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Evaluation of the effect of submucosal dexamethasone injection on pain in patients undergoing third molar removal: A randomised controlled trial

Thesis presented by

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List of abbreviations

Abbreviation	Meaning
CREC	Clinical Research Ethics Committee of the Cork Teaching Hospitals
FMPF	Full-thickness mucoperiosteal flap
GPE	Global perceived effect
HADS	Hospital anxiety and depression scale
MID	Minimal importance difference
NICE	National Institute for Health and Care Excellence
NRS	Numeric rating scale
NSAIDS	Non-steroidal anti-inflammatory drugs
OHIP-14	Oral health impact profile-14 questionnaire
PCS	Pain catastrophising Scale
PPI	Present pain intensity scale
PROMs	Patient reported outcome measures
SFMcGill	Short form McGill pain questionnaire
SIGN	Scottish Intercollegiate Guideline Network
VAS	Visual analogue scale
VDS	Verbal descriptor scale

Abstract

Objectives

Third molar removal is one of the most common oral surgery procedures performed in Ireland. Pain, swelling and trismus are well-documented, undesirable consequences following third molar removal. These sequelae have a negative impact on the patients' quality of life post-operatively. We aimed to compare the effect of a submucosal injection containing 4mg dexamethasone on the post-operative pain experienced by the patient versus a control of standard surgical removal of a mandibular third molar on the contralateral side. We also analysed patient preference of treatment regime.

Methods

A randomised controlled trial was conducted involving 70 patients undergoing surgical removal of bilateral, symetrically-impacted mandibular third molars under general anaesthetic in Cork University Hospital. Each patient acted as their own control in this split-mouth study, with all treatment carried out at one single visit. All subjects received standard local anaesthetic bilaterally in the form of inferior alveolar block and long buccal infiltration with 2% lidocaine with 1:80,000 epinephrine. The site randomised for intervention received a 1ml submucosal injection of 4mg dexamethasone in the buccal vestibule adjacent to the lower third molar following administration of local anaesthetic. Both the patient and investigator were blinded to the intervention site. The primary outcome measure of pain was self-reported and

recorded by the patient for the right and left surgical site for seven days following intervention using a visual analogue scale.

Results

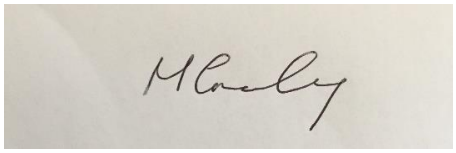
Pain and inflammation are normal physiological responses to tissue trauma such as surgery. The age range of the participants in the trial was 16 to 54 years of age, with the mean age being 22 years (SD 5.7 years) and median age 21 years. The study participants were comprised of 44 females and 26 males. We demonstrated that the reported pain scale (VAS 0-100mm) decreases moderately with the treatment intervention of 4mg dexamethasone as a submucosal injection (Estimate: -3.32, CI: -5.36 to -1.28, $p < 0.01$).

Conclusion

This trial demonstrated a minor but consistent improvement in analgesic effect when submucosal dexamethasone was administered in comparison to control supporting the alternative hypothesis. The effect size detected was minimal (estimated 3% improvement) and as such deemed not clinically meaningful for patients. Therefore, the routine use of submucosal dexamethasone injection in the extraction of impacted third molars should not be recommended.

Declaration of Original Work

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. Input from other researchers is acknowledged within the text. I have read and understood the regulations of University College Cork concerning plagiarism



Dr Miriam Crowley

Acknowledgments

I would like to take this opportunity to thank the patients who participated in this trial, providing their time and effort to complete the study. I would also like to acknowledge the guidance and support provided by my supervisor and mentors at Cork University Dental School and Hospital, namely Dr. Catherine Gallagher, Professor Duncan Sleeman, Dr. Richeal Ni Riordain, Dr. Caroline McCarthy and Dr. Paul Brady, four of whom are the skilled surgeons who performed the surgeries involved in the trial. Your advice and guidance is greatly appreciated.

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I must also express gratitude to my family for their continued support. It is a running joke for my family that I am UCC's longest serving student, involving constant questions as to which course I will sign up for next. Unfortunately, as the realisation that my days of representing UCC on a playing field are well and truly behind me a life of academia does not sound so bad!

To my husband Owen, thank you for your ever-present support, patience and proofreading skills. You made completing a PhD look easy so the undertaking of this Clinical Doctorate is partially your fault.

Chapter 1: Introduction

Third molar removal is the most commonly performed oral surgical procedure, costing society tens of millions in the United Kingdom and the United States of America each year (1-4). There are many factors to consider before a decision to remove a mandibular third molar can be reached, involving a through medical, dental and social history combined with clinical and radiographic assessment. Removal of symptomatic or diseased third molars has been shown to improve oral health and function of patients (5, 6). Each patient requires a holistic, tailored approach. Due to anatomical variations of the third molar tooth in relation to associated vital structures, such as the inferior alveolar nerve, the patient should be involved in the treatment decision-making process. The World Health Organisation (WHO) characterises the presence of an impacted third molar as a developmental condition within their International Classification of Disease (7). However, impaction is a descriptive term and is not an indication for surgery when being considered alone. Management strategies for mandibular third molars can range from clinical monitoring, partial removal in the form of coronectomy or removal.

Following third molar removal, as with other surgical procedures, post-operative pain is a common undesirable outcome (8-10). It is estimated that 40% of patients undergoing day-case surgical procedures experience moderate to severe post-operative pain (11). Despite the focus of research investigations on post-operative pain, it remains poorly managed and a challenge for clinicians (12, 13). Post-operative pain negatively impacts on the patient's quality of life in the days

following intervention (14). This negative impact on an individual's quality of life can have a wider socio-economic impact through days absent from the work place to allow recovery (15).

There are continual efforts in the literature to explore intra-operative and post-operative methods of reducing pain following the removal of mandibular third molars (16-18). Intra-operative techniques aimed at minimising post-operative pain included comparing various local-anaesthetic regimens (19, 20). With the consistently high numbers of people requiring third molar removal each year, it is our aim to undertake a robust clinical trial that can provide reliable evidence to guide clinicians in the challenge of minimising the post-surgical pain experienced by the patients. In order to achieve a sound study design, our methodology introduced some subtle but significant changes when compared to existing trials reported in the literature. In clinical trials that investigated the effect of peri-operative dexamethasone, various routes of administration were employed ranging from oral tablet formulation, intra-muscular, intra-alveolar to intra-venous administration (21-23). Our clinical trial investigates the effects of the submucosal administration of 4mg dexamethasone on pain reported at the surgical site. A submucosal route has the benefit of providing local effects but avoiding systemic administration. Furthermore, submucosal administration local to the surgical is an accessible site for dentists or oral surgeons to access with minimal further training or equipment required.

The majority of clinical trials in this field use a visual analogue scale to measure patient reported pain. As pain reported is a subjective measurement we

strived to minimise any confounding factors. We set out to achieve this by incorporating questionnaires such as the Pain Catastrophising Scale (PCS) to give further insight into each patient's relationship with pain. A key aspect to our study design that differs to those previously reported in the literature is the split-mouth technique. This study design itself is not novel, however previous clinical trials that engaged this design when investigating pain following third molar surgery did so over two appointments with a period of weeks between procedures (24). The intervention being carried out at two separate visits could lead to the introduction of cross-over or observational bias. In our clinical trial patients experience both the intervention and control while under general anaesthetic allowing for real-time comparison of the surgical sites. The split-mouth design also eliminated the potential for cross-over bias. Our inclusion criteria allowed for symmetrically impacted third molars further minimising any differences in intervention technique or difficulty at the control or intervention site.

This clinical trial and its primary results have been presented in an oral format at the Irish Division Virtual Scientific Meeting 2021 of the International Association of Dental Research (25).

Chapter 2: Literature review

2.1 Overview and search strategy

The existing literature was reviewed focusing on three main elements; firstly, the development and eruption of the third molars, secondly, the removal of the third molars and the associated post-operative experience for the patient and finally how we can measure the impact of third molar removal on the patient.

An electronic search was conducted of the Cochrane Library, PubMed and MedLine EBSCO databases between the dates of January 1st 2000 and December 31st 2019. The PICOS framework was followed whilst undertaking the search (Table 1). The reference lists of included studies were also searched for any further trials of relevance. Inclusion and exclusion criteria were applied to the identified articles and any duplicates were disregarded. Eligibility criteria included meta-analysis, systematic reviews, randomised controlled trials, controlled trials, participants aged over 16 years undergoing removal of at least one mandibular third molar. Studies involving the administration of submucosal dexamethasone in varying doses, pre or post-operatively were included.

Table 1.1 Search strategy

Population	#1; Third molars OR wisdom teeth, impacted third molar OR impacted wisdom tooth	24,238
Intervention	#2; Dexamethasone AND (submucosal OR submucosal injection)	16,075
Comparison	#3; Control OR placebo effect	20
Outcome	#4; Post-operative pain AND/OR quality of life AND/OR oedema AND/OR trismus	311680
Study design	Randomised controlled trail AND controlled trial	
Search Combination	#1 AND #2 AND #3 AND #4	166
Database search	Cochrane Library, PubMed, Medline EBSCO	166
Limitations applied; Inclusion and exclusion criteria	Meta-analysis, RCT, systematic-review, clinical trial	5

2.2 Background

Pain, swelling and trismus are undesirable consequences of third molar removal. A multitude of different interventions aimed at reducing post-operative pain following surgical removal of lower wisdom teeth have been researched and reported. Such researched interventions range from pre-operative administration of local anaesthetic (19), intra-operative interventions including novel surgical techniques or alternative local anaesthetic regimes (20, 26) and post-operative interventions such as the use of cryotherapy (27). The administration of corticosteroids as a modulator of inflammation has been examined in various studies (24, 28, 29), however there is no consensus on the optimal route of administration.

There is low-quality evidence that dexamethasone administered as a submucosal injection peri-operatively has been found to reduce early stage post-operative pain for patients (30, 31). High quality evidence is required to provide both statistical and clinical significance to results allowing any potential change in practice. A review of the literature was undertaken to better understand the post-operative experience of the patient undergoing surgical removal of third molars along with the methods used to quantify the impact surgery had on the patient. Surgical removal of third molars is the most commonly undertaken oral surgical procedure, with lower third molars the most commonly impacted tooth (32). In order to better understand the potential reasons behind impaction it is important to explore the development and eruption pathway of these teeth. Accordingly, this literature review will be presented in three sections – third molar development and eruption, extraction and

post-operative experience and how we measure the impact of third molar surgery on patients.

2.3 Third Molars

2.3.1 Development and eruption

Tooth development and timing of eruption can vary significantly with race and ethnicity (33). Third molars erupt between the age of 17 and 24 years, with initial development commencing as early as 5 years in certain populations (34). The stages of third molar development have been described by Demirijian *et al*. (35). The developmental process of teeth can be a valuable biomarker for age. Demirijian described development in eight identifiable stages, ranging from the beginning of calcification in the crypt to the final stage of development, closure of root apices (35, 36).The concept of physiological age is founded on the degree of maturation or development of a specific tissue system. Demirijian's technique is widely used at estimating age in populations based on the dental tissue. Timing of development of third molars is population specific, occurring at a different age in varying ethnic groups (33, 37-39). Crown formation can complete between the age range of 13 - 15.5 years depending on race (34, 40-42). The timing of eruption can be influenced by local factors such as early loss of deciduous tooth however such factors do not influence tooth development and formation (43). As with varying degree of tooth development at certain age points, the timing of eruption can also vary significantly with race and ethnicity (33).

2.3.2 Problems with eruption

Eruption is a descriptive term to describe the relationship of the crown of the tooth in the oral cavity. Teeth can be unerupted, partially erupted, fully erupted or absent.

The congenital absence of one or more teeth is known as tooth agenesis. Many causes for agenesis are suggested in the literature, some contradictory. An individual's race or genetics, developmental or growth delays along with the morphology or size of the jaw are all potential reasons cited as the cause of third molar agenesis (44-46). The prevalence of agenesis of one or more third molar varies between populations. A systematic review and meta-analysis carried out in 2015 found a global rate of 22.63% relating to third molar agenesis (47). This systematic review found a higher prevalence of one third molar absence over multiples of absent teeth. Most commonly the maxillary third molars were found to be absent and with a higher prevalence in females (47).

Teeth are said to be impacted if they are prevented from erupting, either partially or fully into the mouth. This impaction can be caused by soft or hard tissue, including bone or an adjacent tooth. Third molars are the most commonly impacted tooth in the arch (48). These impactions can be a result of a lack of space in the arch or development of the tooth in an abnormal position (49).

2.3.3 Classification of impaction

Assessment of the position of the third molar in relation to the surrounding anatomical structures is an important step in planning surgical removal and an attempt to predict surgical difficulty. Thorough clinical examination and assessment of third molars prior to removal is essential. Sufficient assessment of the crown and root of the tooth are crucial to minimise unforeseen difficulties encountered during the surgery. Mandibular third molars are the most commonly impacted tooth in the

human dentition (48). In 2015 a study was published showing 73% of third molars are impacted in a European cohort (50). Dachi and Howell looked at the prevalence of impacted molars in a cohort of 3874 participants and found the incidence of impaction of mandibular third molars to be 17.5% (51). There are various theories related to the cause of third molar impaction including the orthodontic theory, Polygenic inheritance theory, Mendelian theory, pathological and endocrinal theory (52). A classification system for the position of third molars was first proposed by Winter in 1926 (53). Four criteria were assessed: position of the crown, character of root formation, nature of the bone surrounding the tooth and position of the third molar in relation to the second (53). A second classification system of third molar impaction was presented by Pell and Gregory in 1933 focusing on the distance from the crown of the third molar to the ramus, the relative depth of the third molar within the ramus or relative to the occlusal plane along with the position of the third molar relative to the long axis of the adjacent second molar (54). These systems aim to grade impactions according to the relative difficulty involved in surgical removal (54). Unfortunately, studies have shown these assessment tools to be insensitive in predicting surgical difficulty, however they are widely accepted as a descriptive classification term (55, 56).

Looking to combine and apply the existing impaction classification systems further, Pederson created an index to assess and pre-empt the difficulty for the removal of a third molar focusing on three different factors; angulation of impaction, depth of the tooth relative to the occlusal surface and the relationship of the tooth to the ramus (57). These factors were scored with the sum total corresponding to a

difficulty index ranging from slightly difficult to moderately or very difficult. Each category had weighted options. A score of greater than five was classified as moderately difficult (57). This index has not been validated or widely accepted. Independent patient factors such as age, race, sex and bone density are thought to play more of a role in difficulty of extraction (58). Studies have shown the most relevant of these patient variables to be age, body mass index, root curvature and depth from point of elevation (59). Other studies which show that patient age affects surgical difficulty, have reported that these older patients undergoing 'difficult' third molar removal do not report an increase in the pain experienced by the patient in the post-operative period (9, 60).

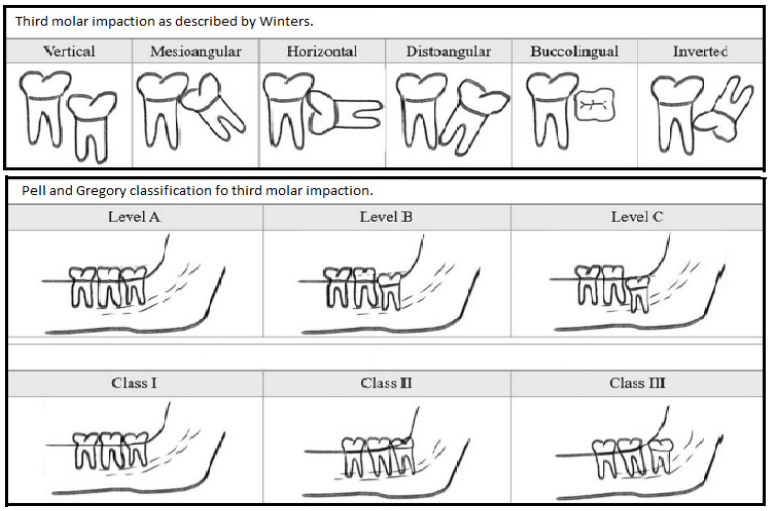


Figure 2.1 Classification of third molar impaction as described by Winter and Pell and Gregory

2.3 Extraction and Post-Operative Experience

2.3.1 Indications for extraction

There is continual debate over management and justification for removal of third molar teeth. Guidelines for the management of third molars were first produced in 1997 by Royal College of Surgeons in England and continue to be revised regularly by various expert groups. The National Institute for Health and Care Excellence (NICE) published guidance in 2000 advocating against the prophylactic removal of mandibular third molars. The NICE guidance was supported by the Scottish Intercollegiate Guideline Network (SIGN) in the United Kingdom. Current advice from these bodies states the removal of pathology free third molars has no health benefit to patients and should be discontinued (49, 61-63). This is contrary to previous published studies advocating for the prophylactic removal of third molars (64, 65), however the methodology of these studies was open to bias. There is now a growing body of evidence suggesting retaining pathology free third molars is simply delaying inevitable surgery and the cause of future pathology associated to the site (66, 67). NICE are currently updating their guidance following a review of the evidence in 2015. These changing recommendations have had an effect on the patient demographic undergoing intervention for third molars along with improved recordkeeping by the dentist reporting the reason for removal. Patient records are showing that there has been a reduction in prophylactic removal of third molars and an increase in pathology such as caries or recurrent pericoronitis being reported as justification for removal of third molars. This change in guidance has also resulted in a change of the age profile of patients undergoing third molar removal in the UK.

