.1.2 Innervation

The periodontal tissue is innervated by sensory fibres of the maxillary and mandibular divisions of the trigeminal nerve. The branches of the maxillary division supply the upper teeth and their supporting structures. The nerves of greatest interest in dentistry are the posterior, middle and anterior superior alveolar nerves, the greater and lesser palatine nerves and the infraorbital nerve, see figure 3 and 4. The second and third molars are innervated by the posterior superior alveolar nerve, while the first molar is innervated by both the posterior and middle superior alveolar nerve. The premolars receive their nerve supply from the middle superior alveolar nerve, and the canines and incisors are innervated by the anterior superior alveolar nerve. The greater and lesser palatine nerve supply the palatal mucosa [6, 16].

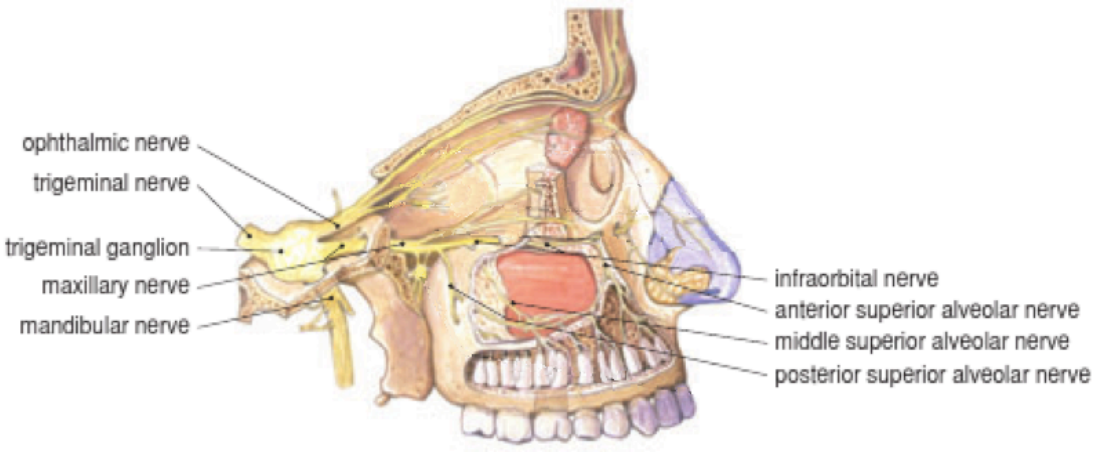


Figure 3 – The branching of the ophthalmic and maxillary nerves (lateral view) [6]

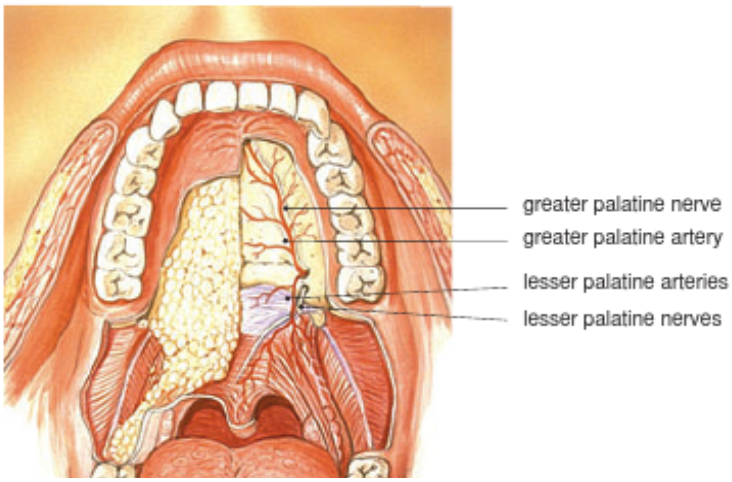


Figure 4 – The palate from below [6]

The mandibular division of the trigeminal nerve innervates the lower teeth and their supporting tissues, see figure 5. The mandibular nerve divides into anterior and posterior trunks. The anterior trunk contains the long buccal nerve supplying the buccal mucosa. The posterior division splits into a number of branches that are important in dental local anaesthesia. These include the inferior alveolar nerve, the mylohyoid nerve, the lingual nerve and the auriculotemporal nerve. The inferior alveolar nerve is of greatest interest as it innervates the pulps of all the teeth on the ipsilateral side of the mandible. At the midline the contralateral inferior alveolar nerve may also provide some of the innervation [6, 16].

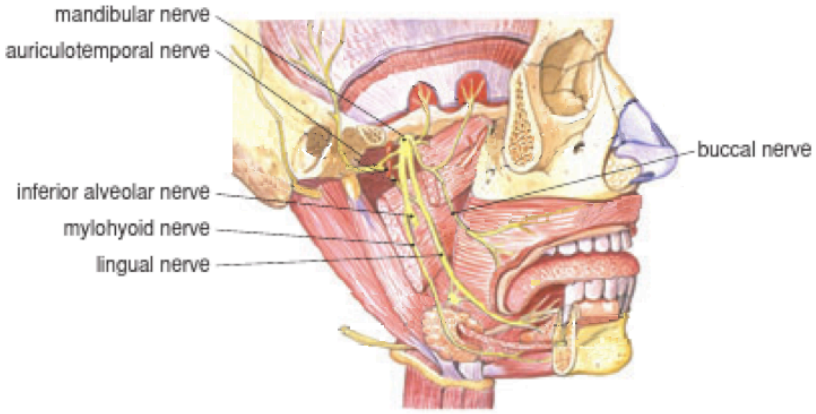


Figure 5 – The mandibular nerve (lateral view) [6]

2.2 PERIODONTITIS

2.2.1 Pathology

The oral cavity comprises a natural habitat for microorganisms, and any individual may host 150 or more different bacterial species at a given time. Whilst the colonization of various bacteria in the oral cavity is most often benign, these microorganisms may occasionally cause damage to the host [9]. If not removed, the bacteria within the oral cavity accumulate to form dental plaque. This may spread to the gingival sulcus and induce an inflammatory response [2, 9]. Inflammatory conditions limited to the gingiva, is known as *gingivitis.* As the destructive processes progress to deeper parts of the periodontium, the diagnosis *periodontitis* is used [11].

The bacteria within dental plaque may cause damage to the periodontal tissue in two ways. Waste products and enzymes produced by the bacteria may cause direct damage of the tissue by digesting host protein and other molecules. The bacteria may also cause damage indirectly by activating inflammatory and immune responses that break down the periodontal tissue. It is the latter pathway that accounts for most harm in periodontitis [9].

As the disease progresses, the gingival sulcus is deepened and a periodontal pocket develops. The oxygen tension and nutritional conditions found subgingivally (in the gingival sulcus) are different from those found supragingivally (on the crown of the tooth), and growth conditions for bacteria therefore differ. Bacterial growth conditions in a deep periodontal pocket favour the growth of gram-negative anaerobic bacterial species. These species are predominant in the development of the destructive inflammatory processes characteristic for periodontitis [2]. It is thus crucial to remove bacterial deposits in periodontal pockets in order to limit further tissue destruction.

2.2.2 Diagnosis

Periodontitis is characterised by inflammatory manifestations of the gingiva. These include redness, swelling and an increased tendency to bleeding upon probing. Moreover, the tissue may present a reduced resistance to probing due to tissue recession and presence of periodontal pockets. In advanced stages of periodontitis increased tooth mobility and alveolar bone loss may also be evident [9].

To facilitate effective treatment planning, the location and extend of periodontal lesions must be recognised throughout the entire dentition. Several examinations may be performed to make an individual diagnosis for each tooth, including measurements of

probing pocket depth, clinical attachment level, bleeding on probing, tooth mobility and radiographs [11].

Probing pocket depth (PPD) is typically recorded in six sites per tooth (mid-buccal, distobuccal, distolingual, mid-lingual, mesiolingual and mesiobuccal). The measurement is performed using a periodontal probe with length marks, measuring the apical extend of the gingival lesion to the nearest mm. PPD measurements give an impression of the extend of periodontal tissue destruction and serve to identify potential sites for dental plaque retention. For more detailed information, measurements of clinical attachment level (CAL) may be used. CAL is calculated as the sum of PPD and gingival recession and provides a more accurate measure of the severity of periodontitis. In practice PPD is, however, the most commonly recorded measure [11].

2.2.3 Treatment

The primary goal of periodontal therapy is to preserve the natural dentition by halting the disease progression [4]. As well as eliminating susceptibility factors such as smoking, initial therapy includes limiting the bacterial load of the oral cavity, hereby reducing the destructive processes of the periodontal tissues. At the initial treatment phase the patient is instructed in relevant oral hygiene measures including self-performed plaque control. Initial treatment also entails regular scaling and root planning (SRP) performed by dental staff [3].

Scaling is defined as "*instrumentation of the crown and root surfaces of the teeth to remove plaque, calculus, and stains from these surfaces"*, while root planning is *"a treatment procedure designed to remove cementum or surface dentin that is rough, impregnated with calculus or contamined with toxins or microorganisms"* [3].