There has been a shift from patients undergoing third molar surgery in their early twenties in 1989, where justification for removal was mainly reported as prophylactic, to the mid-30 age group of patients undergoing removal in 2008, consisting of older adults who have developed pathologies associated with third molars, now requiring removal (1). Compliance with the current guidance in the United Kingdom was stated to be high due to the low cost of implementation (68). Even with the change in guidance, removal of third molars continues to account for a significant proportion of oral surgery procedures. The Royal College of Surgeons England, Faculty of Dental Surgery published an updated guidance and consensus document in April 2021, citing the need for review of the existing guidance due to growing evidence suggesting retention of lower third molars is leading to patient harm (69). They advocate a number of management options for mandibular third molars based on clinical evidence, namely clinical review or intervention when indicated.

In the United States of America the latest guidance is evidence-based, however the guidance is supportive of the surgeons' role in providing patient-centred treatment and assisting the patient in making a decision that is in their best interest (70). This patient-centred approach gives weight to the patients' thoughts and attitudes toward intervention.

2.3.2 Removal technique

Surgical removal of an impacted third molar is the most commonly performed oral surgery procedure. A variety of techniques can be utilised for the removal of the impacted tooth including chisel and mallet, rotary instruments or ultrasonic instruments. The earliest documented technique is the lingual split. This technique described by Ward involves removing overlying distal bone with a chisel and mallet, then fracturing the lingual plate allowing sufficient space to elevate out the impacted tooth (71). When compared to more recent techniques such as rotary bur or piezoelectric surgery, the lingual split technique causes less pain and swelling for the patient, however a higher incidence of nerve injury is observed (72).

Piezosurgey was introduced to oral surgery in 1988 and since then the technology has continued to adapt and grow in its uses. The instrument produces micro vibrations at a frequency high enough to allow a precise cut (73). An advantage of the piezo is its selective cutting, thereby protecting soft tissue, vessels and nerves. The disadvantage continues to be the increase in operative time along with the need to revert back to the rotary bur if tooth sectioning is required (73, 74). Today the most commonly-used technique is buccal bone removal by means of rotary bur and external irrigation. This technique can have a shorter operating time when compared to piezosurgery (73). However, disadvantages include increased post-operative trismus and pain experienced by the patient. No difference is noted in post-operative complications in high versus low speed rotary hand piece for buccal bone removal in the removal of impacted third molars (75).

Procedure duration has been shown to directly impact on post-operative pain experienced (76). Some studies show that despite the longer surgical time taken for piezosurgery this does not show a significant increase in post-operative pain; however this is low-quality evidence open to significant bias (77). Healing post-operatively was shown to be most delayed following rotary bur technique, followed by ultrasonic, then chisel and mallet (78). This slow healing is attributed to the heat that may be generated from the instrument causing necrosis of the bone (78). Studies have reported the greater the experience levels of the operator in any technique, the greater the reduction in post-operative pain reported by the patient (79, 80).

2.3.3 Normal post-operative experience

Many studies and articles document the morbidity associated with removal of impacted third molars and have assessed the impact on quality of life for the patient in the days and weeks following surgery. From a patient perspective, pain can be the main concern following the removal of third molars. Data looking at post-operative pain can be subjective, as pain experienced by an individual cannot be objectively quantified. Conrad *et al.* surveyed a cohort of 249 patients for 14 days following the removal of third molars to investigate the patients' perception of healing following the surgery (60). The cohort was predominantly female and below 25 years of age meaning the data would need to be interpreted with some caution as it is not a true representative population of all patients undergoing third molar removal. The study found that only 30% of patients experienced severe pain on day 1 post-removal. The group reported by post-operative day 4 the pain reported was not affecting the patients activity levels, however functions such as chewing and mouth-opening were

affected ‘quite a bit’ (60). Other studies found the effect on functional ability such as eating, speaking and swallowing were the greatest factors influencing a delayed return to work for the participant as opposed to pain (81, 82). The subjective nature of pain can be seen when studies find women are less likely than men to return to work sooner (81). Lopes carried out a prospective study of 522 patients undergoing third molar removal over a 12-month period finding 49.2% still complaining of pain 7-10 days’ post-surgery. Other complaints experienced by lower numbers at this time scale included swelling, trismus and paraesthesia. Interestingly they found 81% of patients took time off work following surgery, with an average of three days’ sick leave. Conversely 19% of patients they looked at took no time off work (83). The removal of third molars is consistently the most commonly performed oral surgical procedure and with over 150,000 people in England undergoing removal each year, the post-operative effects on the patient can have a knock-on effect in society (84). Studies carried out in Scandinavia and America investigated the duration of disability or loss of productivity for the patients (15, 85, 86). Bienstock and his team prospectively observed a cohort of more than 4000 participants, who had 8748 third molars removed (15, 85). They included both erupted and non-erupted third molars, along with maxillary and mandibular third molars so the figures calculated for days absent from work and loss of ability could be conservative at best. Of the third molars included in the study, 92% had some pathology associated with the tooth. Regardless of these limitations, this group found workers were absent from work for a mean of 1.3 +/- 1.3 days from work following third molar removal. The range of days absent was 0-11 days for the 4004 study participants. The range of days’ patients experienced disability to undertake normal activities was 0-26 days. A Swedish study

investigating the economic impact of mandibular third molar removal found patients had a mean of 1.57 days' absence from work, with a range of 0-22 days. In this study nature of impaction or state of eruption of the third molar were not recorded(86). This group calculated the total costs of removing a third molar, inclusive of direct and indirect costs such as absence from work, at between €500-1000, which is a significant impact on society given the number of patients undergoing removal on an annual basis.

Studies on gender and perception of pain do show women experience pain at a higher intensity than men (87, 88). This finding, that women experience a greater intensity of pain, is reflected again in a randomised controlled trial involving 92 patients finding women perceived a bigger impact on quality of life in the days and weeks following surgery (89).

2.3.4 Pain following dental surgery

The surgical site, when removing lower third molars, is a highly vascularised area comprised of loose connective tissues. As a result of surgical intervention a series of alterations are expected, causing significant morbidity for the patient such as swelling, trismus and pain (79, 90). Pain is defined by The International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' (91). Pain can be a major post-operative outcome of any surgical procedure including extraction of wisdom teeth. Pain mediators are released from tissues following trauma as an inflammatory process is activated. Mediators such as prostaglandin and bradykinin cause firing of peripheral

nociceptors. Repetitive firing of these receptors can lead to central sensitisation and increased responsiveness of neurons responsible for prolonged pain after surgery (92, 93). Patients become increasingly more sensitive to pain the longer they are exposed to the stimulus and the firing nociceptor (94). Consistently, surveys have shown that post-operative pain is not adequately treated (95, 96). Inhibiting or blocking some of these pain and inflammatory mediators are the basis for analgesics. Nonsteroidal anti-inflammatory drugs block the synthesis of prostaglandin and bradykinin producing their analgesic effect (97, 98). This is done by inactivating cyclooxygenase. For oral surgery procedures, onset of pain is generally 4-6 hours following the procedure when the local anaesthetic has worn off (99). The teaching promoting pre-emptive analgesia is commonplace in dental surgery. This theory has been around since the early 1900's with Crile introducing pre-emptive and prevention analgesia in 1913. This involves administering analgesic before the injury or surgical procedure to allow it to be operational in minimising the physiological consequences invoked by the surgery. Pre-emptive analgesics potentially inhibit central sensitisation of central nociceptors and peripheral sensitisation by impeding the formation and release of pain mediators in injured tissues at the surgical site (93). Further evidence to support pre-emptive nonsteroidal anti-inflammatories was provided by Swift and Hargreaves, whose study found significantly reduced post-operative pain reported by patients having received pre-op analgesics (100).

Many analgesics tested for pain management are tested using a dental model as surgical removal of third molars is a common procedure. This results in a wealth of information available on the efficacy of analgesics for dental pain. Combination therapy is recommended for acute post-operative pain following third molar surgery.

The benefit of a multi-modal approach can be appreciated by understanding the pathogenesis of pain and accepting the different pain and inflammatory mediators that are being blocked. Paracetamol and non-steroidal anti-inflammatory (NSAIDS) drugs can provide moderate pain relief, with opioids (101) providing breakthrough pain relief for severe pain. Paracetamol is an anti-pyretic drug with minimal side-effects (102). Paracetamol is commonly used as part of a multi-modal treatment of pain. Paracetamol does not have anti-inflammatory effects so is rarely used alone following surgery but in combination with another drug (103). There are some studies which suggest that this multi-modal approach is unnecessary with similar pain reported using ibuprofen alone versus paracetamol alone in a three day post-operative follow up; however these studies go against the larger body of work reporting otherwise (104).

2.3.5 Influence of corticosteroids on post-operative pain

As previously mentioned due to the vascular nature of the tissues surrounding lower third molars, patients can experience significant swelling and pain post-operatively. Localized inflammation at a surgical site due to tissue damage is a normal physiological response. Corticosteroids have been used for many years to reduce post-operative inflammation; however, their mechanism of action is not completely clear. Dexamethasone is a corticosteroid with mainly glucocorticoid effects, first synthesised in 1957 (105). There is greater affinity for dexamethasone than endogenous cortisol at the glucocorticoid receptors (106). Dexamethasone binds to the receptor, releasing an activated complex. This steroid-protein complex initiates changes in DNA of target genes. These target genes in turn lead to the synthesis of

new proteins, which initiate a further biological response. The main result of this reaction is the blocking of multiple inflammatory genes, supressing prostaglandin and bradykinin formation (107, 108). Bradykinin is an inflammatory mediator produced at the site of tissue trauma causing pain (109). Furthermore, dexamethasone prevents the build-up of leukocytes and macrophages at the surgical site, this is a result of the glucocorticoid causing apoptosis in inflammatory cells reducing the cellular immune response (108). Inflammation is a normal physiological response to tissue trauma and a certain inflammatory response is required for healing. The cardinal signs of inflammation include calor (heat), dolor (pain), rubor (redness) and tumor (swelling) (110). Excessive levels of swelling and inflammation lead to pain and reduced quality of life for the patient (111). It is our hope that in reducing the levels of inflammation experienced by the patient following a submucosal injection of dexamethasone, we will minimise the pain experienced local to the surgical site.

2.3.6 Dexamethasone and third molar removal

Studies have looked at the effect of dexamethasone as a pharmacological method of reducing the pain, swelling and trismus following third molar removal (24, 28, 29). Corticosteroids administered in a variety of routes have been shown to reduce post-operative swelling, however these studies lack comparability or homogeneity (112). Several different protocols of dexamethasone, including differing route of administration and dosage have been described but no consensus or guidance has been standardised. There are confounding factors affecting accurate comparison between studies, such as the formulation of medication, variety of routes used to

administer steroids, the dosage of steroid, the presence of infection at the time of extraction (24, 112). The optimum steroid used should reduce local inflammatory reactions but have little effect systemically. Dexamethasone has good glucocorticoid effect and causes minimal sodium retention, properties which support its use in dentoalveolar surgery. As such, dexamethasone fits the criteria for having negligible mineralocorticoid activity yet a great biologic effect. Dexamethasone also has a long half-life of 36-54 hours which is much greater when compared to other corticosteroids such as hydrocortisone (111). Submucosal administration has advantages when compared to other routes of delivery including low dosage of drug required for effect, drug administration close to the surgical site and low systemic absorption of the drug resulting in fewer side effects (111). The short term exposure and low systemic absorption of the drug results in minimal systemic uptake and adverse effects (24).

2.4 Measuring the Impact of Third Molar Extraction on Patients

2.4.1 Patient reported outcome measures

Patient reported outcome measures (PROMs) are often used in clinical practice to gain feedback on patients' perceptions and views of their health and their healthcare experience. These self-reported questionnaires can help quantify and give weighting to the subjective feelings and views of the patient regarding various outcomes such as pain or quality of life (113, 114). PROMS have been shown to facilitate increased communication between patient and clinician which in turn can lead to shared decision-making for treatment (115, 116). Surveys of clinicians have shown a majority of professionals who use PROMs utilise them as a means to track patient progress (117). There are many tools for assessing patient based outcome measures in clinical trials varying from site-specific, to disease-specific to generic. Fitzpatrick *et al*. set out criteria of eight items to be used by researchers when evaluating and selecting the patient-based outcome measures to be used in their clinical trial (118). These criteria were compiled following a comprehensive review of the literature surrounding PROMs; however, it must be recognised that this is a qualitative summary of the findings and expert opinion. Therefore, the criteria set out by this team may be flawed and should be interpreted with care. The eight criteria include, appropriateness, reliability, validity, responsiveness, precision, interpretability, feasibility and acceptability. The use of patient-centred outcome scales is now seen as invaluable. This is compounded by the finding that surgeon-reported success measures of a procedure can significantly vary from patient-reported outcomes and experience (82).

2.4.2 Pain

The visual analogue scale (VAS) is a one-dimensional scale to measure the pain intensity experienced at a given time. It does not give descriptors of the type of pain being experienced by the patient. A visual analogue scale is a line anchored with terms such as 'no pain' and 'worst pain possible', where the patient is requested to mark on the line indicating where their pain equates. The VAS can be depicted as a vertical or horizontal line, with greater reliability observed with the horizontal style (119). VAS is validated as a measure of pain for patients suffering from chronic pain (120, 121). There has been some criticism of VAS following procedures under general anaesthetic.

Other tools used to report pain experienced include a Numeric Rating Scale (NRS) or a Verbal Descriptor scale (122). The NRS was developed in 1984 and gives a unidimensional report of the pain. Pain is reported using a numeric value 0-10, descriptors of boundaries are often 'no pain' to 'worst possible pain'. The NRS has been shown to be useful in patients in both young and old age groups, those patients with poor English or for use in phone surveys where the investigator can record the number reported by the patient (123).

Questionnaires such as the short form McGill Pain Questionnaire can provide more information related to the pain, providing sensory descriptors relating to the pain in combination with a pain intensity score (124). This questionnaire gives a second dimension to the pain measures by engaging three tools to provide information about the type of pain experienced rather than simply the present pain

intensity. This questionnaire utilises descriptive words, a VAS and a Verbal Descriptor Scale (VDS) to gather as much information as possible about the pain being experienced by the patient. This questionnaire has repeatedly been shown to be valid (124, 125). There are eleven descriptive terms and three affective terms each scored by the patient. The SF McGill quantifies the overall present pain intensity experienced by the patient, using both a 100mm visual analogue scale and a six point Likert scale with end points 'None' to 'Excruciating'. Verbal Descriptor Scales (VDS) were first introduced in 1968 by Keel. Used alone they have limited value as the words used are restrictive; however, they have been adapted and included in questionnaires such as the SFMcGill pain questionnaire (123). When used in combination with other scales they can give further insight into the pain experienced.

2.4.3 Oral health related quality of life

Quality of life is a multidimensional concept. It can be defined as a measurement of the impact a disease or treatment has on a patient's daily life, wellbeing and functioning. The main tools used for the assessment of quality of life are self-reported questionnaires. Oral health-related quality of life questionnaires aim to look at the impact an oral condition has on the patients daily activities and social interaction (126). Patient-reported outcomes are an increasingly important measure in success of treatment in a patient-centred approach to treatment. Although quality of life is a subjective it should be a key focus of patient-centred treatment. The Oral Health Impact Profile (OHIP) was developed in 1994 by Slade (127). This 49-point questionnaire aimed to provide a self-reported measure of oral discomfort, dysfunction and disability. The questionnaire was modelled on the concepts

described the World Health Organisation's classification and hierarchy of impacts of a disease and Lockers model of oral health (128, 129). A shortened validated 14-item version (OHIP-14) was developed by Slade in 1997 which was found to be short, practical and easy to complete (130). The fourteen statements relate to the functional, physical, psychological and social impact a specific oral disorder is having on the patient's quality of life. In this study, the impact of interest is that associated with impacted mandibular third molar teeth (Appendix VI). Each statement is scored on a four-point Likert scale including 'never', 'sometimes', 'often', 'always'. The greater the sum total of the score, the greater the impact of the impacted mandibular molars on the patient's well-being. A maximum score of 42 is possible. It should be noted that all measures in the OHIP questionnaire are adverse or negative outcomes so no possible positive outcome can be derived (131). Questionnaires focusing on quality of life can provide a subjective perception of the impact a disease or treatment intervention can have on a patients overall wellbeing in the short or long term.