SRP is performed using hand or power driven (i.e. ultrasonic) instruments [4]. While for the majority of patients, periodontitis is not a painful condition, SRP may be a painful procedure and therefore it is often performed under local anaesthesia [9, 17].

2.3 PAIN

The International Association for the Study of Pain defines pain as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage"* [18]. There are many ways to classify pain and clear distinctions are not always possible. In general pain may be described as acute pain (e.g. trauma or postoperative pain), cancer pain, and non-

cancer pain (e.g. osteoarthritis pain). Pain may also be classified by its pathophysiological origin as nociceptive or neuropathic [19].

Nociceptive pain is evoked by stimulation of receptors known as nociceptors. Nociceptors have free nerve endings with specific channels that are activated by different kinds of stimuli. These include mechanical stimuli (e.g. incision, tumour growth), thermal stimuli (e.g. burn, frostbite), or chemical stimuli (e.g. algogenic substances) [19]. Once activated, sodium channels in the cell membrane are opened, leading to an influx of positively charged sodium ions. This leads to a depolarisation of the membrane, which, if above the threshold, results in an action potential [20]. The action potential is transmitted via Aδ and C afferent fibres to the central nervous system (CNS), where pain ultimately is perceived [19].

Neuropathic pain is the result of damage to central or peripheral neurogenic structures. Tissue damage may cause deafferentation, where the area is deprived of its afferent transmission system. Hence, neuropathic pain is caused by a dysfunction of the pain signalling system in the damaged area, rather than the injury itself. Causes that may lead to neuropathic pain include surgery, neurodegenerative conditions and infections [18, 19].

Inflammation may be present in several medical conditions and tissue damage may also induce an inflammatory response. During an inflammatory response algogenic substances are released, which may activate nociceptors and induce pain. Algogenic substances can also cause hypersensitivity of nociceptors resulting in hyperalgesia in the inflamed area. Inflammation may also lead to tissue acidification, which contributes to hyperalgesia and development of pain. Presence of tissue damage and inflammation consequently causes hypersensitivity of the tissue and increases the risk of pain perception [19, 21].

Perception of pain is, however, not merely a product of nociceptive stimulation; it is also determined by psychological and emotional factors [22]. The Gate Control Theory was introduced in 1965 and hypothesised that the intensity of pain and unpleasantness was not only determined by the magnitude of painful stimuli, but that cognitive activities also affected perception [23].

The theory describes a gating mechanism in the CNS where inhibitory processes can be activated to “close the gate” and thus inhibit pain transmission. According to the theory, cognitive processes can thus modulate or alter pain impulses before reaching the brain and therefore alter the pain experience. The theory may be used to describe several pain

phenomena, for example why patients suffering from dental anxiety experience a higher level of pain during dental procedures than non-anxious patients [24, 25].

The Gate Control Theory describes pain in terms of three components: sensory, affective and evaluative. The sensory component gives information about the time, location and intensity of pain. Affective activities indicate the presence of discomfort and unpleasantness, while the evaluative component embrace cultural and social values, past experiences, probable outcome, meaning of pain, etc. [23].

2.3.1 Pain assessment

As described above, pain is very subjective and assessment of the same painful stimulus may vary between individuals [19]. Additionally the same individual may assess the same painful stimulus differently at two individual points in time depending on factors such as anxiety, previous experience, expectation and anticipation [24]. While there are numerous methods for pain assessment, patient self-reports have been shown to be the most reliable indicator of the existence and intensity of pain. The Visual Analogue Scale, Verbal Rating Scales and McGill Pain Questionnaire are all recognised methods for self-reported pain assessment [19].

2.3.1.1 Visual Analogue Scale

The Visual Analogue Scale (VAS) is a 100 mm horizontal straight line with word anchors at the extremes describing pain intensity. One end (0 mm) corresponds to “no pain” while the opposite end (100 mm) implies “worst imaginable pain”. The patient assesses their pain by a indicating a point on the line that represents the pain intensity [19]. VAS is used extensively in clinical research and in addition to measuring pain, it has been validated to measure various other subjective phenomena such as anxiety, discomfort, nausea, etc. [26].

2.3.1.2 Verbal Rating Scales

Many different Verbal Rating Scales have been developed. Verbal Rating Scales use adjectives to describe different levels of pain severity. Typically the adjectives comprise the extremes of pain intensity (e.g. “no pain” and “extreme pain”) and additional descriptors reflecting intermediate pain intensities. Patients assess their pain by inspecting the list of adjectives, and selecting the description, that best defines their level of pain [19, 27].

2.3.1.3 McGill Pain Questionnaire

As pain is a multidimensional experience, simply using quantitative measures to describe pain is often inadequate. McGill Pain Questionnaire (MPQ) is a method widely used in clinical research providing a qualitative measure of clinical pain that can be treated statistically [28, 29]. MPQ is based on the three interrelated dimensions of pain defined by the Gate Control Theory: sensory, affective and evaluative [23]. A Danish version of MPQ has been developed and validated for use in research [30].

The questionnaire is comprised of 20 subclasses of quantitatively and qualitatively ordered word descriptors of pain. 16 of the subclasses are designed to measure the three dimensions of pain defined by the Gate Control Theory, and the remaining four subclasses are miscellaneous. The designation of the 16 subclasses related to the Gate Control Theory is shown in figure 6 [31].

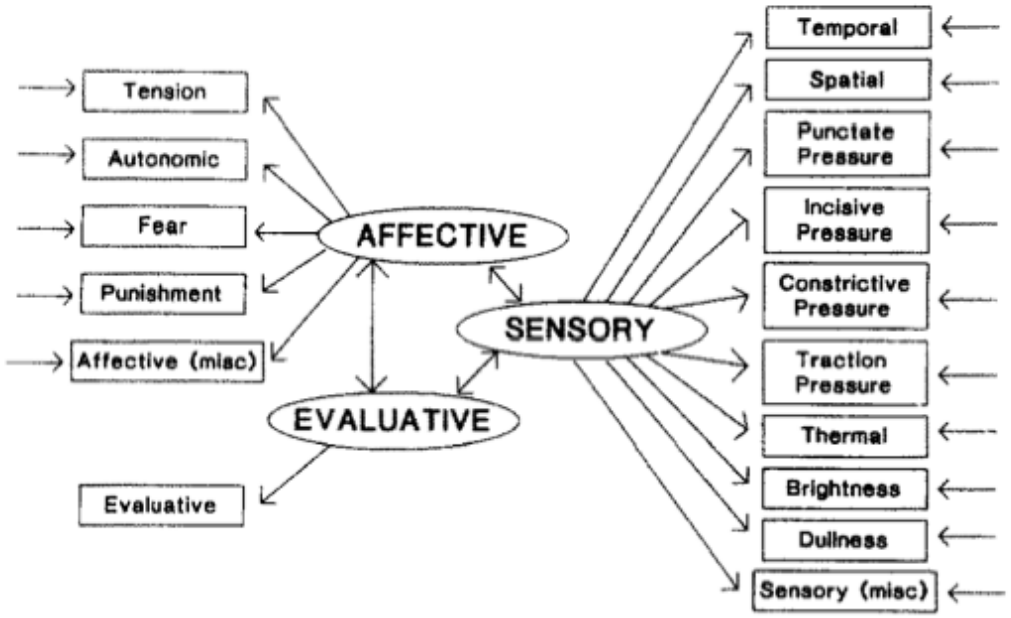


Figure 6 - Path diagram for the theoretical structure of McGill Pain Questionnaire [31]

Each word descriptor in the questionnaire is assigned two numerical measures; a scale value related to the pain category, and a rank value depending on the word's rank within the subclass. These values are used to compute two Pain Rating Indexes designated as PRI(S) and PRI(R) respectively. The total PRI scores may be used as an overall measure of pain intensity, and the subclasses provide a mechanism to study a number of variables in

relation to the three dimensions of pain [31]. The number of words chosen (NWC) may be used as an indicator of the pain intensity [29].

2.4 LOCAL ANAESTHETICS

Local anaesthetics are commonly used in clinical practice as treatment and prevention of pain. They exert their effect by binding to the intracellular part of voltage-gated sodium channels resulting in a blockade of sodium ion entry. Hereby nerve depolarisation is prevented, inhibiting the propagation of action potentials and impulse conduction along the nerve [7, 20]. By preventing neuronal signalling local insensibility to painful stimuli is achieved [16].

The first reported clinical use of local anaesthetics dates back to the 19th century where cocaine isolated from cocoa leaves was used for eye surgery [32]. Today a number of local anaesthetic molecules are recognised with varying pharmacokinetic and pharmaco-dynamic properties. The molecular structure of local anaesthetics is similar, consisting of three components: a lipophilic aromatic ring, an intermediate amide or ester link and a secondary or tertiary amine component, see figure 7. Each of these components contribute to the individual properties of the local anaesthetic agent [33].

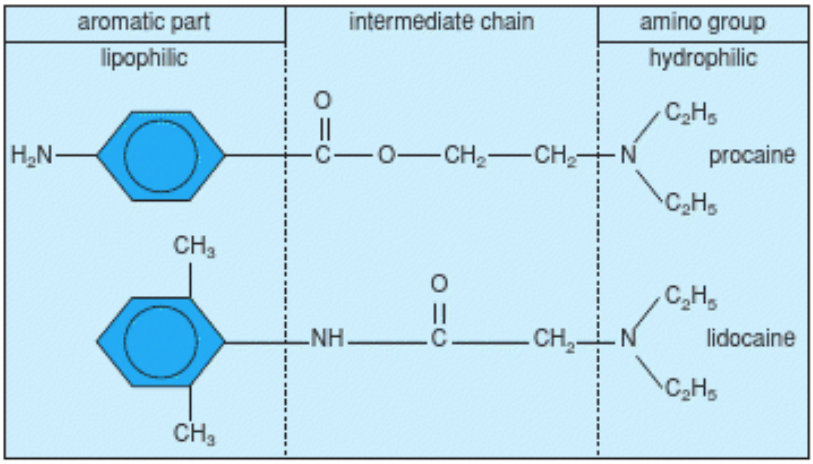


Figure 7 - Molecular structure of an ester-linked (procaine) and an amide-linked (lidocaine) local anaesthetic [6]

Depending on the intermediate chain, local anaesthetics may be classified into two groups: esters (e.g. procaine) and amides (e.g. lidocaine). These groups differ in route of metabolism as well as their potential to induce allergic reactions [7]. Amide anaesthetics

are metabolised in the liver while esters are rapidly hydrolysed in the bloodstream by plasma esterases resulting in a shorter half-life [33].

As the target of local anaesthetics is the intracellular part of the sodium channel, the molecules must access the receptor from within the nerve cell. Penetration of the lipid nerve cell membrane is therefore vital [20]. The optimal penetration is achieved by non-ionised and lipophilic molecules [6]. Affinity for the sodium channel is also related to the ionisation and lipid solubility of the molecule, because ionised and lipophilic molecules bind more readily to the receptor [20, 34].

The lipid solubility of a local anaesthetic is determined by the aromatic component as well as aliphatic groups on either the intermediate chain or the amine. Lipid solubility may be measured by the oil and water partition coefficient. Due to low water solubility local anaesthetics are often prepared as hydrochloride salts to improve the solubility and stability in aqueous media. In solution the local anaesthetic agents exist as both ionised cations (R_3NH^+) and non-ionised base (R_3N), the distribution of which is determined by the local pH and the pKa value of the drug molecule. The proportion of ionised molecules may be calculated by the Henderson-Hasselbalch equation [20, 34]:

$$\text{Log } (R_3NH^+ / R_3N) = pKa - pH$$

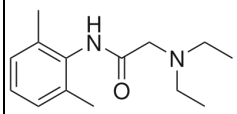
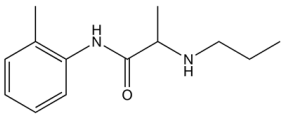
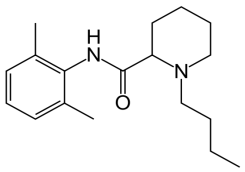
2.4.1 Local anaesthetic drugs

Lidocaine was discovered in 1948 and soon became the dominating local anaesthetic agent replacing to a large extend ester type local anaesthetics. Today lidocaine remains one of the most commonly used local anaesthetics [16, 20]. Many other agents with similar chemical structure to lidocaine have been developed. One of these is prilocaine. With a slight alteration in chemical structure, prilocaine was invented in hope of developing an alternative to lidocaine with equivalent efficacy and decreased toxicity [20]. Although prilocaine never gained the same status as lidocaine, it is a commonly used local anaesthetic.

Bupivacaine was developed in 1957 as a modification of an existing local anaesthetic. An aliphatic group was added to the amine of the local anaesthetic mepivacaine in order to achieve a longer duration of action. Today bupivacaine is the prime example of a long acting anaesthetic [32, 35]. Despite their similar chemical structure, lidocaine, prilocaine

and bupivacaine have different clinical properties. Their physicochemical properties can be used to explain these differences, see table 1 [20].

Table 1 - Physicochemical and clinical properties of lidocaine, prilocaine and bupivacaine [36]

Property	Lidocaine	Prilocaine	Bupivacaine
Structure			
Molecular weight (base)	234 Da	220 Da	288 Da
pKa (25°C)	7.91	7.90	8.16
Partition coefficient[1]	2.4	25	346
Aqueous solubility[2]	24	-	0.83
Protein binding	64%	55%	96%
Speed of onset	Fast	Fast	Intermediate
Equieffective anaesthetic concentration	1	1	0.25

[1]n-octanol/pH 7.4 buffer.
[2]mg HCl salt/mL at pH 7.37 and 37°C.

Lidocaine and prilocaine have lower dissociation constants (pKa) resulting in a higher proportion of non-ionised molecules in aqueous solution compared to bupivacaine. This causes a more rapid onset of action as the non-ionised base more readily penetrates the nerve membrane [20]. Bupivacaine has a higher pKa value and lipid solubility and therefore a higher affinity for the sodium channel compared to lidocaine and prilocaine. Bupivacaine is therefore more potent and has a longer duration of action. Bupivacaine's long-acting properties can also be attributed its high degree of protein binding, as the protein-bound fraction of the drug acts as a reservoir that can replenish the drug that continuously is lost from the site of action [6].

2.4.2 Toxicity

Although most local anaesthetics are considered relatively safe, they occasionally induce local and systemic adverse effects. Local adverse effects extend from mild allergic reactions to anaphylaxis, the latter being extremely rare [37]. Allergy towards local anaesthetics of the ester type is more common compared to allergy towards the amide type [7].

Systemic adverse events of local anaesthetics are usually a result of excessive dosage, rapid absorption or accidental intravascular injection [38]. The most predominant systemic effects are related to the cardiovascular system and the CNS [34]. CNS toxicity is due to the lipophilic nature of local anaesthetics, which allows penetration of the blood-brain-barrier [6]. CNS toxicity may be manifested by mild reactions such as restlessness and dizziness to more severe symptoms such as unconsciousness [38]. Toxic symptoms of the cardiovascular system include cardiac dysrhythmias, hypotension and cardiac arrest [38]. If used correctly, systemic toxic reactions to local anaesthetics are very rare in clinical practice [38].

Due to its higher potency, bupivacaine has greater toxic potential compared to lidocaine and prilocaine [38]. Although very rare, mild systemic adverse reactions have been reported at plasma concentrations of 6-10 μg/ml for lidocaine and 1 μg/ml for bupivacaine [39, 40]. These plasma concentrations are higher than those achieved by local anaesthesia in dentistry. Intraoral injection of 200 mg lidocaine in solution results in a maximum plasma concentration of 2 μg/ml [41]. The systemic absorption from topically applied local anaesthetics is even smaller. A phase I trial showed that administration of a lozenge containing 25 mg bupivacaine resulted in a peak plasma concentration of approximately 0.370 μg/ml [42].

2.4.3 Local anaesthetics in dental practice

In addition to the physicochemical properties of local anaesthetic agents, clinical properties are also determined by factors such as the site and method of administration [43]. In dental practice local anaesthetics are most often administered by injection or topical application [16].

2.4.3.1 Injection

Injection of an anaesthetic solution is often used as the standard method of anaesthesia for dental procedures. It offers a better penetration and more rapid onset of action compared

to most topical preparations [6]. Injections may be performed using two techniques; infiltration or regional block. When using infiltration, the anaesthetic solution is injected near the nerve endings, where impulse transmission is inhibited. Regional block targets any part of the nerve trunk proximal to the nerve endings and thus anaesthetises a larger area. Regional anaesthesia is used when infiltration methods are ineffective or to avoid multiple injections when larger areas are to be anaesthetised [16].

In the maxilla the compact bone is relatively thin, which facilitates the diffusion of anaesthetic solution. Therefore anaesthetic solution administered by infiltration can easily spread, and local anaesthesia be achieved. Regional block of the maxilla is most commonly achieved by targeting behind the maxillary tuberosity [6].

The buccal compact bone of the mandible is of greater thickness compared to the maxilla, which inhibits diffusion of anaesthetic solution. Therefore regional block is required for effective anaesthesia in the area of the mandibular molars and premolars. Regional anaesthesia can be achieved by reaching the lingual nerve or the inferior alveolar nerve. If necessary, regional block may be supplemented with infiltration anaesthesia. In the area of the mandibular canines and incisors the cortical bone is thinner and effective local anaesthesia may occasionally be achieved merely by infiltration [6].

Numerous local anaesthetics are available as solution for injection in dental practice. Lidocaine is often provided as a 2% solution (20 mg/ml) for use in dentistry [16]. It may be manufactured with a vasoconstrictor, such as adrenalin, for a number of reasons. The vasoconstriction reduces bleeding from the anaesthetised area and minimises diffusion of the local anaesthetic into the blood circulation. This results in a prolonged effect, as the local anaesthetic is not lost from the site of action. Furthermore the reduced systemic absorption reduces the probability of systemic toxicity [20]. Adrenalin itself may however induce adverse reactions. These include adrenergic effects on the cardiovascular system such as tachycardia and increased blood pressure [6].