2.4.4 Patient anxiety and personality and pain

Correlation has been seen between pain reported and the personality of the patient. This can be rationalised as the nature and severity of pain is a product of the tissue damage along with patient cognitive experiences. Studies have shown that anxiety and stress can be tied to the reported pain level (132). Many studies have shown a link between high anxiety levels pre-operatively and greater perceived pain levels following an intervention (133, 134). It is thought that this heightened pain can be reasoned as an attentional bias towards the pain (135). To identify any probable

predisposing and undiagnosed anxiety or depressive disorders investigators can utilize tools to identify probable cases of anxiety and depression within the study population. The Hospital Anxiety and Depression Scale (HADS) was developed in 1983 by Zigmond and Snaith (136). HADS is a fourteen-item, self-rated scale designed to assess psychological distress in a non-psychiatric population (Appendix IV) (136). This questionnaire is a concise yet effective measure used to identify anxiety levels. This scale is easy to complete in a pre-admissions area and takes approximately 5 minutes. This is critical in our study where there are varying levels of anxiety among patients regarding extraction and in order to reduce confounding factors. It was originally designed to identify depression and anxiety disorders away from a psychiatric hospital setting and has been found to be effective (137, 138). The questionnaire is broken down into two subscales, 7 items forming an anxiety subscale and 7 items in a depression subscale, with the items intermingled throughout. Each item is scored by ticking one of four responses which relates best to the patient, ranging from “no not at all” to “yes definitely”. These responses are scored from 0-3. The maximum score in each subscale is 21. A score ranging between 8-10 is considered a mild or possible case of anxiety and/or depression and a score ≥11 as a probable case of psychological distress (136). A score of 0-7 inclusive represents a non-case. HADS has been widely validated across a number of clinical specialities, including dentistry (139-141). HADS has been shown to be a reliable tool for assessing and screening for anxiety and depression in a non-psychiatric setting (137).

The Pain Catastrophising Scale (PCS) was developed in 1995 by Sullivan *et al.* (142). Catastrophising was defined in 2001 by Sullivan as ‘ an exaggerated negative mental

set brought to bear during actual or anticipated painful experiences' (143). Catastrophising is seen as multidimensional, comprising of rumination, magnification and a feeling of helplessness. Catastrophisers were described as people who had a tendency to magnify or exaggerate the value of a pain (144). Sullivan designed and developed his scale using concepts from previous studies on catastrophising (144-146). The questionnaire consists of 13 statements describing the thoughts and feelings one may experience while in pain. The statements are broken down into three subscales; Rumination, Magnification and Helplessness. Each statement allows the patient to reflect on a time when they have experienced pain and how they reacted to the pain at that time. Each item is scored on a five-point scale with end points (0) not at all and (4) all the time. The PCS has a maximum possible score of 52. The likelihood of catastrophising increases with an increasing score. Those scoring >30 are identified as clinically relevant. This information allows us to interpret the reported pain scores with greater sensitivity. This scale has been validated as being a significant predictor of physical and emotional distress expressed by an individual when experiencing pain (142). Other studies prior to the development of this tool have also shown a relationship between patient distress and catastrophising and the amount of pain expressed or tolerated (147-149). This scale is important to aid clinicians in interpreting self-reported pain measures with greater sensitivity.

Dental phobia is one of the most common fears and phobias reported (150). Women are found to be more likely to report a dental fear or phobia than men (151, 152). Dental fear has previously been described as a conditioned reaction to a previous experience or traumatic event; however it is thought that it may have links

to patient anxiety disorders (153-155). Patients with high dental anxiety are found to report greater pain at recall following procedures such as tooth extraction (156), again highlighting the importance of getting baseline anxiety and catastrophising scores for studies where self-reported pain is a primary outcome.

2.5 Summary of Literature Review

Third molars erupt between the age of 17 and 24 years, with variation seen due to race and ethnicity. Mandibular third molars are the most commonly impacted tooth in the arch (48). Surgical removal of third molars is the most commonly performed oral surgery procedure. Due to changing guidance there has been a shift in age profile of the patients undergoing third molar removal in the United Kingdom, from patients in their early twenties in 1989, to patients in their mid-thirties in 2008 (1). This shift in patient age profile could have a potential economic impact due to a greater number of patients being in full-time employment rather than education. Various techniques are recognised for surgical removal of third molars. Buccal bone removal with external irrigation is the most common method today.

There is significant short-term morbidity associated with the removal of impacted third molars. Both pain and the impact on oral function such as eating or speaking has been found to delay a return to work for patients with studies reporting absence from work of up to 26 days following removal. Following surgical trauma, pain and inflammatory mediators are released at the surgical site. For oral surgery procedures, onset of pain is generally 4-6 hours following the procedure when the local anaesthetic has worn off. Interventions should be taken to minimise the post-operative pain experienced by the patient. The benefit of a multimodal approach to post-operative can be seen when pain and inflammatory mediators are targeted. Surveys have consistently shown that post-operative pain is not adequately treated (95, 96). Dexamethasone is a corticosteroid with mainly glucocorticoid action. Once

bound to the receptor, dexamethasone initiates a chain of events resulting in the suppression of inflammatory mediators. The optimum steroid used should reduce local inflammatory reactions but have little systemic effect. Dexamethasone fits this criterion as it has negligible mineralocorticoid activity yet a great biologic effect.

Patient-reported outcome and experience measures can help quantify the subjective feeling and views of the patient regarding various outcomes such as pain and satisfaction. The visual analogue scale (VAS) is a one-dimensional scale to measure pain intensity at a given time point. Descriptive questionnaires, such as the Short Form McGill Pain Questionnaire can provide a second dimension to the pain experienced. Some correlation has been shown linking patient gender, personality type, and anxiety levels with the degree of pain reported.

2.6 Knowledge Gaps and Study Aims

Although there is a body of low-quality evidence to suggest submucosal dexamethasone may reduce post-operative pain in the short term there is a lack of high quality, randomised controlled trials. Following a review of the literature we decided to carry out a prospective, double-blind, split-mouth, randomised controlled trial investigating the effect of a submucosal injection of 4mg dexamethasone on post-operative pain following third molar surgery. Secondary outcomes of patient preference of treatment modality and interference with speech or diet were also assessed.

In our study we hypothesise a submucosal injection of dexamethasone will reduce the pain experienced by the patient and decrease the impact on quality of life for the patient following third molar surgery. Our unique angle is assessing the response to submucosal administration of 4mg dexamethasone as a submucosal injection versus a control of no injection, in a patient requiring surgical removal of bilateral, symmetrically impacted wisdom teeth, at the same visit. To the best of our knowledge this methodology has not been previously carried out. As the patient is acting as their own control, confounding factors (age, bone density, race, smoking status) are limited greatly. The patient is blinded to the intervention site minimising any reporting bias. Furthermore, the patient is having both lower third molars removed at the same appointment allowing for a real-time comparison of pain experienced and, eliminating cross-over bias. Treatment is carried out under general

anaesthetic, which has the benefit of ensuring the patient is blinded to the intervention site.

2.7 Hypothesis

H_0: There is no difference in post-operative pain following surgical removal of lower third molars when a submucosal injection of 4mg dexamethasone is administered in the buccal vestibule pre-operatively.

H_1: There is a difference in post-operative pain following surgical removal of lower third molars when a submucosal injection of 4mg dexamethasone is administered in the buccal vestibule pre-operatively.

H_0: There is no difference in patient preference following treatment when 4mg dexamethasone is administered as a submucosal injection pre-operatively compared to no dexamethasone injection during the surgical removal of mandibular third molars.

H_1: There is a difference in patient preference following treatment when 4mg dexamethasone is administered as a submucosal injection pre-operatively compared to no dexamethasone injection during the surgical removal of mandibular third molars.

2.8 Aims and objectives

Study aim: To confirm the reduction in post-operative pain experienced by the patient and to reduce any impact on quality of life experienced by the patient via the administration of a submucosal injection of dexamethasone at the surgical site.

Objectives

- To determine if a single dose submucosal injection of dexamethasone local to the surgical site has an effect on the period of acute post-operative pain in comparison to local anaesthetic alone.
- To assess the patients' quality of life in the days following surgical removal of lower third molars, local anaesthetic alone versus local anaesthetic plus submucosal dexamethasone
- To determine patients' post-operative preference and satisfaction with regard to a submucosal injection of dexamethasone versus local anaesthetic alone during lower third molar extraction

Chapter 3: Materials and Methods

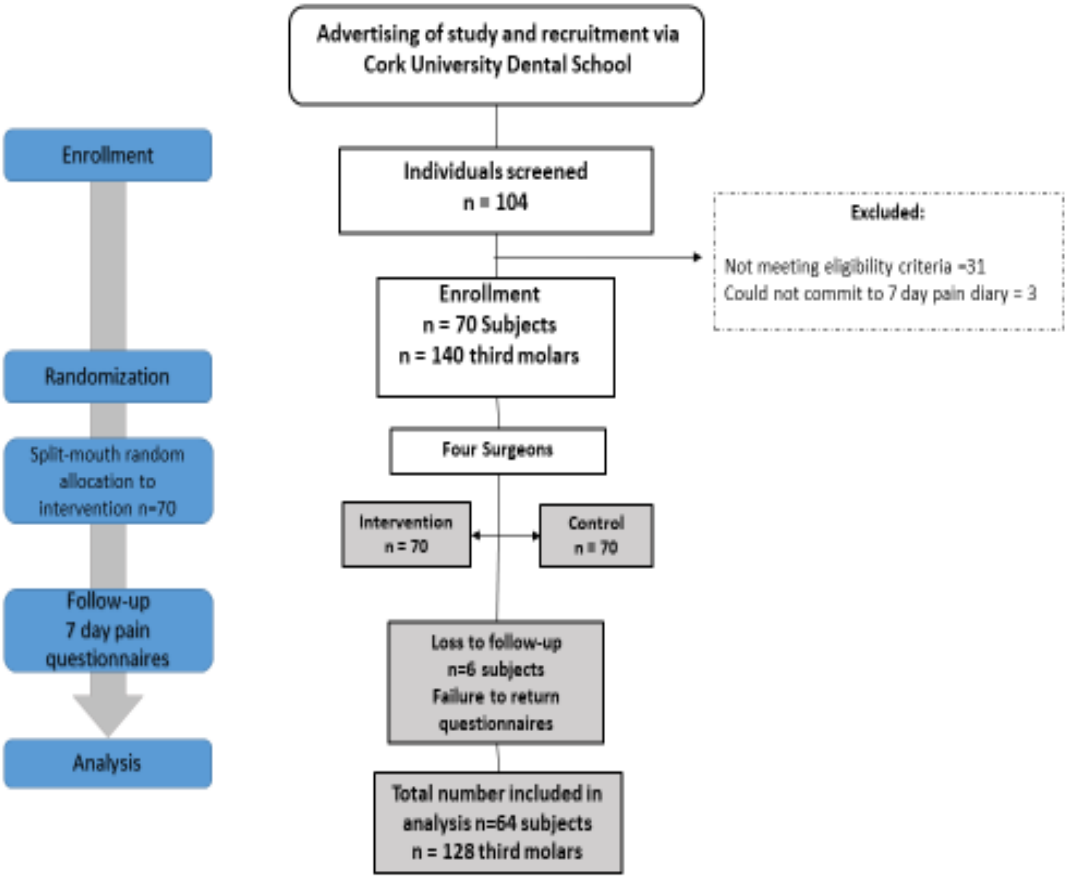
3.1 Ethical Approval and informed consent

Prior to commencement, ethical approval was sought and granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), reference number; ECM4(b)18/06/19 (Appendix I). All volunteers provided written informed consent before participation (Appendix II).

3.2 Study Design

We designed a split-mouth, randomised controlled trial in which the volunteer received either the intervention or control at both the lower left and lower right mandibular quadrant. Treatment was carried out in one session, with the patient under general anaesthetic. Patients completed questionnaires both pre- and post-operatively. Data collection was continued daily for seven days following the procedure, with each participant required to complete daily pain questionnaires. We used a per-protocol analysis of the final data.

Figure 3.1 Flow Chart of Study Design and Follow-up



3.3 Sample Size

A sample size of 52 was calculated to have a power of 80% to detect a mean difference of 10mm between the treatment and control groups on the visual analogue scale (VAS), representing pain levels. An approximate standard deviation of 25 was used. This standard deviation was calculated based on the mean difference seen in a study of similar design and outcome measures (20).

3.4 Recruitment

Seventy participants requiring bilateral mandibular third molar removal under general anaesthetic were recruited from a treatment waiting list at Cork University Dental School and Hospital requiring bilateral mandibular third molar removal under general anaesthetic. All patients were assessed by a dentist or oral surgeon in Cork University Dental School and Hospital prior to placement on the treatment waiting list. Each patient had an orthopantomogram at the consultation prior to placement on the treatment waiting list. This radiograph was assessed by a single investigator (MC) prior to recruitment in order to ensure the inclusion criterion, of symmetrical impaction of the lower third molars, was met.

Inclusion criteria:

- Male and female >16 years
- ASA 1 or ASA2 (157)

- Radiographically symmetrically impacted mandibular third molars as classified by Winter's criteria requiring surgical removal

Exclusion criteria:

- Pregnant or lactating women
- Use of non-steroidal anti-inflammatories within the 24 hours prior to surgery
- Pre-existing pain conditions
- Poorly-controlled systemic diseases or learning disability
- Patient refusal
- Allergy to dexamethasone

3. 5 Randomisation

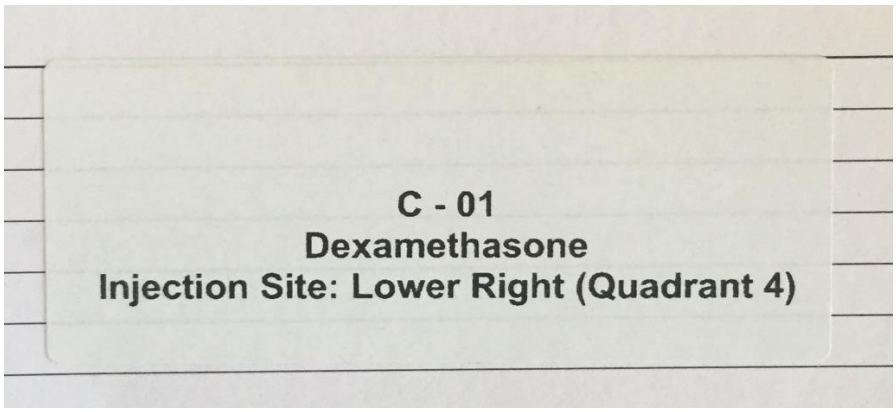
Each study participant would experience both the intervention and control due to the split-mouth study design. The site to receive the intervention was randomly selected. The Randomisation sequence was carried out independently by a statistician. For each surgeon (four surgeons), blocked randomisation was used to ensure that equal numbers of patients received the treatment on the lower left and right quadrants. Six blocks of size four and 2 blocks of size two in this order (AABB, ABAB, ABBA, BABA, BBAA BAAB, AB, BA) were set. Blocks of size 2 were used to aid concealment of the randomisation scheme. The 8 blocks were randomised using a uniform random number generator in STATA with values between 0 and 1 (158). The first 8 random numbers were placed in order beside the 8 blocks and the two columns were then sorted from highest to lowest according to the random number. The letters defined the assignment of the treatment as follows:

A= Dexamethasone Injection Site: Lower Right (Quadrant 4)

B= Dexamethasone Injection Site Lower Left (Quadrant 3)

The first 18 Letters were used for the random assignment of treatment site for Surgeon A. The randomisation method was then repeated for the three other surgeons. Surgeon number, patient study number and the intervention site were printed on individual labels and placed on post-cards inside a sealed envelope. The outside of the envelope had the surgeon code and patient study number. An example of the post-card contained inside the opaque envelope is shown in Figure 3.2.

Figure 3.2 Sample Randomisation post-card once removed from the sealed opaque envelope



The researcher (MC) was blinded to the treatment site until statistical analysis was completed. Each case was numbered sequentially as they were recruited. For each case the randomly selected site for intervention was given to the surgeon in an identical, sealed, non-transparent envelope as described immediately prior to the surgery. The investigator was not involved in the surgery in order to maintain impartiality. The patient was under general anaesthetic for the procedure and

remained blinded to the site that received the intervention of interest, submucosal dexamethasone.

3.6 Operative Intervention

All patients received perioperative analgesics. Either oral pre-operative analgesics or intra-operative intravenous analgesics were used depending on the date of treatment. Due to a change in admission facilities resulting from Cork University Hospital's response to Covid-19, our dental theatre staff were no longer able to safely administer oral pre-medications to patients. This was due to a reduced capacity admissions and recovery area for the patients and as such made privacy and supervision of pre-operative patients challenging for the nursing staff. As there was insufficient space to administer medication and supervise the patient we had to adjust our pre-medication protocol. As a consequence, study participants recruited after April 2020 received intravenous analgesics intra-operatively as opposed to oral analgesics pre-operatively. Pre-operative oral analgesia consisted of paracetamol, ibuprofen and oxycodone. For those recruited after April 2020, intravenous paracetamol and diclofenac were administered intra-operatively.

The patient was monitored non-invasively with electrocardiography, pulse oximetry and blood pressure monitoring prior to induction of anaesthesia. Each patient received a standardised general anaesthetic provided by a consultant anaesthetist. Anaesthesia was induced with intravenous propofol and maintained with a sevoflurane in oxygen mixture. Following pre-oxygenation, the patient was intubated with a nasoendotracheal tube of appropriate size. Intra-operative anaesthetic and vital sign monitoring included heart rate and rhythm, anaesthetic

depth, oxygen saturation, end tidal carbon dioxide, blood pressure and sevoflurane in oxygen concentration.

Figure 3.3 A patient undergoes surgical removal of mandibular third molars under general anaesthetic

A standard surgical trolley was set up prior to all procedures. Using aseptic technique, 1ml of 4mg/ml dexamethasone was drawn up from a 2ml ampule into a labelled 5ml syringe by the investigator (MC) and placed on the trolley for the surgeon. Bilateral mandibular third molar removal was carried out by a single, experienced surgeon for each patient. Regional anaesthesia of an inferior alveolar nerve block and long buccal infiltration of 2% lidocaine with 1:80,000 epinephrine was administered to the lower right and left quadrant, immediately prior to incision. A 2.2ml cartridge was used for the inferior dental block followed by a further 2.2ml as a long buccal infiltration were delivered. The site randomised for the intervention

received a 1ml injection of 4mg dexamethasone, via a 22-gauge needle, in the buccal vestibule adjacent to the lower third molar following administration of local anaesthetic.

All cases involved raising a full-thickness mucoperiosteal flap. Buccal bone removal and sectioning of the tooth was carried out as required using a surgical bur and copious irrigation. In suitable cases the tooth was sectioned using a hammer and osteotome, negating the requirement for buccal bone removal. The tooth was delivered from the socket using a Coupland's elevator. Each socket was irrigated with normal saline and the flap replaced using 4.0 Vicryl absorbable sutures. Duration of surgery, from incision to final suture placement, was recorded individually for the right and left mandibular third molar removal by the investigator (MC), who was in a room adjacent to the theatre.

3.7 Pre-operative data collection

Patient demographics including age, gender, smoking status, and contact details were recorded following informed consent to study participation. A number of baseline questionnaires were completed by the patient under the supervision of the investigator (MC). Facilitated by MC, the Pain Catastrophising Scale, Hospital Anxiety and Depression Scale and the Oral Health Impact Profile-14 were completed pre-operatively by each study participant.

3.8 Post-operative Data Collection

Immediately post-operatively the surgeon completed a standardised surgical questionnaire. Details of the surgery including state of tooth eruption, extraction technique employed, classification of impaction, along with assessment of difficulty were recorded. These details were recorded individually with respect to right and left surgical site.

3.8.1 Surgical Questionnaire

3.8.1.1 State of Eruption

The state of eruption and nature of impaction of the mandibular third molars involved in this study were assessed at two stages. Initially, in order to meet the inclusion criteria of this study, an orthopantomogram of potential study participants were assessed by a single investigator (MC) and if deemed to have symmetrically impacted lower third molars for removal, patients were offered recruitment in the study. This step was taken prior to enrolment to ensure the paired samples, for the intervention and control side, were closely matched and the subject met the inclusion criteria of the trial. A second assessment of the state of eruption and nature of impaction was reported and recorded by the operating surgeon immediately following surgery, using our surgical questionnaire (Appendix VII). Aided by this questionnaire the operating surgeon assessed and recorded the state of eruption, from unerupted to partially erupted or fully erupted as they identified intra-orally. Due to the required surgical element of the trial no fully erupted third molars met the inclusion criteria.

3.8.1.2 Classification of Impaction

The nature of the impacted third molars were classified accorded to Winter (53). This was recorded for each case by the operating surgeon with respect to the intervention and control side. To be eligible for enrolment in the study a single investigator (MC) had classified the impaction of the mandibular third molars from a radiograph deeming the right and left molar to be symmetrically impacted.

3.8.1.2 Surgical technique

Depending on the type and cause of the impaction (bone/soft tissue/adjacent tooth), differing surgical techniques may be employed to relieve the impaction, allowing for the removal of the tooth by elevation. The operating surgeon recorded the surgical technique employed in each case on the surgical questionnaire immediately following the procedure. As no tooth was fully erupted in the mouth, all cases involved surgery of some kind. All surgical techniques involved raising a full-thickness mucoperiosteal flap (FMPF).

3.8.1.3 Difficulty of Extraction

Immediately following surgery, the operating surgeon ranked the difficulty of the extraction. Although this is a subjective measure the ranking was requested to give further surgical information to any potential outlying pain scores. Three tick box options were given to the operating surgeon, routine, complex or highly complex.

3.8.2 Pain Assessment

Thirty minutes following extubation, two further questionnaires were completed by the patient assisted by the investigator (MC). These included Short form McGill Pain questionnaire and a pain diary.

3.8.3 Short Form McGill Pain Questionnaire

This questionnaire was used to investigate the multi-dimensional nature of pain, investigating the characteristics of the pain being reported by the participants in combination with a VAS and a Present Pain Intensity scale (PPI) (Appendix VIII). The SF McGill incorporates the overall intensity of the pain using the VAS and PPI scores, complimented by descriptive, sensory and affective subscales.

3.8.4 Pain Diary

Patients were required to complete a structured pain diary for seven days following surgery (Appendix IX). The pain diary contained quality of life and functional questions, a record of analgesic consumption and a Visual Analogue Scale (VAS) to assess pain experienced at the right and left surgical site independently. The VAS scale was 100mm in length, 0mm equating to no pain and 100mm equating to maximal possible pain.

3.9 Discharge Advice

Prior to discharge, the patient and their chaperone received standard post-operative instructions. A standard prescription and directions for use were given pertaining to post-operative analgesia. Post-operative analgesics consisting of paracetamol 1g six hourly and a non-steroidal anti-inflammatory, dexketoprofen 25mg eight hourly were prescribed. An opioid, oxycodone 5mg tablets 4-6 hourly as required, was also prescribed for breakthrough pain. No patients received a prescription for prophylactic antibiotics. Each patient was discharged with a questionnaire pack and a stamped addressed envelope for ease of return upon completion. The questionnaire pack comprised of a pain diary and Short form McGill Pain Questionnaire, each to be completed daily for seven days. On day 7 post-operatively two additional questionnaires were required; the Hospital Anxiety and Depression Score and a Dental Visit Satisfaction Scale.

3.10 Follow-up

Each patient was contacted by telephone on post-operative day 4 and post-operative day 7 in order to check-in with the patient and to ensure return of the questionnaire pack following completion.

3.11 Patient Satisfaction

Patient-satisfaction is an important measurement in any patient-centred treatment. The Dental Visit Satisfaction Scale is a ten item scale, with three subscales of communication, understanding and competence developed by Corah *et al.* in 1985 (Appendix X) (159). Patient-satisfaction can be used as a measurement of treatment success. A patients expectation of a what is a good service can vary greatly, depending on patient age, gender, nature of the illness and their attitude towards to problem (160). The Dental Visit Satisfaction Scale is best suited to assessing outcomes from a single dental visit; it is a short and practical tool that is suitable for rapid completion following the visit. Patients are to respond to each of the ten satisfaction questions, which are presented in a five-point Likert style ranging from 'Strongly Disagree' to 'Strongly Agree'. We required study participants to complete this satisfaction scale on day-7 following treatment. As the treatment was carried out under general anaesthetic, question 8 ('The Dentist was too rough when he worked on me') was not directly applicable. Patients were asked to respond to each of the ten satisfaction questions.

3.12 Statistical Analysis

Statistical analysis was performed with assistance of a biostatistician, Dr. Wiley Barton from Teagasc Moorepark, Fermoy, Co. Cork. All statistical analysis was conducted within the *R* statistical software environment (161) using version 4.0.1 and RStudio (v.1.3.959) (162) on Windows 10. Data was imported to *R* and assessed for normality using the *MVN* (v.5.8) package with the Mardia's multivariate normality test (163). Normality testing determined a non-normal distribution of the study's variables. Non-parametric tests were used accordingly. Wilcoxon signed rank and rank-sum tests were used to compare paired and unpaired variables, respectively. Spearman's correlation was used for the comparison of association between variables. All p-values were adjusted for multiple comparisons using the Benjamini–Hochberg method with an adjusted p-value < 0.05 used to measure significance (164).

Regression analysis was implemented with *lm* from the base *stats* package and the lmer function from *lme4* (v.1.1-23) (165). Linear mixed-effects model generation resulted from repeated *step-down* comparison of variable effects, resulting in a model with functional least complexity. A significant contribution of variables was determined with an ANOVA p-value < 0.05 and comparison of Akaike Information Criterion and Bayesian Information Criterion (AIC and BIC, respectively). The final model comparing treatment effect on reported VAS score included surgery time, eruption state, and pain diary day as fixed variables and volunteers as the random effect with pain diary day weights added. Graphical representations were

generated using the *ggplot2* (v.3.3.1) package (166). Regression model plots used fitted lines for un-weighted simple regression (SurgeryT vs. VAS/ Figure X), locally fitted loess regression (days vs. VAS), and mixed-effect linear regression with ribbons representing 95% confidence intervals and *line-points* representing raw mean and standard error.

Chapter 4: Results

4.1 Demographics

Seventy patients were enrolled in the study between October 2019 and October 2020. The age range of the participants was 16 to 54 years of age, with the mean age being 22 years (SD 5.7 years). The median age of our study population was 21 years. The study participants were comprised of 44 females and 26 males. The majority of the participants, 82.86%, were non-smokers. Table 4.1 demonstrates the clinical and demographic characteristics of the study population as a whole and as treated by each surgeon.

Table 4.1 Demographics of study participants

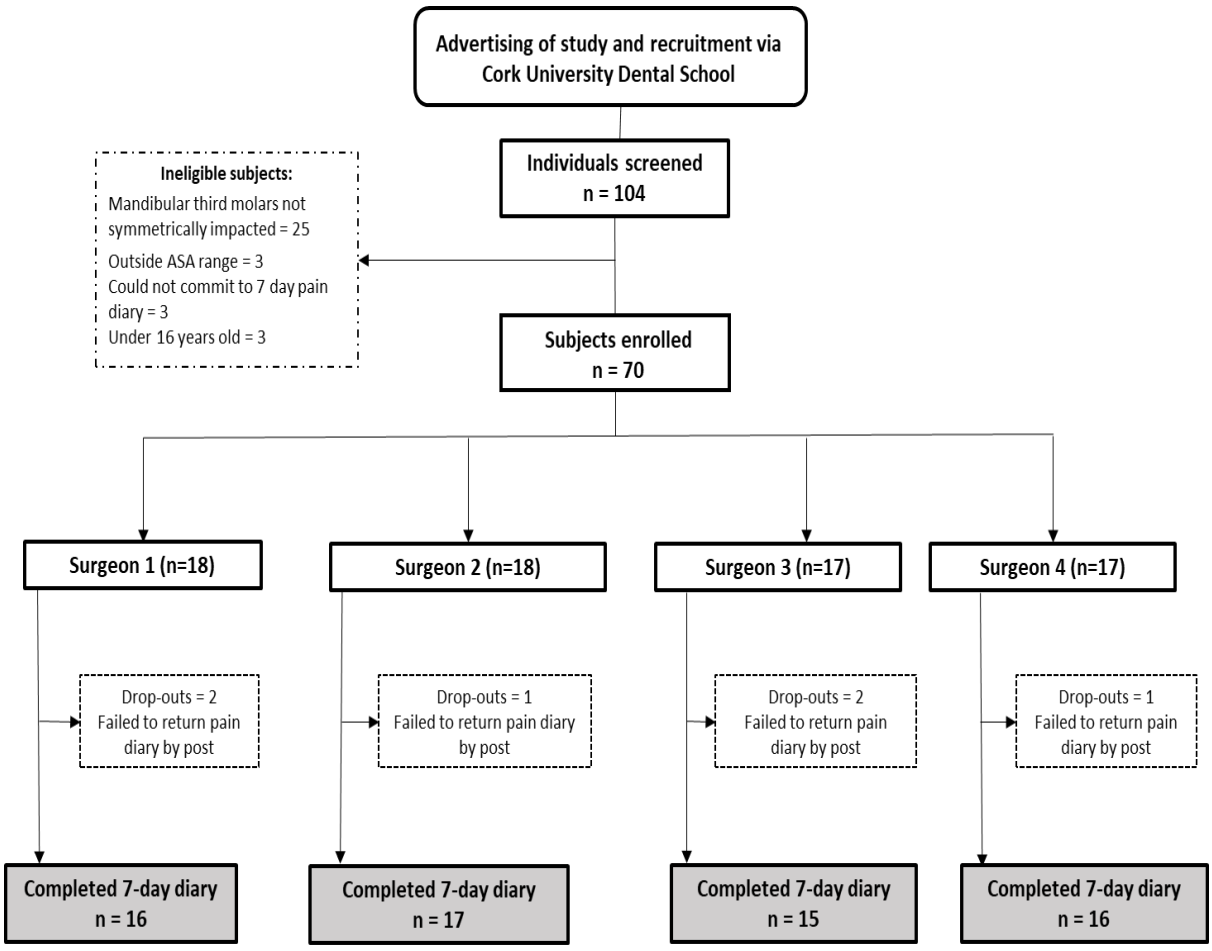
Baseline patient characteristics

Number of participants	**Surgeon 1 N = 18**	**Surgeon 2 N = 18**	**Surgeon 3 N = 17**	**Surgeon 4 N = 17**	**Total N = 70**
Female n, (%)	11 (61.1%)	13 (72.2%)	9 (53%)	11 (64.7%)	44 (62.9%)
Age (years), mean (SD)	23.6 (3.95)	23.5 (8.48)	20.9 (3.91)	20.2 (4.88)	22.1 (5.73)
Non-smoker n, (%)	13 (72.2%)	15 (83.3%)	16 (94.1%)	14 (82.4%)	58 (82.9%)

4.2 Recruitment and Attrition

Sixty-four of the seventy participants enrolled in the study completed and returned the pain diary questionnaire pack following the seven days and were included in the final analysis. Failure to return the pain diary was considered failure of study completion. This was the sole reason behind participant attrition (Figure 4.1).

Figure 4.1 Study recruitment and attrition per operating surgeon



4.3 Pre-operative assessment

4.3.1 Hospital Anxiety and Depression Scale

A single investigator (MC) was present to assist the study participants with completion of the HADS prior to surgery. Tables 4.2 and 4.3 show the distribution of study participants between the anxiety and depression subsets of the scale. The pre-operative HADS data from one participant was absent. In our study population the vast majority, 75% in the anxiety subgroup and 89% in the depression subgroup were deemed not to be a case of psychological distress. Conversely, almost 15% in the anxiety scale and 3% in the depression scale were classified as probable cases. The cases are generally spread evenly throughout the surgeon groups, with no single surgeon treating a majority of probable cases of patients experiencing undiagnosed psychological distress.

Table 4.2 Pre-operative HADS Anxiety

Participant characteristics				
	Category	**Frequency** (*F*)	**Total** (*N*)	**Percentage frequency** (*P = 100 × (F/N)*)
HADS anxiety				
Surgeon 1	non-case borderline case	14 2 1	17	82.35% 11.76% 5.88%
Surgeon 2	non-case borderline case	13 1 4	18	72.22% 5.56% 22.22%
Surgeon 3	non-case borderline case	12 2 3	17	70.59% 11.76% 17.65%
Surgeon 4	non-case borderline case	13 2 2	17	76.47% 11.76% 11.76%
Total	non-case borderline case	52 7 10	69	75.36% 10.14% 14.49%

Table 4.3 Pre-operative HADS Depression

Participant characteristics				
	Category	**Frequency** (*F*)	**Total** (*N*)	**Percentage frequency** (*P = 100 × (F/N)*)
HADS depression				
Surgeon 1	non-case borderline case	14 2 1	17	82.35% 11.76% 5.88%
Surgeon 2	non-case — —	18 — —	18	100% — —
Surgeon 3	non-case borderline case	14 2 1	17	82.35% 11.76% 5.88%
Surgeon 4	non-case borderline —	16 1 —	17	94.12% 5.88% —
Total	non-case borderline case	62 5 2	69	89.86% 7.25% 2.9%

4.3.2 Pain Catastrophising Scale

Each study participant completed a Pain Catastrophising Scale (PCS) as part of our baseline pre-assessment protocol (Appendix V). Table 4.4 demonstrates the number of study participants who reached a clinically relevant score on completion of the PCS. The number of 'catastrophisers' is very low overall, with 4 cases identified. One participant's pre-operative questionnaire was incorrectly given to the patient at discharge, along with the seven-day pain diary, and unfortunately was not returned to us.