2.4.3.2 Topical application

When applied topically, the local anaesthetic must permeate the oral mucosa in order to reach the desired site of action [7]. The anaesthetic agent must possess certain physicochemical properties to enable transmucosal absorption. The drugs that are best absorbed are lipid soluble, non-ionised and with a molecular weight below 20.000 Da [13]. The low molecular weight of lidocaine, prilocaine and bupivacaine favours absorption across the oral mucous membrane. Bupivacaine's high lipid solubility and dissociation

constant makes it the best candidate for transmucosal drug delivery followed by prilocaine and lidocaine.

The oral mucosa is highly vascularised and easily accessible, making it an ideal site for drug delivery [14]. The amount of drug absorbed depends on the histological character of the mucosa and the mucosal contact time [15]. To facilitate transmucosal absorption, the drug must have a prolonged exposure to the surface of the oral mucosa [15]. Numerous topical formulations for intraoral use exist, offering varying exposure time and thus varying potential absorption. Different formulations include gels, creams, lozenges, and patches [7].

2.4.3.2.1 Bupivacaine lozenge

A lozenge containing bupivacaine has recently been developed providing a new method of intraoral local anaesthesia. The lozenge dissolves in the saliva and distributes bupivacaine to the oral mucosa and the top third of the oesophageal mucosa. The formulation provides a continuous release and a slow spread of the drug [15]. The lozenge has been investigated for use before upper gastrointestinal endoscopy (UGE) in a single-blinded randomised controlled trial including 100 patients. In this study the bupivacaine lozenge showed to significantly improve the patient acceptance of UGE and gag reflexes compared to the standard method of anaesthesia by a lidocaine pharyngeal spray [8]. The clinical potential of the lozenge in dentistry is yet to be investigated.

2.4.3.2.2 Other topical formulations

A number of topical anaesthetics have been investigated for pain management during SRP. Table 2 gives an overview of the different clinical studies conducted.

Table 2 - Clinical studies evaluating the use of topical local anaesthetics for scaling and root planning.

Study	Number of patients	Formulations	Methods	Major findings
Svensson et al. 1994 [44]	20	EMLA®	Using a split-mouth design, EMLA® and placebo was applied in each side of the oral cavity respectively. Pain and unpleasantness during scaling was measured using a Visual Analogue Scale.	EMLA® reduced the pain and unpleasantness of scaling in both jaws when compared to placebo. The influence on pain was more marked than the effect on unpleasantness.

Donaldson et al. 1995 [45]	14	EMLA® Lidocaine gel 5%	Using split-mouth design, each subject received both treatments in a customised intraoral splint. The maximum probing pocket depths that did not cause discomfort were recorded before and after application of topical anaesthetics.	Both treatments increased the depth of probing before discomfort was experienced. EMLA® produced a significantly higher increase in probing depth compared to lidocaine gel.
Friskopp et al. 2001 [46]	30	Oraqix®	Oraqix® was applied to patients with periodontitis in different durations (30 s, 2 min, 5 min) prior to scaling and root planning. On completion of scaling and root planning of each tooth (2–3 teeth treated per patient), the patients rated their pain on a Visual Analogue Scale. Duration of anaesthesia was measured as pain on probing.	The mean durations of anaesthesia were 18.1, 17.3, and 19.9 min in the 30 s, 2 min, and 5 min groups, respectively. The median Visual Analogue Scale pain score was 7.5 mm in the 30 s group, 28.5 mm in the 2 min group, and 15.5 mm in the 5 min group, with a significant difference between the 30 s and 2 min groups.
Donaldson et al. 2003 [47]	130	Oraqix®	Patients received Oraqix® or placebo gel in periodontal pockets in one quadrant of the mouth for 30 s prior to scaling and root planning. Pain was measured using a Visual Analogue Scale and a Verbal Rating Scale.	Oraqix® showed a significant reduction in Visual Analogue Scale pain score compared to placebo. There was no significant difference in pain reported by Verbal Rating Scale between the two groups.
Jeffcoat et al. 2001 [48]	122	Oraqix®	Oraqix® or placebo was applied in the periodontal pockets before scaling and root planning. Pain was measured using both a Visual Analogue Scale and a Verbal Rating Scale.	Oraqix® showed significant reductions in reported pain both by Visual Analogue Scale and a Verbal Rating Scale. The results indicated a more pronounced effect in pain sensitive patients and patients with more severe periodontal disease.
Magnusson et al. 2003 [49]	85	Oraqix®	Patients screened for pain sensitivity upon probing. Patients reporting a VAS score above 30 mm were included in the study. Oraqix® or placebo was applied in the periodontal pockets before scaling and root planning. Pain was measured using a Visual Analogue Scale and a Verbal Rating Scale.	Oraqix® reduced Visual Analogue Scale and Verbal Rating Scale scores significantly compared to placebo. The results did not show any relationship between the extent of disease and the efficacy of Oraqix®.

Van Steenberghe et al. 2004 [50]	170	Oraqix® Lidocaine-adrenalin injection (2%)	Patients received both treatments before scaling and root planning at two individual appointments. The patients were asked for their preferred method of anaesthesia and also assessed the adequacy of anaesthesia and occurrence of post-procedure problems.	The majority of patients (70%) preferred Oraqix® to injection anaesthesia (22%). 80% of patients reported adequate anaesthesia with Oraqix® and 96% with infiltration anaesthesia. Post-procedure problems were significantly less with Oraqix® than injection.
Carr et al. 2001 [51]	20 + 20	Lidocaine patch 20% Benzocaine gel 20%	20 subjects received either the patch or the gel in one side of the mouth and a placebo control in the opposite site. Another group of 20 subjects received the gel in one side and the patch in the other side. Pain perception to needle stick and scaling and root planning was measured by Visual Analogue Scale and Verbal Pain Scale.	Pain scores to needle stick were significantly reduced by the lidocaine patch and benzocaine gel when compared to placebo. The lidocaine patch reduced pain and discomfort of scaling and root planning when compared with placebo whereas the benzocaine gel did not differ from placebo. When the different jaws were compared the lidocaine patch was more effective than the benzocaine gel in the maxilla but not in the mandible.
Carr et al. 2001 [52]	60	Lidocaine patch 20% Benzocaine gel 20%	Subjects evaluated the effectiveness of a lidocaine patch, a benzocaine gel and placebo for pain caused by needle stick and scaling and root planning. Subjects rated their degree of pain/discomfort using verbal pain score measurements.	The lidocaine patch was superior to placebo in reducing pain of needle stick and scaling and root planning. Benzocaine gel did not differ significantly from placebo in either regard. When compared directly, the lidocaine patch was superior to the benzocaine gel in reducing pain of needle stick and scaling and root planning.

EMLA® is a eutectic mixture of lidocaine (25 mg/g) and prilocaine (25 mg/g) available as cream and patches. It was developed in the late 1970s and early 1980s and is today one of the most commonly used topical anaesthetics in dermatological practice [53]. Although EMLA® is not licensed for intraoral use, it is often used in dental practice. Svensson et al. have shown EMLA® to be more effective in reducing pain and unpleasantness provoked by scaling of gingival pockets compared to placebo [44]. Another study showed EMLA® to

be superior to 5% lidocaine gel in providing a pain free probe penetration into the gingival sulcus [45].

The promising results of EMLA® for intraoral use led to the development of a topical formulation designed for use in dental practice. Oraqix® has a similar composition to EMLA® containing 25 mg/g lidocaine and 25 mg/g prilocaine. A thermosetting agent enables the formulation to be fluid at room temperature and increase viscosity to become an elastic gel when applied to the periodontal pocket [54].

Several studies have shown Oraqix® to be superior to placebo in reducing pain and discomfort associated with SRP [47-49]. Van Steenberghe et al. compared the use of Oraqix® to infiltration anaesthesia for periodontal treatment. Infiltrations showed a greater anaesthetic efficacy, however 70% of the patients preferred treatment with Oraqix®. Reasons for this preference included less post-operative numbness and inconvenience. The main reason for preference towards infiltration was greater comfort during treatment [50].

3. EXPERIMENTAL

3.1 APPROVALS AND MONITORING

The study was approved by the Regional Ethics Committee, Copenhagen, Denmark (jour. no. H-B-2012-113), the Danish Health and Medicine Agency (EudraCT no. 2012-003430-16) and the Danish Data protection agency (jour. no. 2007-58-0015). The external Clinical Research Organisation, Quintiles, monitored data throughout the study. The study was registered at the public database ClinicalTrials.gov and was conducted according to current ICH-GCP guidelines.

3.2 DESIGN

3.2.1 Study design

The study was conducted using a randomised, split-mouth, two period crossover design, see figure 8. Each subject underwent two individual SRPs with an interval of a few weeks. The first SRP was performed in the right side of the oral cavity and the second SRP in the left side. Randomisation determined whether patients received a bupivacaine lozenge or lidocaine-adrenaline injections as anaesthetic treatment at the first SRP. At the second SRP patients received the opposite anaesthetic treatment.