Table 4.4 Patient characteristics for Pain Catastrophising Scale

	Surgeon 1	**Surgeon 2**	**Surgeon 3**	**Surgeon 4**	**Total**
Number of participants	17	18	17	17	69
Clinically relevant score >30	1(5.9%)	0	1(5.9%)	2(11.8%)	4(5.8%)

4.3.3 Effect of pre-operative assessment scores on pain

Spearman's correlation was used to measure the association between the pre-operative questionnaire scores and the pain scores reported on the visual analogue scale. There was no significant correlation found between the pre-operative Hospital Anxiety or Depression scores and reported pain. There was a moderate positive association found between the pain catastrophising scale and the pain reported on the visual analogue scale (R_S=0.369, P=0.017)

4.3.4 Oral Health Impact Profile

Each patient completed a shortened version of the Oral Health Impact Profile (OHIP-14) as a validated means of assessing the oral health-related quality of life experienced by our study population (Appendix VI). Table 4.5 shows the mean OHIP-14 score of our study population as a whole and according to each surgeon group. There are high levels of consistency seen throughout the surgeon groups.

Table 4.5 Patient characteristics OHIP-14

	Surgeon 1	**Surgeon 2**	**Surgeon 3**	**Surgeon 4**	**Total**
Number of participants	18	18	17	17	70
OHIP 14 Mean (SD)	20.12 (6.93)	20.33 (3.93)	19 (5.53)	18.94 (5.61)	19.61 (5.49)

4.4 Surgical Assessment

4.4.1 State of Eruption

Table 4.6 shows the frequency of distribution for the state of eruption of the mandibular third molar per treating surgeon group and total study population. Just two cases in total were assessed as not symmetrical in eruption, showing a high degree of agreement between the investigator and operating surgeons in their assessment of the teeth. One case of asymmetry was reported by Surgeon 1 and another single case by Surgeon 4. Almost half (45.7%) of the teeth removed during this clinical trial were found to be unerupted.

Table 4.6 Frequency distribution for State of eruption of Mandibular Third Molar

	Description	**Treatment (Intervention/Control)**	**Frequency** (*F*)	**Total** (*N*)
Surgeon 1	Partially erupted	Untreated Treated	15 16	18 18
	Unerupted	Untreated Treated	3 2	18 18
Surgeon 2	Partially erupted	Untreated Treated	13 13	18 18
	Unerupted	Untreated Treated	5 5	18 18
Surgeon 3	Partially erupted	Untreated Treated	5 5	17 17
	Unerupted	Untreated Treated	12 12	17 17
Surgeon 4	Partially erupted	Untreated Treated	4 5	17 17
	Unerupted	Untreated Treated	13 12	17 17

	Description	Treatment (Intervention/Control)	Frequency (*F*)	Total (*N*)
Total	Partially erupted	Untreated	37	70
		Treated	39	70
	Unerupted	Untreated	33	70
		Treated	31	70

4.4.2 Classification of Impaction

Table 4.7 shows the classification of impaction of the mandibular third molars as reported by the operating surgeon in that case. The type of impaction is reported as symmetrical in 97% of paired samples. This shows high levels of agreement between operating surgeon and the investigator (MC). Surgeon 3 and Surgeon 4 each reported a single case as being of involving teeth of differing impaction class. Overall, a majority of the teeth removed in this clinical trial (55%) were classified as a mesio-angular impaction. Following from the mesio-angular cases, in decreasing order of frequency the cases involved in this trial included vertical impaction (21.4%), disto-angular impaction (15%) and less frequently horizontally impacted (8.57) third molars.

Table 4.7 Frequency Distribution for Winter Classification of Impaction

	Description	Treatment	**Frequency** (*F*)	**Total** (*N*)	**Percentage frequency** (*P = 100 × (F/N)*)
Surgeon 1	Mesio-angular	Untreated	9	18	50%
		Treated	9	18	50%
	Disto-angular	Untreated	4	18	22.22%
		Treated	4	18	22.22%
	Horizontal	Untreated	1	18	5.56%
		Treated	1	18	5.56%
	Vertical	Untreated	4	18	22.22%
		Treated	4	18	22.22%
Surgeon 2	Mesio-angular	Untreated	6	18	33.33%
		Treated	6	18	33.33%
	Disto-angular	Untreated	2	18	11.11%
		Treated	2	18	11.11%
	Horizontal	Untreated	2	18	11.11%
		Treated	2	18	11.11%

	Description	Treatment	**Frequency** (*F*)	**Total** (*N*)	**Percentage frequency** (*P = 100 × (F/N)*)
	Vertical	Untreated Treated	8 8	18 18	44.44% 44.44%
Surgeon 3	Mesio-angular	Untreated Treated	11 12	17 17	64.71% 70.59%
	Disto-angular	Untreated Treated	4 4	17 17	23.53% 23.53%
	Horizontal	Untreated Treated	2 1	17 17	11.76% 5.88%
Surgeon 4	Mesio-angular	Untreated Treated	12 12	17 17	70.59% 70.59%
	Disto-angular	Untreated —	1 —	17 —	5.88% —
	Horizontal	Untreated Treated	1 2	17 17	5.88% 11.76%
	Vertical	Untreated Treated	3 3	17 17	17.65% 17.65%
Total	Mesio-angular	Untreated Treated	38 39	70 70	54.29% 55.71%
	Disto-angular	Untreated Treated	11 10	70 70	15.71% 14.29%
	Horizontal	Untreated Treated	6 6	70 70	8.57% 8.57%
	Vertical	Untreated Treated	15 15	70 70	21.43% 21.43%

4.4.3 Surgical technique

Of the 140 mandibular third molars removed, 24 molars elevated out following the raising of a FMPF, releasing the soft tissue impaction. Seven paired samples (14 teeth) were elevated out following the raising of a FMPF and subsequently sectioning the tooth using a hammer and osteotome. Thirteen of the 140 involved in the study required a FMPF, buccal bone removal with a rotary bur and irrigation coolant before the tooth was elevated out. Over 60% of cases (89 teeth) required the highest degree of surgical intervention to enable removal of the mandibular molar teeth, a FMPF, buccal bone removal with a rotary bur and irrigate combined with sectioning of the tooth itself before the elevation of the tooth in fragments from the socket. The surgical technique was identical in 95.7% of the cases involved in this clinical trial.

Different surgical techniques were utilised for removal of third molars in three patients. Removal of these patients and reanalysis did not affect the direction of the primary outcome. Therefore, they have been included in the presented data block.

Table 4.8 Frequency distribution of the Surgical removal technique employed

	Surgical technique	Control/ intervention site	Frequency (*F*)	Total (*N*)	Percentage frequency (*P = 100 × (F/N)*)
Extraction technique					
Surgeon 1	Bone removal + tooth division + elevation	Untreated Treated	11 11	18 18	61.11% 61.11%
	Hammer and osteotome	Untreated Treated	7 7	18 18	38.89% 38.89%
Surgeon 2	Bone removal + tooth division + elevation	Untreated Treated	9 9	18 18	50% 50%
	Elevation only	Untreated Treated	9 9	18 18	50% 50%
Surgeon 3	Bone removal + tooth division + elevation	Untreated Treated	12 12	17 17	70.59% 70.59%
	Bone removal + elevation	Untreated Treated	2 4	17 17	11.76% 23.53%
	Elevation only	Untreated Treated	3 1	17 17	17.65% 5.88%
Surgeon 4	Bone removal + tooth division + elevation	Untreated Treated	13 12	17 17	76.47% 70.59%
	Bone removal + elevation	Untreated Treated	3 4	17 17	17.65% 23.53%
	Elevation only	Untreated Treated	1 1	17 17	5.88% 5.88%
Total	Bone removal + tooth division + elevation	Untreated Treated	45 44	70 70	64.29% 62.86%
	Bone removal + elevation	Untreated Treated	5 8	70 70	7.14% 11.43%
	Elevation only	Untreated Treated	13 11	70 70	18.57% 15.71%
	Hammer and osteotome	Untreated Treated	7 7	70 70	10% 10%

4.4.4 Difficulty of Extraction

We can see in Table 4.9 that no case was described by any surgeon as highly complex.

Of the cases treated, 77.8% were deemed to be routine surgical extractions.

Table 4.9 Frequency distribution of Extraction Difficulty as Classified by the Operating Surgeon

	Description	Treatment quadrant	**Frequency** (*F*)	**Total** (*N*)
Difficulty of extraction				
Surgeon 1	Routine	Right Left	15 15	18 18
	Complex	Right Left	3 3	18 18
Surgeon 2	Routine	Right Left	11 11	18 18
	Complex	Right Left	7 7	18 18
Surgeon 3	Routine	Right Left	13 13	17 17
	Complex	Right Left	4 4	17 17
Surgeon 4	Routine	Right Left	15 16	17 17
	Complex	Right Left	2 1	17 17
Total	Routine	Right Left	54 55	70 70
	Complex	Right Left	16 15	70 70

4.4.5 Duration of surgery

Table 4.10 demonstrates the mean time in seconds for the surgical removal of the mandibular third molar. This was recorded separately for both the right and left side from incision to completion of final suture. There is some variability of surgery duration between surgeon groups. All surgeons had grossly similar caseloads of the various surgical techniques, raising the question does a decrease in surgery duration come with operator experience? There is consistency seen for the duration of surgery within the surgeon groups for the intervention and control providing consistency within the paired samples and the pain scores reported by the participants.

Table 4.10 Mean Surgery Duration for Intervention and Control Site

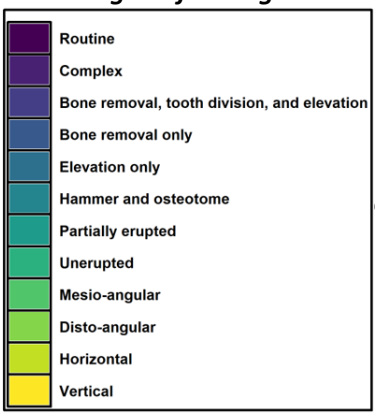
Variable (n)	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4	Total
Participants	17	18	17	17	69
Intervention side Mean Time in seconds (SD)	328.65 (151.53)	436.94 (231.98)	726.24 (317.98)	572.24 (307.76)	514.87 (295.30)
Control side Mean time in seconds (SD)	317.35 (153.86)	394.67 (205.28)	695.00 (355.28)	536.53 (183.37)	484.57 (273.11)

4.4.6 Summary of Surgical Assessment

Figure 4.2 represents the data collected from the surgical questionnaire graphically (Appendix VII). There is a high degree of consistency in the type of impaction (97%), state of eruption (97%) and surgical technique employed (95.7%) for removal between the intervention and control side.

Figure 4.2 Histogram depicting Surgical Variables

Colour legend for Surgical Variables

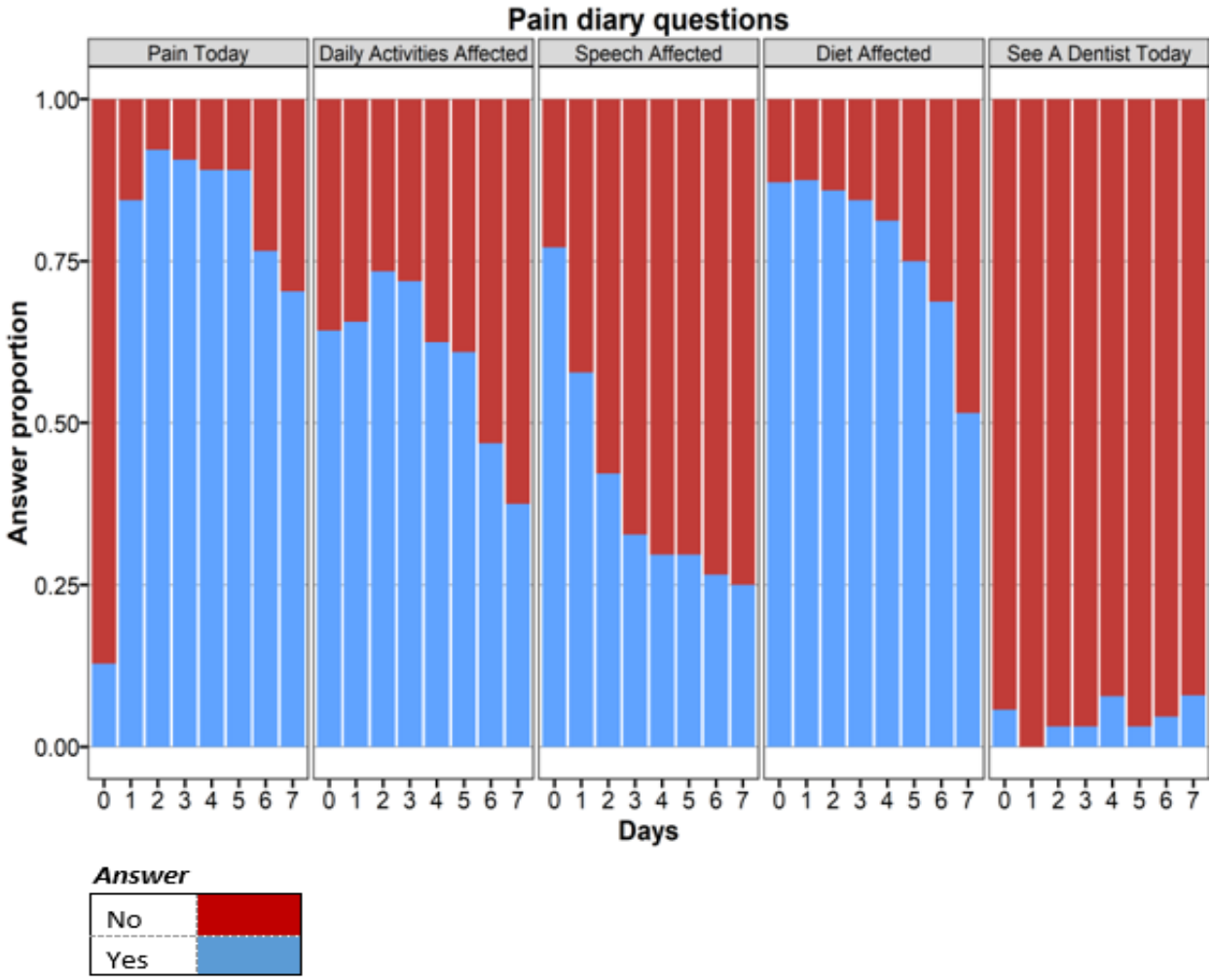


4.5 Post-operative assessment

4.5.1 Pain Diary

Figure 4.3 graphically represents the findings from the structured pain diary. It can be seen in the graph that over 75% of participants reported experiencing some level of pain on post-operative day 2 – 5 inclusive. The diet of over 50% of the study population remained affected by surgery until day 7 following third molar removal.

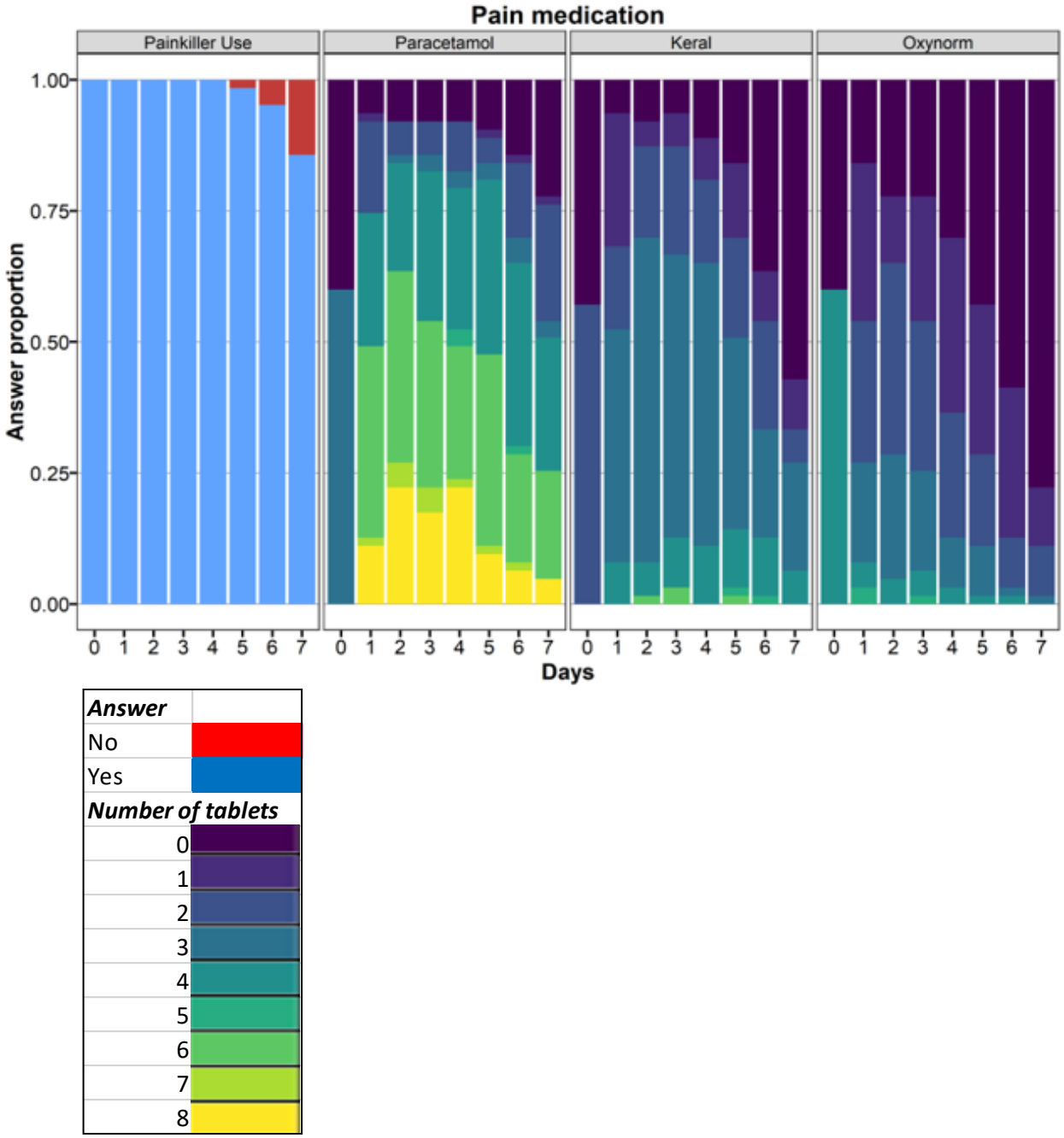
Figure 4.3 Bar Chart representing results from Pain Diary



4.5.2 Analgesic Consumption

Each patient received a standard prescription and post-operative analgesic management advice. Figure 4.4 outlines the proportion of participants requiring analgesic medications each day and the number of each medication consumed. From post-operative day 0 to day 4 inclusive, 100% of study participants consumed some form of analgesic medication: 2% of participants did not consume any analgesics from post-operative day 5, with 14% of participants not using analgesics by post-operative day 7. The proportion of participants requiring oxycodone as break through pain medication declined daily from post-operative day 3. The number of analgesics consumed declined as the week progressed.