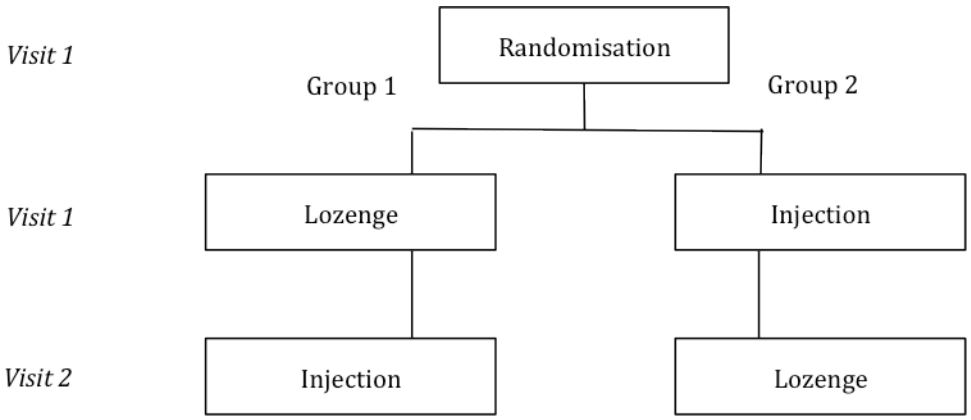


Figure 8 - Flow diagram of study design

3.2.2 Inclusion of patients

Patient enrolment took place at three individual dental clinics experienced in periodontitis

treatment. Investigators screened and contacted relevant patients. Patients who fulfilled the following in- and exclusion criteria were included in the study:

Inclusion criteria:

- Diagnosed with rapidly or slowly progressive marginal periodontitis in the hygiene phase, where two SRPs are to be performed within a short time frame.
- Age above 18 years
- Ability to speak, read and understand Danish
- Ability to give oral and written consent

Exclusion criteria:

- Known allergy to bupivacaine or other amide local anaesthetics
- Other gingival conditions (e.g. lichen planus)
- Pregnancy
- Breast feeding

3.2.3 Endpoints

3.2.3.1 Primary endpoint

The primary endpoint of the study was to demonstrate an effect on pain and discomfort *during* SRP by the bupivacaine lozenge that was not worse than that of lidocaine-adrenalin injections. Pain and discomfort was measured by VAS.

3.2.3.2 Secondary endpoints

Secondary endpoints included:

- To demonstrate an effect on pain and discomfort *after* SRP by the bupivacaine lozenge that was not worse than that of lidocaine-adrealin injections. Pain and discomfort was measured by VAS
- To demonstrate an effect on pain during SRP measured by MPQ by the bupivacaine lozenge that was not worse than that of lidocaine-adrenalin injections
- To show a more positive patient evaluation of the lozenge compared to lidocaine-adrenalin injections

3.3 STUDY MEDICATION

Details of the study medication used in the trial are listed in table 3.

Table 3 - Properties of the study medication bupivacaine lozenge and Xyloplyin Dental Adrenalin.

Study medicine	Bupivacaine lozenge	Xyloplyin Dental Adrenalin
Dosage form	Lozenge	Solution for injection
Active ingredient(s)	Bupivacaine	Lidocaine Adrenalin
Dose	25 mg/lozenge	20 mg/ml (lidocaine) 12.5 µg/ml (adrenalin)
Batches	109351 309352	2137
Manufacturer	Pharmacy of The Capital Region of Denmark	Dentsply Ltd.

3.4 METHODS

3.4.1 Procedure

3.4.1.1 Randomisation

Randomisation was carried out at visit 1 after the patient had signed the informed consent form and prior to the first SRP. The order of treatment was determined by drawing a sealed opaque envelope. The envelopes were pre-packed in blocks of 4 at the Clinical Research Centre, Hvidovre University Hospital by an independent individual.

3.4.1.2 Administration of local anaesthetic

For patients receiving the bupivacaine lozenge, the lozenge was administered approximately 15 minutes prior to SRP. The patients were instructed to suck the lozenge and distribute the saliva throughout the oral cavity, primarily focusing on the side subject to SRP. The time taken to dissolve the lozenge was noted.

When receiving Xyloplyin Dental Adrenalin, the dentist administered the injections just before SRP was commenced. Occasionally supplemental infiltrations were administered during the procedure. The injection technique (regional, infiltration), site of administration (maxilla, mandible), number of injections and amount of solution injected was noted.

3.4.1.3 Scaling and root planning

Relevant dental staff experienced in periodontitis treatment performed the SRP. The professional performing the SRP evaluated the procedure afterwards by a 4-point scale: 1 = very easy; 2 = easy; 3 = difficult and 4 = very difficult. The PPDs of the involved teeth, the procedure time and the equipment used was also noted.

3.4.1.4 Patient assessment

Prior to SRP, the patient's pain, discomfort and anxiety was measured using VAS. After the SRP, patients assessed pain and discomfort both during and after the procedure by VAS. The pain and discomfort in relation to the administration of the local anaesthetic was also measured using VAS. The pain before and during the SRP was also assessed using MPQ. Additionally the patient assessed the two pharmaceutical formulations by a questionnaire.

3.4.2 Statistical analysis

3.4.2.1 Power calculation

The power calculation was done using a paired t-test, enabling detection of a difference of 10 mm on a VAS. A power of 90%, a significance level of 5% and a standard deviation of 20 mm on VAS was used for the calculation. This resulted in a study population of 36 patients. Due to anticipation of dropouts, it was decided to include a total of 40 patients.

3.4.2.2 Analysis of variables

All statistical analyses were performed with SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA) with a significance level of 0.05.

Variables were tested for normal distribution before analysis. Variables following normal distribution *(Kolmogorov-Smirnov)* were analysed by paired t-test, while those that did not follow normal distribution were analysed by Wilcoxon ranked sign test. Categorical data was analysed by Fisher's exact test, because of the low number of participants. The effect of different variables on VAS scores was tested by linear regression analysis. Patients were only included once in regression analysis.

3.4.3 Literature search

Literature search was done using PubMed (pubmed.gov), The Danish Royal Library (kb.dk) and the Google scientific search engine, scholar.google.com, using the key word shown in table 4 in different combinations. Reference lists from the obtained articles were

used to find original articles and further literature. External supervisors also provided some of the literature.

Table 4 - Key words used for literature search

Adverse events, anaesthesia, anaesthetics, anxiety, assessment, buccal delivery, bupivacaine, dental, dentistry, diagnosis, drug delivery, gate control theory, gingivitis, immune response, infiltration, injection, lidocaine, lignocaine, local, lozenge, McGill Pain Questionnaire, maximum dose, mucous membrane, oral mucosa, pain, pathology, patient discomfort, patient satisfaction, periodontal tissue, periodontitis, permeability, pharmacology, plasma concentration, physicochemical properties, prilocaine, physiological factors, regional anaesthesia, root planning, scaling, taste, topical administration, toxicity, treatment, Visual Analogue Scale, Verbal Rating Scale

4. RESULTS

Inclusion of the desired 40 patients was not feasible within the available time frame. The analysis is therefore based on a lower number of subjects than the power calculation, and consequently no final conclusions can be drawn. It should also be noted that the study is not sized to give power to the subsample analyses explored.

4.1 PATIENT DEMOGRAPHICS AND BASELINE DATA

In the three participating clinics a total of nine patients were enrolled and randomised in the study, see figure 9. Five patients were randomised to receive the lozenge at the first visit (group 1) and four patients were randomised to receive injections at the first visit (group 2). One patient from group 2 was withdrawn from the study during treatment with the lozenge due to insufficient anaesthesia. A total of five patients from group 1 and three patients from group 2 completed the study and were included in the analysis.

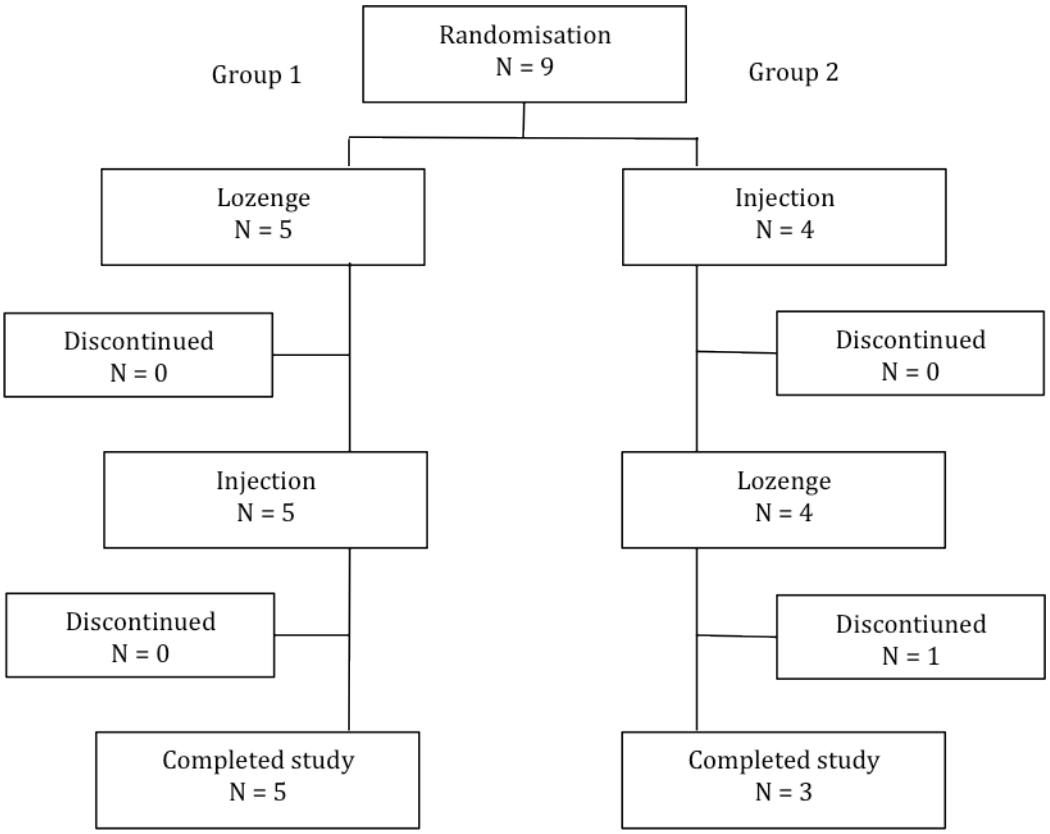


Figure 9 – Flow chart showing the patient randomisation.

Five males and three females participated in the study. Demographic data of the study population is shown in table 5.

Table 5 - Demographic data of the study population.

	Mean (SD)	Mean (SD)
Age (years)	48 (10)	35-61
Body Mass Index (m^2/kg)	26.7 (3.9)	23.0-33.0

Two patients had taken analgesia (acetylsalicylic acid or paracetamol) before both treatment visits. These patients took the same amount before each visit. One patient had taken paracetamol only prior to the visit involving treatment with the lozenge. The indications for analgesia were prophylaxis, cold and head ache.

Table 6 gives an overview of the number of teeth involved in SRP and PPD measurements over 5 mm in the treatments. The average number of teeth involved in SRP when treated with injections and lozenge, respectively was not significantly different *(p=0.64)*. Within subjects, the number of teeth involved in SRP of the right and left side of the oral cavity was not significantly different *(p=0.26)*.

There was no significant difference in the number of PPD measurements above 5 mm in the sides treated with lozenge and injections *(p=0.80).* The difference between the right and left side of the oral cavity within subjects ranged from 2 to 22 PPD measurements over 5 mm. The number of PPD measurements over 5 mm in the right side of the oral cavity was not significantly higher than in the left side of the oral cavity *(p=0.27)*.

Table 6 – Number of teeth, number and depth of probing pocket depth measurements over 5 mm involved in scaling and root planning. n = number of probing pocket depths over 5 mm.

	Lozenge			Injections		
	n	Mean (SD)	Range	n	Mean (SD)	Range
Number of teeth involved in scaling and root planning per patient (N=8)	-	12 (2)	8-15	-	12 (3)	6-15
Number of probing pocket depths over 5 mm per patient (N=8)	-	22 (17)	5-55	-	21 (9)	5-33
Depth of probing pocket depths over 5 mm for all patients (mm)	173	6 (1)	5-10	165	6 (1)	5-10

4.2 TREATMENT

The mean amount of anaesthetic solution injected was 5.2 ml (SD: 2.0, range: 2.2-7.4 ml), corresponding to 104 mg lidocaine hydrochloride and 65 mg adrenalin. The number of injections ranged from three to 19 with a mean of eight injections. In the maxilla infiltrations were primarily used, while regional anaesthesia in the mandible was used for seven out of eight subjects (88%).

The lozenge was completely dissolved for all subjects within an average time of 13.4 min. None of the subjects swallowed the lozenge and all subjects thus received a dose of 25 mg bupivacaine using the lozenge.

The duration of the SRP procedure ranged from 12 to 43 min with a mean of 22.5 min. Within subjects the duration of the first SRP was significantly longer than the second SRP *(p=0.03)*. The duration of the SRP procedures involving injections and lozenge, respectively, was not significantly different *(p=0.66)*.

4.3 PATIENT EVALUATION

4.3.1 Visual Analogue Scale

At baseline all subjects reported a VAS score of 0 mm for pain and discomfort. Figure 10 shows VAS scores for pain and discomfort during and after SRP.

During SRP the VAS pain scores were significantly higher when treated with the lozenge compared to injections *(p=0.03)*. The VAS scores for discomfort were also higher during treatment with the lozenge with borderline significance *(p=0.05)*.

After the SRP there was no significant difference between the lozenge and injections in VAS pain scores *(p=0.14)*. VAS discomfort scores after SRP were significantly lower for treatment with the lozenge compared to injection *(p=0.04)*.

Period effect was tested for by comparing the results from visit 1 and visit 2. No significant period effect was seen for VAS pain scores *(p=0.83)* or VAS discomfort scores *(p=0.63).* Carry-over effect was assumed to be negligible, because the time interval between the treatment periods was well above the time that would be expected for the local anaesthetics to be eliminated. It was therefore not included in the analysis.

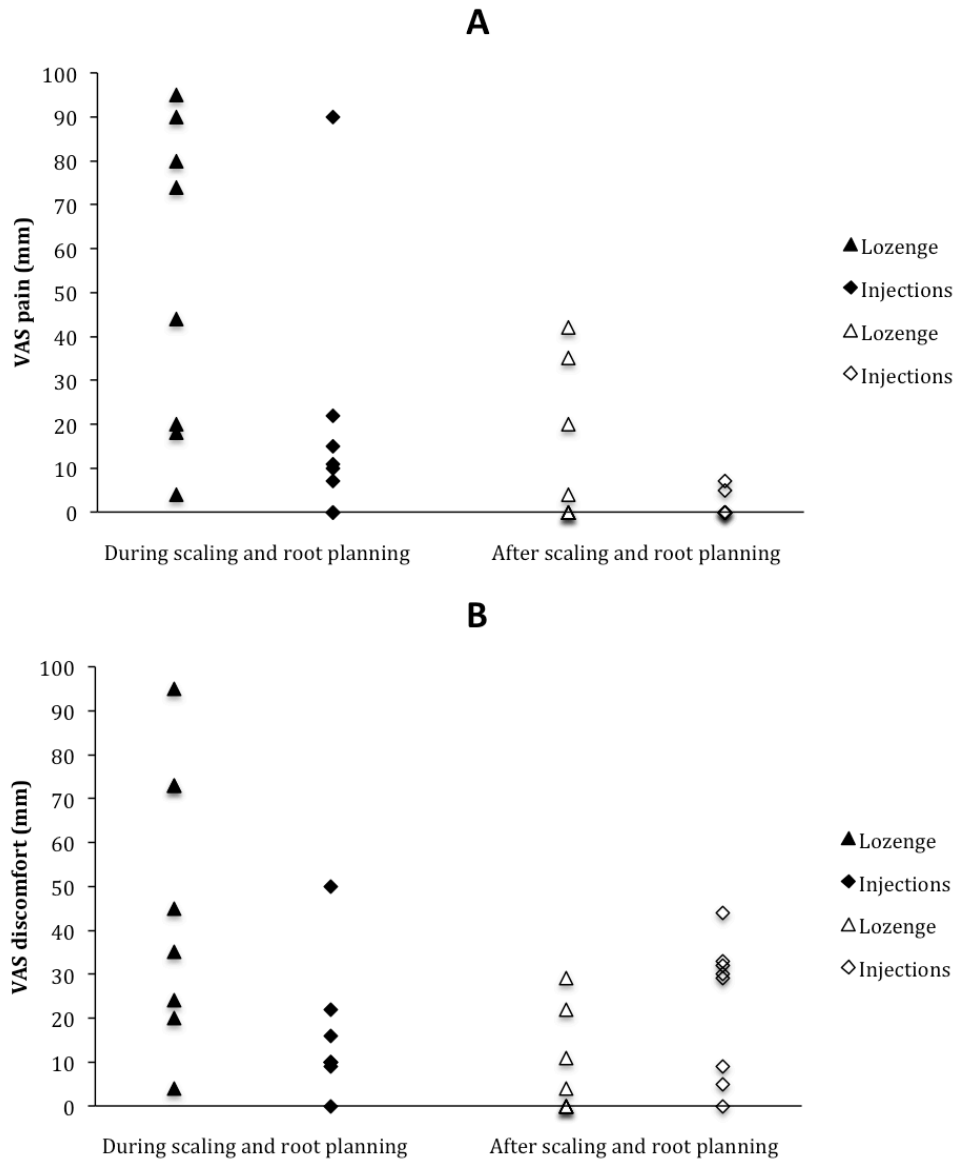


Figure 10 - A: VAS pain scores during and after scaling and root planning. B: VAS discomfort scores during and after scaling and root planning.