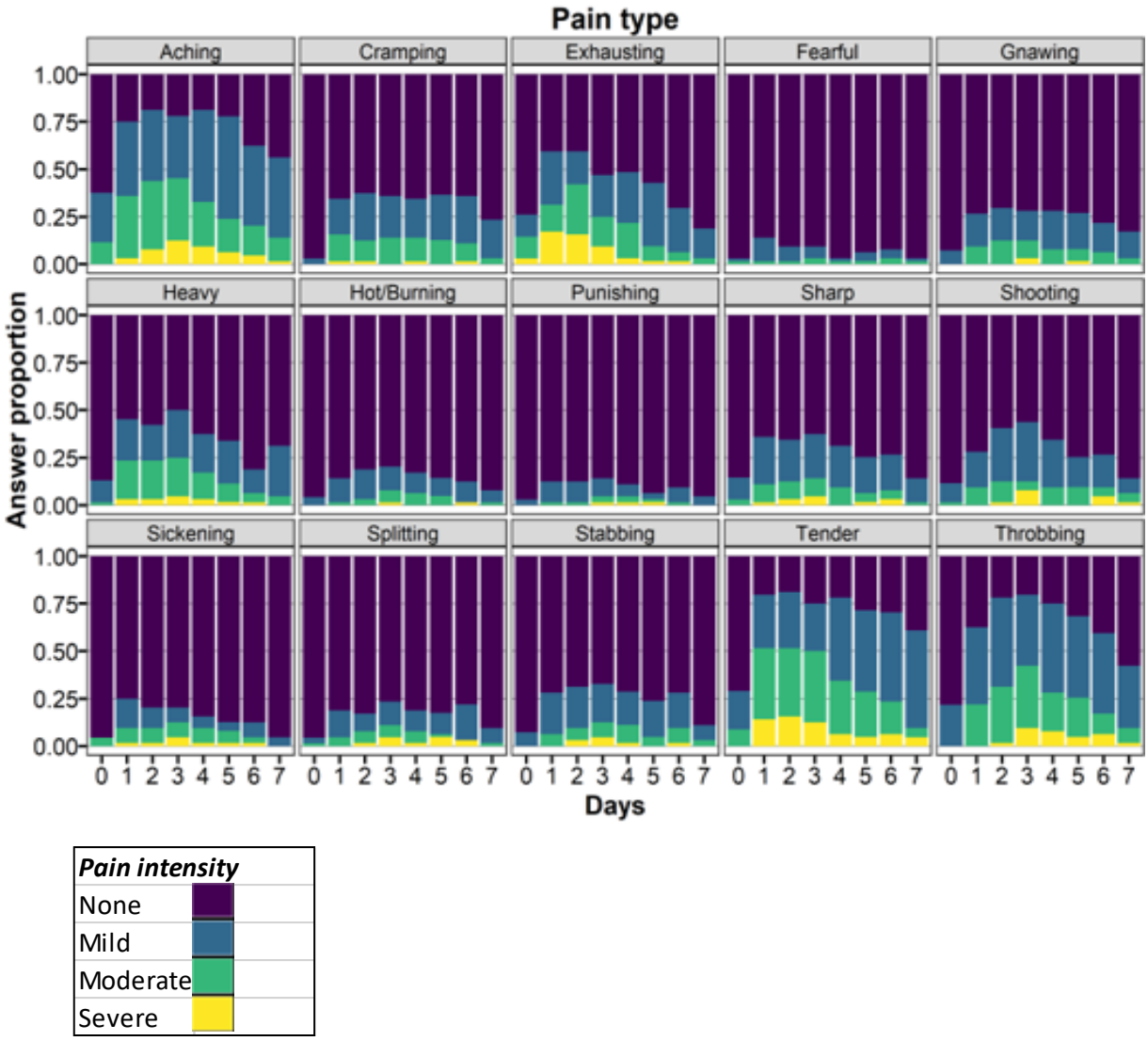
Figure 4.4 Post-operative Analgesic Consumption



4.5.3 Short Form McGill Pain Questionnaire

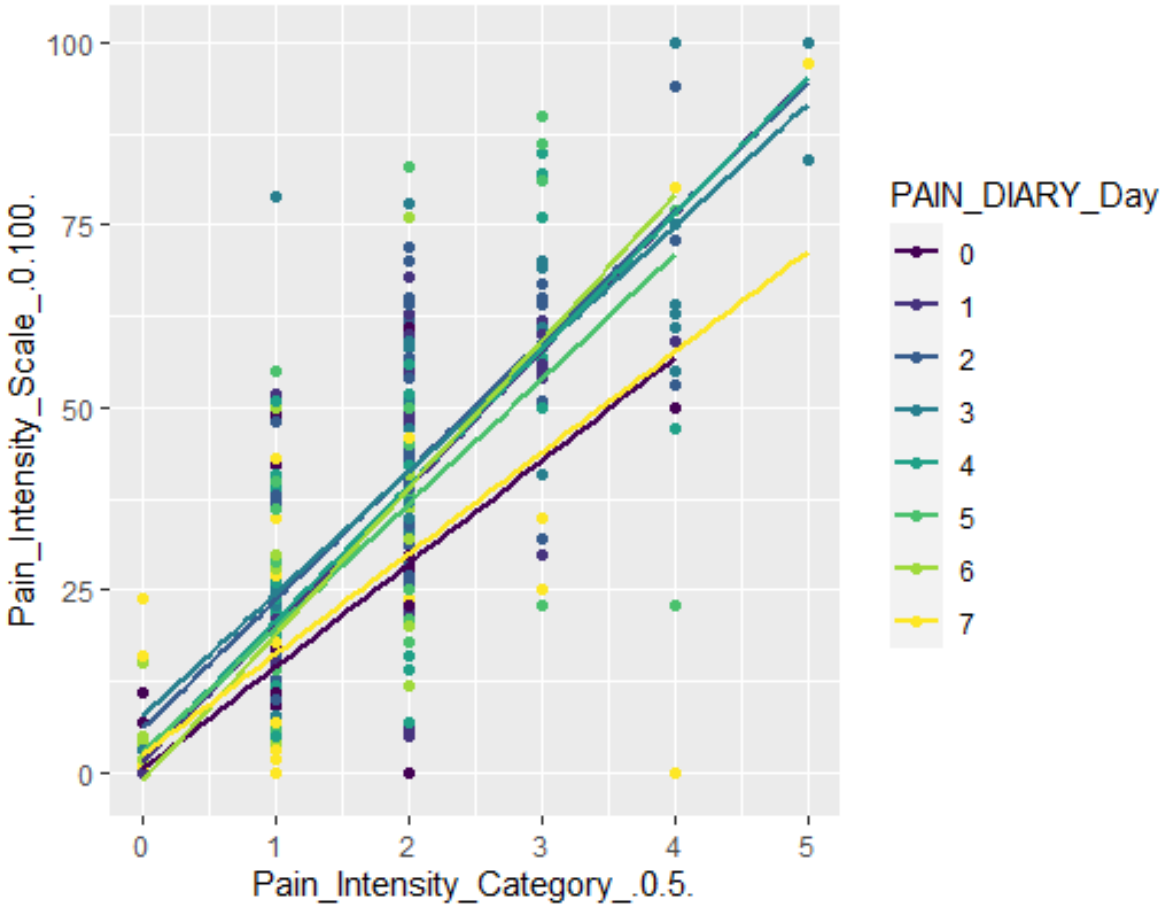
Figure 4.5 outlines the eleven sensory terms and four affective terms used to describe pain in the Short Form McGill Pain Questionnaire (SF McGill). Tender, throbbing, and aching are consistently the most commonly-used characteristic terms to describe the sensory pain experienced. Exhausting is the most prevalent descriptor of the affective nature of the pain.

Figure 4.5 Frequency Distribution of Short Form McGill Pain Questionnaire



The SF McGill also quantifies the overall present pain intensity experienced by the patient, using both a 100 mm visual analogue scale and a six-point Verbal Descriptor Scale (VDS), which has end points of 'None' to 'Excruciating'. Figure 4.6 represents the merged scores from the PPI and Visual analogue scale on each day post-op. The graph indicates the more severe descriptors on the VDS, 'Horrible' and 'Excruciating' are most commonly used on post-operative day 2 and 3.

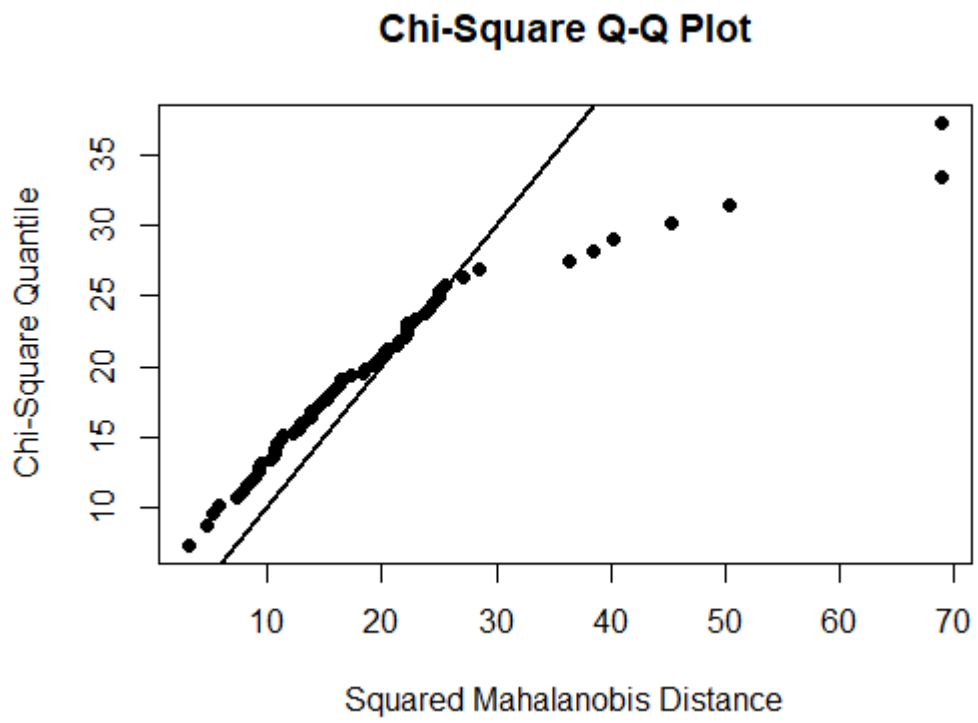
Figure 4.6 Short Form McGill Pain Questionnaire; Present pain intensity and Visual Analogue Scale



4.5.4 Pain Assessment

The VAS pain data was tested for normality using a Chi Squared Q-Q plot (Figure 4.7) and found not to be normally distributed. As a result, the data was analysed using non-parametric tests.

Figure 4.7 Chi-Square Q-Q Plot with Data Following Non-Parametric Distribution



4.5.6 Visual Analogue Scale

Each study participant recorded the pain present on the right and left side independently using a 100mm visual analogue scale. This was completed daily from post-operative day 0 to day 7 inclusive, following surgery. As the data was not normally distributed, Wilcoxon Signed Rank test was used to analyse the paired data samples. Figure 4.8 illustrates each participant score reported for the intervention and control side. The mean pain score (full line) is marginally lower for the intervention (dexamethasone receiving) side. This was consistent across days 0 to 7 post-operatively; however, this difference did not reach statistical significance. The daily p-value ranged from P=0.07 to P=0.73, never reaching statistical significance.

Figure 4.8 Pain recorded on Visual Analogue Scale on Day 0 – Day 7 post-op.

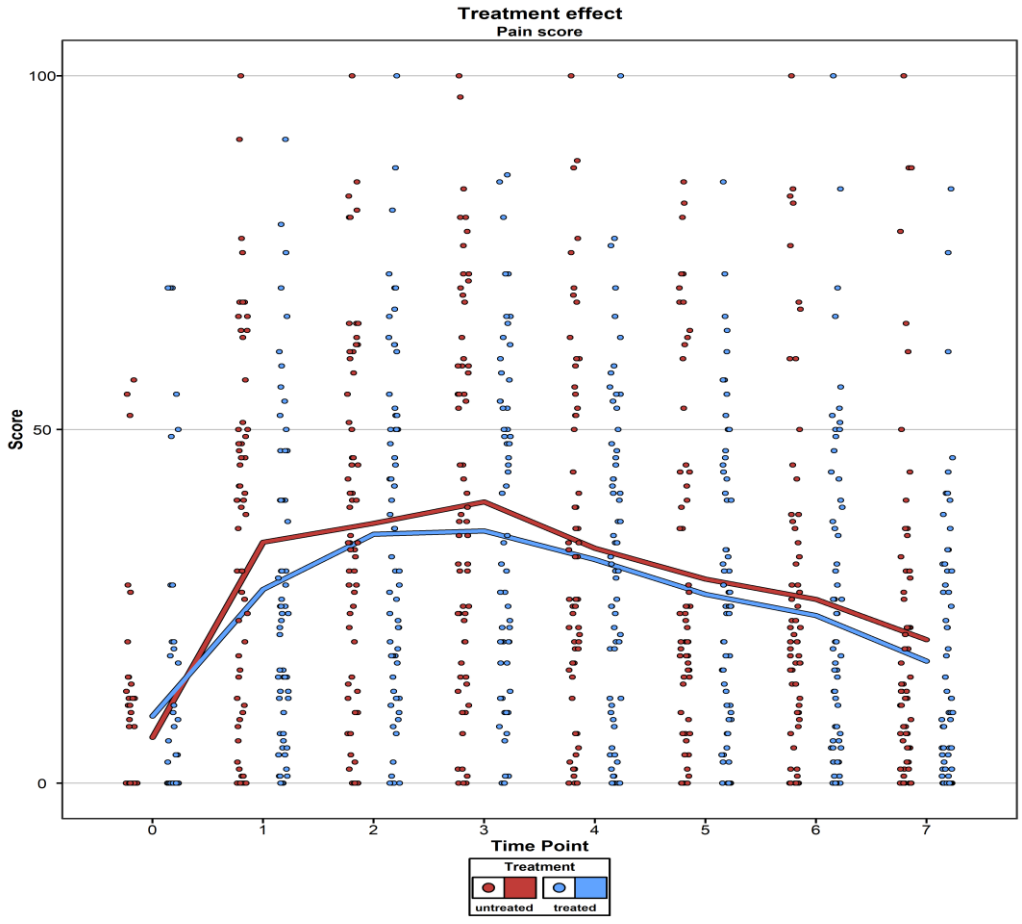


Figure 4.9 Mean pain reported for intervention and control with 95% confidence intervals