The mean VAS pain score in relation to administration of injections was 23 mm (SD: 23, range: 0-52 mm). All patients reported a VAS pain score of 0 mm in relation to administration of the lozenge. Mean VAS discomfort scores were 31 mm (SD: 33, range: 0-92 mm) for injections and 7 mm (SD: 8, range: 0-20 mm) for the lozenge. VAS pain scores in relation to administration of injections were significantly higher than in relation to administration of the lozenge *(p=0.02)*. The difference in VAS discomfort scores during administration was not significant *(p=0.07)*.

Figure 11 shows the individual VAS pain scores, number of PPD measurements over 5 mm and SRP duration times for each patient. Patients number 3, 4 and 6 had a difference of more than 10 PPD measurements over 5 mm between the two sides of the oral cavity. Of these patients, only patient 3 had a larger VAS pain score in the side with more PPDs over 5 mm.

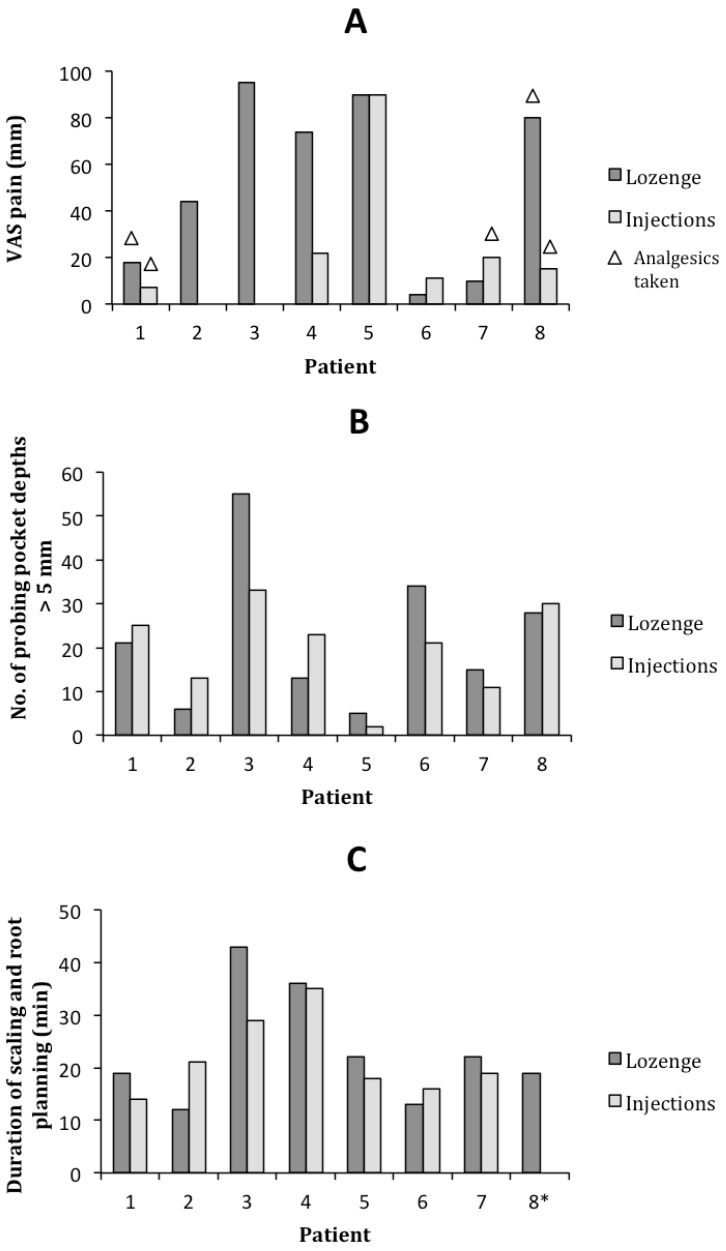


Figure 11 – A: Individual VAS pain scores (mm) for treatment with lozenge and injections. B: Number of probing pocket depths over 5 mm in the sides of the oral cavity treated with lozenge and injections. C: Duration of scaling and root planning (min) during treatment with lozenge and injections. *The duration of the second scaling and root planning was not recorded for patient 8.

Patients 2 and 3 had different durations of SRPs (> 9 min) at the two visits (see figure 11). Patient 3 had a higher VAS pain score at the longer SRP, while patient 2 had a lower VAS score (0 mm) at the longer SRP.

A regression analysis showed that during treatment with the lozenge, a longer duration of SRP resulted in higher VAS pain scores *(beta=2.2, p=0.07)* and VAS discomfort scores *(beta=2.3, p=0.01).* The correlation was only significant for VAS discomfort scores. During treatment with injections longer durations of SPR resulted in lower VAS pain scores *(beta=-0.6, p=0.75)* and VAS discomfort scores *(beta=-0.8, p=0.39).* These correlations were not significant.

Regression analysis showed that during treatment with the lozenge a higher number of teeth involved in SRP resulted in higher VAS pain scores *(beta=3.1, p=0.65)* and VAS discomfort scores *(beta=3.0, p=0.61).* During treatment with injections a higher number of teeth involved in SRP also resulted in higher VAS pain scores *(beta=2.6, p=0.50)* and VAS discomfort scores *(beta=0.64, p=0.74).* None of these correlations were significant.

During treatment with the lozenge a higher number of PPD measurements over 5 mm resulted in higher VAS pain scores *(beta=0.34, p=0.71)* as well as VAS discomfort scores *(beta=0.76, p=0.31).* These correlations were not significant. During treatment with injections a higher number of PPD measurements above 5 mm resulted in lower VAS pain scores *(beta=-2.1, p=0.08)* as well as VAS discomfort scores *(beta=-1.0, p=0.10).* These correlations were not significant.

For treatment with the lozenge, the visits where patients had taken analgesics did not show a significant reduction in VAS pain scores compared to the visits where no analgesics had been taken *(p=0.91).* The same was shown for treatment with injections *(p=0.65).*

4.3.2 McGill Pain Questionnaire

At baseline all subjects reported no pain using MPQ. During SRP two patients reported no pain when treated with injections, while all patients reported some degree of pain during treatment with the lozenge. The results from MPQ are summarised in table 7. The total PRI(R) and PRI(S) were not significantly different between treatment with the lozenge and injections *(p=0.45 and p=0.28)*. The number of words chosen (NWC) was not different between the two treatments *(p=0.82)*.

Table 7 - Results from the McGill Pain Questionnaire. Total Pain Rating Indexes for rank (PRI(R)) and scale values (PRI(S)) and Number of Words Chosen (NWC).

	Lozenge			Injection		
	N	Mean (SD)	Range	N	Mean (SD)	Range
Total PRI(R)	8	7 (6)	1-17	6	6 (6)	0-16
Total PRI(S)	8	8.9 (7.3)	1.4 – 20.3	6	7.5 (7.6)	0.0 – 20.2
NWC	8	3 (3)	1-9	6	3 (3)	1-7

During SRP all patients chose pain descriptors from the sensory subclass when treated with the lozenge, while five patients (83%) chose words from the sensory subclass when treated with injections. "Shooting" *("Jagende")* was the most frequently used word during treatment with the lozenge, while "Boring" *("Stikkende")* was chosen most frequently when treated with injections.

No patients chose any words from the affective subclass during either treatment.

Patients could only choose one word from the evaluative subclass. Four patients (50%) chose a word from the evaluative subclass during treatment with the lozenge with the most popular word being "Annoying" *("Irriterende")*. Two patients (33%) used descriptors from the evaluative subclass during treatment with injections. The words were "Intense" *("Pinagtig")* and "Annoying".

Three patients (38%) chose words from the miscellaneous subclass when treated with the lozenge, while four patients (67%) chose words from the miscellaneous subclass when treated with injections. "Agonizing" *("Pinefuld")* was the most frequently used word during treatment with the lozenge, while "Cool" *("Kølig")* was chosen most frequently when treated with injections.

4.3.2 Patient evaluation of the pharmaceutical formulations

Three patients (38%) preferred treatment with the lozenge, while two patients (25%) preferred injections. Three patients did not indicate preferred treatment. To elaborate their assessment of the pharmaceutical formulations, patients had the opportunity to write a comment. Some representative comments are shown in table 8.

Table 8 - Examples of patient comments on the lozenge and injections after scaling and root planning

Positive on lozenge	Negative on lozenge
- It worked! - My incisors were less sensitive than usual - It was no worse than injections - It was better than no anaesthesia - It seemed like a good and cheap alternative anaesthetic treatment - The lozenge was more comfortable than injections	- It was not as effective as injections - I did not feel sufficiently anaesthetised - The duration of anaesthesia was not very long - Taking the lozenge itself was almost more uncomfortable than the SRP - I felt queasy when taking the lozenge because of the effect on the throat
Positive on injections	Negative on injections
- I did not feel a thing - It worked better than the lozenge - It was very effective	- After the procedure it is inconvenient that the mouth is completely numb and cannot be controlled - I am not willing to pay a high price for injections

4.4 DENTIST ASSESSMENT

None of the SRPs were evaluated by the dentists as "very difficult". Three (38%) and two (25%) SRPs were evaluated as "difficult" during treatment with the lozenge and injections, respectively. Four SRPs (50%) were evaluated as "easy" during treatment with the lozenge while five SRPs (63%) were evaluated as "very easy" during treatment with injections. The difference in evaluations between treatment with lozenge and injections was not significant *(p=0.26).*

5. DISCUSSION

Pain is one of the most common patient concerns associated with dental treatments and fear of pain has been shown to play a major role in preventing patients from seeking dental care [24]. Management of pain during SRP is therefore important to ensure patient compliance with treatment. Especially in periodontitis where the condition itself is often not painful, and patients may not feel an incitement to seek treatment, which may be painful [17].