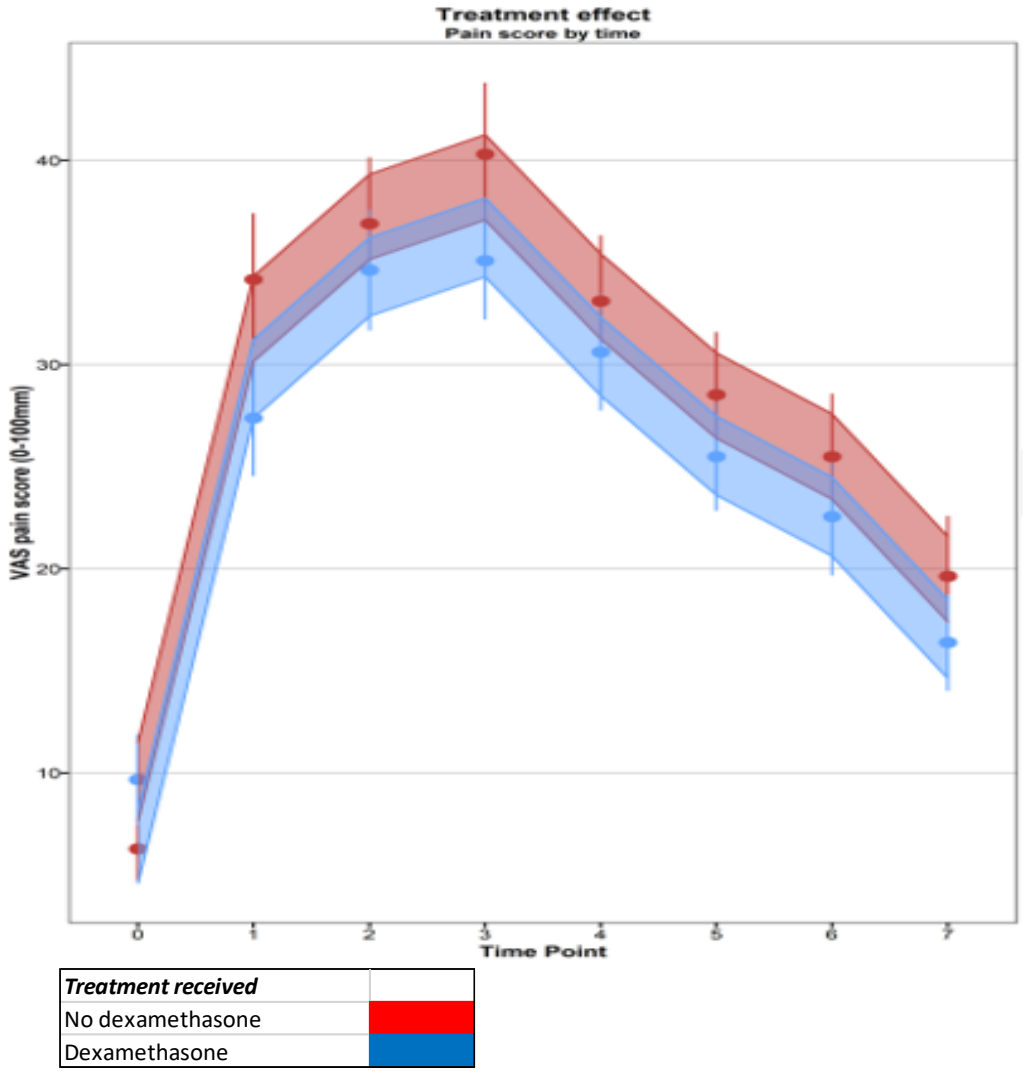
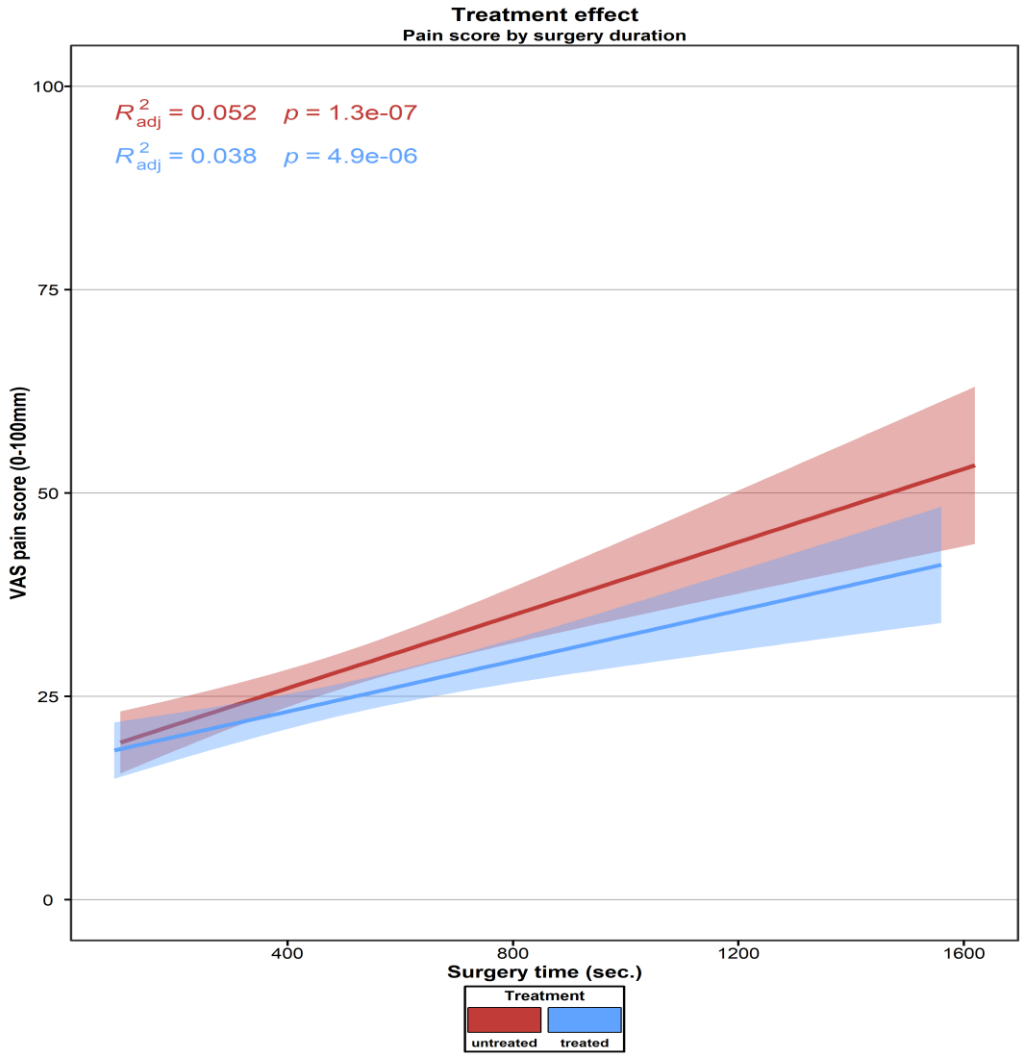


Figure 4.9 illustrates the mean scores as reported on the visual analogue scale for the intervention and control site for seven days following treatment with the 95% confidence interval in shading. Although the graph demonstrates that pain scores in the dexamethasone-receiving sides were consistently lower than that in the control sides, the overlapping confidence intervals highlight that the difference in means between treatment and control is not significant. The whiskers represent the largest values less than or equal to 1.5x IQR, and the centre line represents the median.

4.5.7 The effect of surgery duration on pain reported

The data was analysed to see if there was an association between pain reported and the duration of the surgery for the intervention and control side. Figure 4.10 outlines the VAS score recorded for the intervention (dexamethasone receiving) and control site, alongside the duration of the surgical procedure. We can see there is a positive correlation between increasing surgical duration and pain reported on the VAS, however the overlapping confidence intervals indicate that it does not reach statistical significance.

Figure 4.10 Effect of Surgical Duration on Pain Score



4.5.8 Linear mixed effects modelling

The effect of the treatment (4mg submucosal injection of dexamethasone) was assessed with a mixed-effect linear regression model. The model used participants as the random effect, which was fit to the data following an iterative step-down procedure. The fixed effects included surgery time (seconds), tooth eruption state, and pain diary day. Tooth extraction technique, and impaction type were excluded from the model due to insignificant contributions to the fit ($p > 0.05$). Outliers in the data were treated by applying weights to the model according to pain diary day. The final model demonstrated that the reported pain scale (VAS 0-100mm) decreases moderately and significantly with the treatment (Estimate: -3.32, CI: -5.36 to -1.28, $p < 0.01$, Marginal $R^2 = 0.229$, Conditional $R^2 = 0.526$). It should be noted that although there is a consistent reduction in pain reported at the intervention site, this estimated reduction of pain is estimated to be -3.32 on the visual analogue scale which is a minimal change with doubtful clinical significance.

Table 4.11 Linear mixed-effects model

	value		
Predictors	*Estimates*	*CI*	*p adjusted*
(Intercept)	-21.32	-36.39 – -6.25	**0.006**
Treatment [drug]	-3.32	-5.36 – -1.28	**0.002**
Surgery time	4.93	2.26 – 7.60	**<0.001**
Eruption state	12.58	6.89 – 18.27	**<0.001**
Pain diary day [1]	22.84	18.35 – 27.34	**<0.001**
Pain diary day [2]	27.83	23.37 – 32.29	**<0.001**
Pain diary day [3]	29.76	25.23 – 34.29	**<0.001**
Pain diary day [4]	23.93	19.52 – 28.34	**<0.001**
Pain diary day [5]	19.07	14.81 – 23.33	**<0.001**
Pain diary day [6]	16.09	11.85 – 20.33	**<0.001**
Pain diary day [7]	10.08	5.96 – 14.20	**<0.001**
Random Effects			
σ^2	384.63		
$\tau_{00\ site.ID}$	240.89		
$N_{\ site.ID}$	69		
Observations	1020		
Marginal R^2 / Conditional R^2	0.229 / 0.526		

4.5.9 Patient Satisfaction

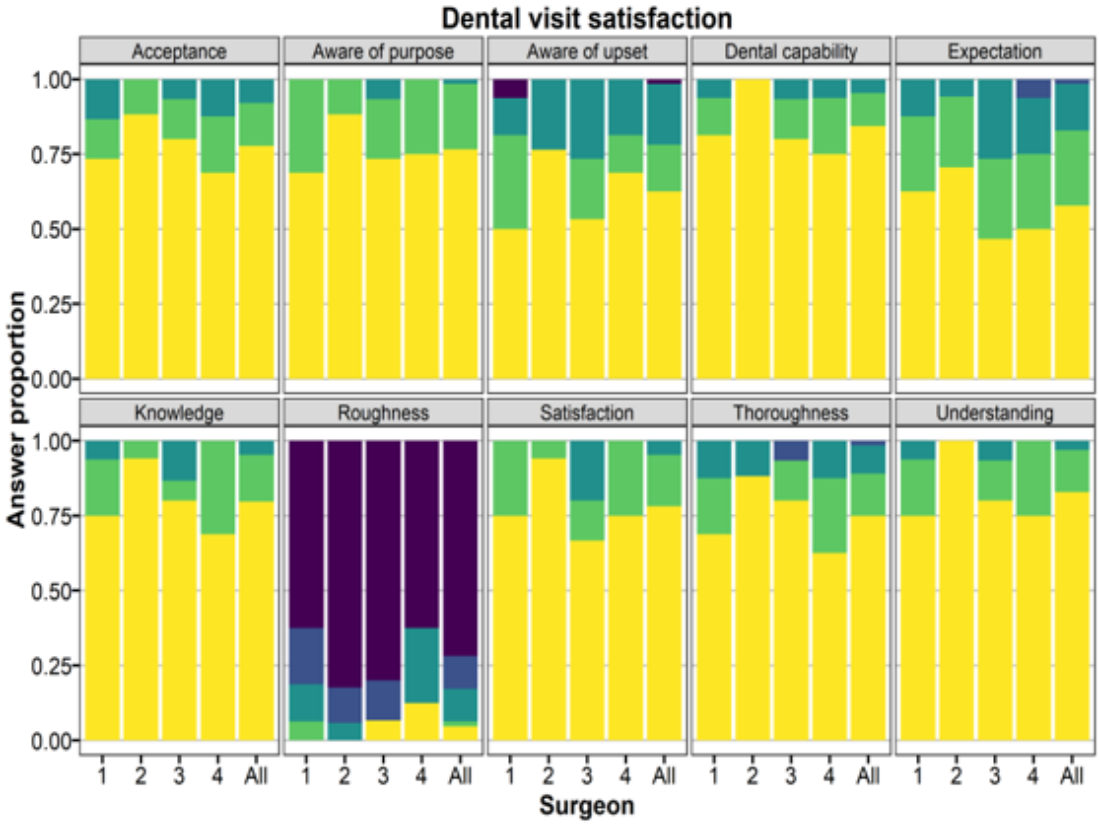
Figure 4.11 illustrates the findings reported in the Dental Visit Satisfaction Scale. 78.12% of participants strongly agreed they were 'satisfied with what the dentist did'. There was no unsatisfied patient following treatment and participation in the study. Over 75% of volunteers either strongly agreed or agreed they felt they knew what to expect in the weeks following surgery. The statement 'The Dentist was too rough when he worked on me' was not directly applicable to our study as the patient was under general anaesthetic while the procedure was being carried out and should have been excluded from the questionnaire. Nevertheless, regardless of the patient being under anaesthetic for the procedure 72% of volunteers strongly disagreed with the statement.

A free comment was left by 51% of respondents on post-operative day 7. Positive comments included expressions of thanks for the theatre staff involved in the patient journey. For example, 'All staff were very helpful and kind, provided excellent care'; 'As very nervous patient I felt at ease'; 'Very pleased with treatment: while I was in pain afterwards, this was expected and I felt the pain killers provided were very good'; 'Staff fantastic, I was really pleased.'

Negative comments were related to the duration of pain and the duration of the recovery period. For example, 'I wasn't aware there would be dead skin left, that was the worst part'; 'Still slight pain, I did not expect it to take so long to recover'. Other study participants left comments which condensed their thoughts on the recovery period or their current status on the road to full recovery. For example; 'No pain on

the left side of my mouth, right tender and slightly throbbing'; 'Right side more swollen and took longer to return to normal' and 'Currently no discomfort on left side, small darting pain lower right'.

Figure 4.11 Bar Chart Representing Dental Visit Satisfaction Scale Response

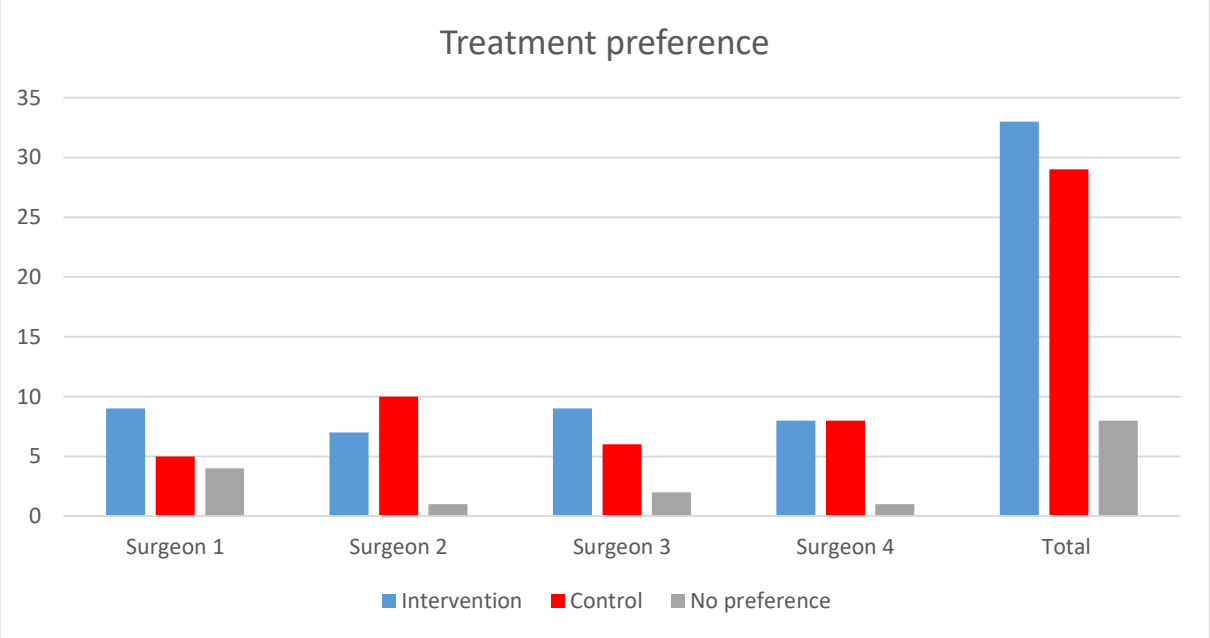


Satisfaction statement response	
Strongly disagree	
Disagree	
Neither agree or disagree	
agree	
Strongly agree	

4.5.10 Patient Preference

On post-operative day 7 patients were asked to indicate their preference of treated side (right or left). The graph below, figure 4.12 shows the distribution of preference indicated for the intervention (dexamethasone receiving) and control side. 11% of participants did not indicate a preferred side. Of those who recorded a preference (59 volunteers), a slight majority (54%) indicated a preference for the dexamethasone receiving side.