This study evaluated the effect of a new topical anaesthetic on pain and discomfort during SRP of periodontitis patients. Due to a small study population, the analysis is extremely underpowered and therefore no final conclusions can be drawn. Nevertheless data does show a few trends.

Injections showed a significant reduction of pain and discomfort during SRP measured by VAS compared to the lozenge. Treatment with the lozenge reduced patient discomfort after SRP measured by VAS. Treatment with the lozenge resulted in a large range of VAS scores for pain and discomfort. For treatment with the lozenge, sub-analyses showed a tendency of higher VAS scores, when the duration of SRP was long and when many deep periodontal pockets were present.

According to the results of MPQ, patients did not describe the pain during SRP differently when treated with lozenge and injections. The pain was predominantly characterised by the sensory dimension of pain while the affective subclass was not used. This indicates a quality of pain characterised by pressure rather than discomfort and unpleasantness. This is inconsistent with the VAS discomfort scores, which showed a mean of 46 mm and 15 mm during SRP using lozenge and injections, respectively.

The inconsistency between VAS and MPQ results may be explained by several factors. The subjective nature of pain makes objective assessment difficult and even intraindividual pain assessment may vary greatly [19]. Moreover MPQ can be an unreliable measure of pain, if the patient has not fully understood the instructions or does not understand the meaning of the words. The small number of patients included in the analysis may also explain the discrepancy.

Patient comments indicated a very effective anaesthesia by injections. Some patients reported a good anaesthetic effect of the lozenge while some patients reported an

inadequate duration of anaesthesia with the lozenge. Several patients reported an unpleasant and inconvenient post-operative numbness caused by injections.

The more pronounced anaesthetic effect of injections is not surprising. Injections deposit anaesthetic solution close to nerve endings providing a very targeted and localised effect. Bupivacaine from the lozenge must permeate the oral mucous membrane before reaching nerve supply and exerting its effect. The anaesthetic concentration at the site of action will therefore most likely be higher using injections, provided that bioequivalent doses are administered. With a relative potency of 1:4 (lidocaine: bupivacaine) the mean amount of lidocaine injected in this study (104 mg) corresponds well with 25 mg bupivacaine.

The higher VAS discomfort scores for injections after SRP may be explained by post-operative numbness, which is often caused by injections [7]. This is also supported by patient comments. The duration of anaesthesia using the lozenge is much shorter, minimising this problem [42]. In this study, the duration of anaesthesia using the lozenge was occasionally too short. The positive correlation between duration of SRP and VAS scores may imply that the duration of anaesthesia by the lozenge is insufficient for longer SRP procedures.

The large variation in VAS scores during treatment with the lozenge may be explained by other factors than duration of SRP and number of deep periodontal pockets. In addition to the subjectivity of pain, the variation may be explained by a differing effect of the lozenge between subjects. Drug delivery from a lozenge is subject to many factors such as saliva volume and flow as well as the character of the mucosa [55]. Studies have shown large regional differences in the oral cavity in clearance and retention of substances dissolved in saliva. Greatest concentrations of substances dissolved in the saliva are usually achieved in the upper labial vestibule, while the sublingual concentration is usually lowest [56]. In periodontitis patients, presence of inflammatory exudate may limit flow of saliva into to the gingival sulcus. Moreover, acidic conditions in the oral cavity due to inflammation may reduce absorption of the local anaesthetic [9, 20].

Although the anaesthetic effect of the lozenge may be spread to other areas than the gingiva, this can have psychological benefits to the patient. The sensation of being anaesthetised may contribute to the actual anaesthetic effect, giving psychological comfort to the patient. A psychological effect was demonstrated in a study by Martin et al., who showed that subjects who were informed that they were to receive a topical anaesthetic prior to dental injections anticipated less pain than those not provided such information

[57]. In addition, several studies have shown a significant placebo effect of topical anaesthetics e.g. in association with needle penetration of gingival mucosa [7].

It was not possible to determine which treatment the patients preferred, due to the small study population. Although the anaesthetic effect of the lozenge appeared inferior to that of injections, topical administration in dentistry presents a number of advantages. Patients' fear of dental injections is widespread, and many patients even avoid treatment because of anxiety towards injections [58, 59]. The non-invasive character of a lozenge makes it a more comfortable and less intimidating alternative for patients [15]. A study by Matthews et al. showed that many adult patients would prefer a less effective anaesthesia if dental injections could be avoided [60]. In a clinical trial by Van Steenberghe et al., a majority of patients preferred the non-injectable anaesthetic gel Oraqix® to injections, despite a superior anaesthetic effect of injections [50].

A survey of US and European patients who had recently undergone SRP evaluated patient concerns regarding injections. The survey showed that while not completely eliminating dental anxiety, the availability of a new non-injectable anaesthetic would assist in relieving patient fear. Almost half of the patients surveyed reported that they would be more likely to seek treatment if the new non-injectable anaesthetic was used [59].

A significant disadvantage of dental injections is that they require administration from dental staff. A lozenge does not require special equipment or expertise. It is self-administrative and thus more cost-effective, allowing dental staff to focus on the procedure rather than administration of anaesthetics [15]. Regional block anaesthesia is also associated with a risk of nerve damage [5]. Therefore topical application of local anaesthetics provides not only a more patient acceptable alternative, but also a safer one.

5.1 STUDY LIMITATIONS

The design of the current study has a number of limitations. The study was not blinded and thus the results are subject to any bias present by patients and investigators. The design could be optimised to be double-blinded, so that neither the investigators nor the patients were aware of the treatment received.

For patients to be blinded, a double-dummy design would be required, as the sensation of the needle insertion otherwise would reveal the treatment. Alternatively a single-blinded study design could have been employed, where only the investigator was blinded to the

treatment. This would require someone to administer the anaesthetic prior to treatment by the investigator.

Another limitation to the study is the varying severity of periodontitis within the patient population. The crossover design allows for within subject comparison, however, many subjects had a different number of deep periodontal pockets in the left and right side of the dentition. The basis for within subject comparison was therefore not ideal. The random order of treatment may compensate partly for this difference.

To improve this aspect, the trial could have been designed to only include patients with similar disease severity in the left and right side of the oral cavity. Alternatively SRPs could have been performed for the entire oral cavity.

The participating patients' usual anaesthetic treatment was not noted. This may have affected patient assessments, as patients would have different anticipation to the treatment. The high number of investigators involved in the study may also have affected the results. The treatment time and equipment used during SRP differed between investigators and the technique used for SRP and injections also varied. The subjective dentist assessments might also have been more consistent if only one investigator was involved.

6. CONCLUSION

The results show a trend towards a superior anaesthetic effect of the lidocaine-adrenaline injections in reducing pain and discomfort during SRP of periodontitis patients. The bupivacaine lozenge may reduce post-procedure discomfort. Qualitative pain description by MPQ was similar between the two treatments. It was not possible to make final conclusions on patients' treatment preference. The small study population makes the analysis of this thesis underpowered. A larger study population is required for significant results.

7. FUTURE PERSPECTIVES

Although the analysis indicated an inferior anaesthetic effect of the bupivacaine lozenge to that of injections, the potential of the lozenge for pain management during SRP should be further investigated. Future studies could include patients with less anaesthetic needs than injections. A placebo-controlled trial or a study comparing the effect of the lozenge to that of Oraqix® could be a future prospect.

The patient, who discontinued from the current study during treatment with the lozenge, was subsequently treated with Oraqix®. The investigator reported a surprisingly good anaesthetic effect of the combination; superior to that of Oraqix® alone. A possible future study could therefore investigate a combination treatment with Oraqix® and the lozenge.

In order to investigate the anaesthetic potential of the lozenge in dentistry, other clinical trials could be designed. Sensory and pain threshold in different sites of the oral cavity could be examined using an algometer or pinprick tests. Pulpal anaesthesia induced by the lozenge could be examined using an electric pulp tester, and measurements of pain upon probing could also be relevant.

A number of other dental procedures could potentially benefit from the lozenge. For example prior to injections, where needle insertion as well as injection of solution may be painful. Also in association with teeth mouldings and x-ray procedures, which may provoke gag-reflexes and induce discomfort. The lozenge could also be used for anxious patients prior to treatment to provoke a sense of psychological comfort.

Especially in paediatrics fear of dental treatment is a challenging issue, and improved compliance could be achieved with a less intimidating method of local anaesthesia [7]. A flavour variant of the bupivacaine lozenge targeting children could therefore be a prospect for future development.

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