Figure 4.12 Bar Chart Indicating Patient Preference of Treatment Site



Chapter 5: Discussion and Conclusion

5.1 Discussion

5.1.1 Study design

We conducted a randomised, controlled, split-mouth trial involving patients undergoing surgical removal of symmetrically impacted lower third molars. A split-mouth trial is a study design in which each participant receives two or more treatment interventions in separate areas of the mouth (167). To be considered a 'split-mouth' trial the treatment can be delivered to separate quadrants, such as in our study, or to separate surfaces of individual teeth or to different dental arches where suitable in other situations. This design concept was first introduced in 1968 by Ramfjord *et al.* while investigating treatments of periodontal pockets (168). To suitably undertake this study design, a number of scientific assumptions need to be met. Specifically, the disease should be uniformly distributed and the effect of the intervention being evaluated should be localized and not 'spill-over' its effects to the comparison site (167). To address these scientific assumptions, our inclusion criteria restricted participants to those with symmetrically impacted mandibular third molars. Furthermore, our intervention under investigation, 4mg of dexamethasone was to be administered as a submucosal injection local to the surgical site. The submucosal nature of the injection retains the medication, localized in the soft tissues surrounding the surgical site, as opposed to a topical or systemic administration of the drug which could disperse around the oral cavity, affecting the control side. For split-mouth trials, randomisation is within the study site as opposed to within the study population. Each volunteer is to receive all intervention

modalities. In order to ensure equal number of participants received our intervention or control on the right or left side of the mouth respectively, we used blocked randomisation in combination with a random number generator to provide our sequence.

Each patient acts as their own control, providing paired samples, thereby greatly controlling background variation and limiting inter-individual variability, such as gender, age, race, smoking status, bone density, personality, dental anxiety, relationship with pain and analgesia. In the literature there is some criticism of split mouth trials surrounding a possible cross-over effect. The concern is that the participant would bring their experience of one procedure to the second procedure, creating an observer bias. This observer bias can be defined as an unconscious distortion of observations as a result of preconceived notions (169). Our study design addressed this potential limitation by having each participant undergo both the control and intervention during one single procedural appointment. In addition to this, all treatment is carried out while the patient is under general anaesthetic thereby ensuring participant blinding of the assigned intervention site.

The investigator, surgeons and participants were blinded to the randomisation sequence by having an independent statistician carrying out this task. The investigator (MC) was blinded to the assigned intervention site by not being present in theatre for the procedure. The randomisation site for each case was contained in an opaque envelope until directly given to the operating surgeon

immediately prior to the procedure, in order to further ensure concealment. These details were discarded following the procedure and the randomisation sequence was held confidentially with the statistician until all the data had been collected and input.

A strength of the split-mouth study design is that it can enhance the statistical power of a study. Due to the paired data samples, a split-mouth study can obtain a more powerful estimate of treatment effect with a smaller sample size. In today's society, where time and financial constraints are substantial, a well-designed split-mouth trial can allow the maximum amount of information be obtained from a trial and from each participant. A further advantage of this study design is that it allows determination of patient preference as each study participant has undergone both modalities.

Limitations of the study-design were minimised. A known limitation of split-mouth trials includes the restrictions on recruitment of participants due to the requirement of symmetrical disease patent. It could be challenged that due to the restriction of recruitment to those with symmetrically impacted mandibular third molars our team could have an effect on the external validity of the trial. As third molar impaction is almost commonplace across many different groups in society we do not see this as a disadvantage in our study (50, 51). In clinical trials where a pathologic process exists, for example caries rate or periodontitis is being investigated, a split-mouth design where participants are limited to those with caries

or severe periodontal disease in two or more quadrants may not have external validity as recruitment criteria is limited to those with high disease prevalence (170, 171).

Our clinical trial engaged four operating surgeons of varying degrees' experience to carry out the surgery. Each surgeon was experienced and registered on the Specialist Register of Oral Surgeons held by the Irish Dental Council for the duration of the trial. Having four surgeons of differing experience represents a strength of the study. A relatively large and varying pool of operators makes the trial outcomes valid and applicable to Specialist Oral Surgeons as a whole community. This is in contrast to a trial which involves one highly experienced or skilled surgeon, in which the findings may lack external validity. The fact that study participants were recruited from the Cork University Dental School, and represent a cohort who had been referred by another dental professional, either their general dentist or orthodontist, somewhat limits the applicability of the results to oral surgeons as opposed to general dentists undertaking third molar removal in community practice.

We based our sample size and power calculation on a study of similar design with the same primary outcome measure (20). Allowing for a potential non-completion rate of 25% a study population of 70 was recruited. Due to the paired samples and reduced variability a sample population of this relatively low size was suitable. An alternative approach to estimating the standard deviation is that was could have run an internal pilot study to calculate a more accurate standard deviation

and required sample size, however due to time and financial constraints along with lack of direct access to an independent statistician this option was not feasible.

Our study was designed to detect a difference in mean VAS score between treatment groups of 10 mm. There is no consensus available as to what mean change in VAS constitutes a clinically meaningful difference for patients undergoing third molar removal (172). One Dutch study investigated what would be a clinically relevant change in VAS following third molar removal; however the study is of low-quality (172). The volunteers were recruited from a population who were already participating in one of three different third molar removal studies. Each participant was undergoing removal of one third molar, however the three trials were incorporating different removal techniques. Furthermore, the state of eruption, classification of impaction or the presence of pathology was not disclosed in this trial, all surgical factors which could have a direct impact on the post-operative pain score reported by the patient. In this Dutch study data was collected with respect to a 100mm VAS three times daily on days 1 -7 inclusive following removal. A Global Perceived Effect scale was completed on day 2 and day 7 following surgery asking participants to provide evaluation of their recovery on a seven-point scale. This trial reported a relative pain reduction of 50% on the VAS or an actual pain reduction of 25mm on the VAS as a meaningful reduction. The GPE scale asks patients to rate on a numerical scale how much their pain has improved or deteriorated over a period of time (173). It is questionable whether this is an appropriate tool for comparing pain following third molar removal. This tool is designed to compare a base-line pain

and comparison with pain scores reported following an intervention. Often those having their third molars removed have no pain immediately pre-operatively and there is significant pain which gradually decreases following surgery. Other tools such as the Minimal Importance Difference (MID) are used in conjunction with the VAS, but again these tools are designed to investigate the change in chronic pain rather than acute surgical pain (174). Prior to commencing further clinical trials investigating pain as a primary outcome measure it would be worth calculating what is a clinically significant reduction in pain for this cohort. We estimated a reduction of 10mm on the visual analogue scale as clinically meaningful. However, a difference of 20mm or greater may provide more impactful findings. It is our opinion that a difference of less than 10mm on the VAS or a change of less than ten percent on any pain reporting tool is unlikely to have a clinically meaningful difference for the patient population.

Our primary method of data collection was via questionnaires. We created a booklet format, incorporating the Pain Diary, Short Form McGill Pain Questionnaire and Dental Visit Satisfaction Scale to ensure ease of completion for the participants in the week following surgery. A booklet format also gives a professional appearance to the questionnaires (175). All questionnaires used simple language, free from medical jargon to allow for varying cognitive ability amongst the participant population. We aimed to keep the number of questionnaires used throughout the study to a minimum to increase responder compliance. Each study participant was given a stamped addressed envelope to encourage return of the questionnaire booklet on completion of the data collection period. Previous studies have found this can increase response rate (176).

Structured pain diaries are commonly used as a tool in clinical practice across a range of specialities to track a patient's symptoms. Human recall of past events has its limitations, even more so when trying to recall previous symptoms while sitting in a clinician's surgery. Pain diaries are a clinician's solution toward capturing accurate data from patients reporting in real-time rather than relying on recall at a review or follow-up appointment (177, 178). However, it has been shown that pain dairies actually increase patient perception of symptom severity (179). In a study investigating patients' recovery following acute lumbar back pain in which two groups of patients were followed, one group were required to complete a pain diary, the other were not. Commencing the study both groups had similar recall of symptoms, however following completion of a pain diary that group had symptom amplification at subsequent follow-up (179). Another study by the same group found that the use of a pain diary actually slowed the recovery in patients' suffering from whiplash injury (180). Pain diaries can act as an aid to facilitate communication between the patient and clinician. In this clinical trial, a pain diary was used to capture the pain intensity at two different sites in the same patient. Any amplification of symptoms, for example due to pre-existing pain catastrophising tendencies, would be mirrored for both the right and left surgical sites. As our outcome measurement was a difference between two sites in a paired sample, rather than an overall pain score, any symptom amplification should be reflected in pain scores at both surgical sites. For this purpose of recording a difference in pain over two sites within on patient, the pain diary is a suitable and appropriate tool to allow real-time reporting of experience by the patient.

5.1.2 Study Population Characteristics

Seventy patients were enrolled in the study. The age range of the participants was 16 to 54 years of age, with the mean age being 22 years. This is in keeping with other studies involving third molar removal (16, 181). The age range in our study and others reflect the age when mandibular third molars erupt and have the potential to cause problems for the patient. Thirty-three of the seventy cases included in our study involved third molars that were classified by the surgeon as unerupted. In our department, patients listed to undergo orthognathic surgery routinely have unerupted mandibular third molars removed, if present, 6-12 months prior to the bilateral sagittal split osteotomy. This would account for the large proportion of study participants having unerupted, asymptomatic third molars removed.

Our inclusion criteria limited study participants to those that were fit and healthy, with only those classified as ASA1 or ASA2 included. Non-smokers accounted for 83% of participants. These restrictions on study subjects may make the findings less applicable to the general population. However, examining the data reported by the Central Statistics Office we see a prevalence of 17% of the population over 15 years of age are smokers. This data corresponds well with our study population (182). Forty-four of the 70 participants were female. Males and females have been shown to have differing pain thresholds and levels of pain tolerance (183). Females are known to be more likely to seek treatment for medical issues than their male counterparts and our study population is reflective of this (183). As we undertook a split-mouth study design, each patient reported on both the intervention and control site providing matched pairs of data. As we were looking for a difference in pain

reported within each individual participant, the confounding factors that may have been present if we were comparing VAS scores between participants is removed. With this study design we did not require equal number of male and female participants.

Our study used validated tools in the form of the Hospital Anxiety and Depression Scale and the Pain Catastrophising Scale in order to gather a baseline overview of the psychological variables of participants included in our study population (138, 184). Non-surgical factors have been shown to impact on the pain reportedly experienced by the patient (185). The paired samples investigated in a split-mouth study such as ours negates many of these non-surgical factors by design. With each participant reporting on both the intervention and control, combined with the analysis focusing on the difference between these paired samples the inter-participant variability has less impact on the final study outcomes. Nonetheless, these questionnaires may provide useful data beyond patient demographic details. Our volunteer cohort was found largely to be a non-anxious, non-distressed population. These questionnaire scores are helpful to have to investigate if they have impact on the pain reported on the visual analogue scale. Our post-hoc linear effects model found the results from the Pain Catastrophising Scale and the Hospital Anxiety and Depression Scale did not have an impact on pain reported by the individuals in our study population. The level of potential anxiety, depression and catastrophising amongst our volunteers was relatively evenly distributed between the four operating surgeon groups. Treatment may be carried out under general anaesthetic for a number of reasons including some clinician-orientated factors such as the difficulty

of the procedure and some patient-orientated factors such as anxiety. Fear of the dentist is one of the most commonly reported fears (186). The reason for this anxiety is usually multi-factorial but can be contributed to by previous personal experience, experiences of family and friends or a more general anxiety trait of an individual (187). Within our study population we identified 25% of participants of being either a borderline or probable case of anxiety. This is not unexpected when dental fear is so common, estimated at 36% of the general population in the United Kingdom, combined with the surgical nature of third molar removal giving rise to greater anxiety or fear than something less daunting such as a dental check-up (188). Through the use of pre-operative questionnaires in our study population we identified a moderate positive association found between the scores reported in the Pain Catastrophising Scale and the pain reported on the Visual Analogue Scale. In the post-hoc linear effect model, the score derived from the Pain Catastrophising Scale did not affect the outcome in the step-down process so it was not included in the final model. We identified no significant correlation between the pre-operative Hospital Anxiety or Depression Scores and reported pain in our study population.

5.1.3 Surgical Assessment

There were almost equal numbers of patients requiring the removal of unerupted (46%) and partially erupted (54%) lower third molars within our study population. These cases were listed for the surgeons in order of placement on the general anaesthetic waiting list at Cork University Dental School. Surgeon 3 and Surgeon 4 had a greater proportion of unerupted third molar cases, with Surgeons 1 and 2 having a greater proportion of partially-erupted cases. As the speed of surgery, or

patient outcomes of the surgeon as individuals, were not being investigated this is not seen as having an impact on our primary outcome measurement of pain. However, we did note a moderate association between the state of eruption of the impacted third molar and pain scores reported in each case. This association was supported by its influence on the post-hoc linear effects model (estimates 12.58, CI 6.89 – 18.27, P <0.001).

All cases invited to participate and subsequently enrolled in the study were assessed radiographically by a single investigator (MC) and deemed to have symmetrically erupted and impacted mandibular third molars. Symmetry is a crucial aspect in our study-design in order to minimise any anatomical reason for different levels of pain to be experienced at either surgical site except for the intervention. Due to waiting times, there can sometimes be months between placement on a treatment waiting list and the treatment being undertaken. In some cases, the state of eruption at one site may have changed from what is observed on the radiograph. Pre-operatively a single investigator (MC) was able to assess easily if there was a difference in state of eruption intra-orally by simply looking in the patient's mouth. If one tooth was visible and the other not, the subject was no longer eligible for inclusion in the trial. The type of impaction is not as easily assessed in this way by the investigator prior to surgery, so there is greater reliance on the relevant radiograph. For example, in some cases radiographic assessment has identified symmetrical impaction and due to factors such as time, pathology, loss of adjacent teeth the classification may have progress and changed. Alternatively, when assessed from a

different perspective, such as intra-orally during removal, a tooth radiographically assessed as vertically impacted could now be classified as distoangular. This could be due to the positioning of the patient for the radiograph, the angulation of the x-ray beam or further growth of the patient or through assessor variability. There was excellent agreement observed between Surgeon 1, Surgeon 2 and the investigator with 100% of cases classified as symmetrically impacted. Surgeon 3 and Surgeon 4 each reported a single case involving asymmetrically impacted third molars for removal. These high levels of agreement between the operating surgeons and the investigator support the internal validity of the study with respect to the inclusion criterion.

A variety of surgical techniques was employed by each surgeon in the course of the trial. Technique used is determined by the type of impaction of the tooth in combination with operator preference. Surgeon 1 was the only operator to utilize the 'Hammer and Osteotome' as a technique. When previously compared to other techniques the hammer and osteotome was found to have a shorter healing period (78). Regardless of the technique employed it is operator experience that has been demonstrated to impact on patient-reported pain experienced in the recovery period (79, 80).

There have been many attempts at creating a valid tool for predicting the difficulty of the extraction such as Macgregor's 'WHARFE' assessment tool, Winter's lines, and the Pell and Gregory classification (53, 54, 189). These tools base their

estimate exclusively on radiographic variables. None have been found to be widely validated or accepted as an accurate predictor. Tools that rely completely on radiographic assessment do not take into consideration factors that may not be visible on the radiograph. Research published more recently suggests that difficulty cannot be predicted pre-operatively but only intra-operatively (190). Immediately following the procedure, the surgeon recorded if the removal was 'Routine', 'Complex' or 'Highly complex'. The choice of classification of difficulty was entirely at the discretion of the treating surgeon. The aim of recording this surgeon-reported outcome was to provide a possible explanation to any outliers in the pain score data; however, none of the four surgeons reported any of the 140 individual cases of third molar removal as 'Highly Complex'.

The use of patient-centred outcome measures in medicine and surgery has been substantially increasing over the past number of decades (191-193). Patient-reported outcomes offer valuable information on the effects of an illness or intervention as perceived by the patient. There is a growing body of evidence reporting that oral disorders or conditions can have a significant impact on an individual's physical, mental and social well-being (194). The short version Oral Health Impact Profile has been shown to be a practical and valid tool in an oral surgery setting (195). In this trial, volunteers were asked to complete the OHIP-14 questionnaire pre-operatively in order to measure the impact the presence of third molars had on the patients' quality of life. The fourteen questions can be divided into seven subscales; including functional limitation, physical pain, physical disability and

social disability. Patients are required rate each statement on a Likert-type scale and a summary or weighted score can be calculated. In our study many of the participants had never experienced pain with respect to their third molars, which is not typical of a cohort imminently undergoing removal. Almost half of participants (47%), were having the teeth removed in advance of orthognathic surgery. With this knowledge one might speculate that the OHIP scores from these participants would be significantly lower than those who were having their teeth removed due to pathology, however this was not found to be the case in our cohort. All study participants scored virtually the same summary score on the OHIP-14 questionnaire. Those individuals with unerupted, pathology and problem-free third molars, may have been undergoing extensive orthodontic intervention resulting in them scoring highly in the psychological and physical disability domains: 'Have you ever felt self-conscious about your teeth?'; 'Have you ever had to interrupt meals because of your teeth?' or 'Have you found it uncomfortable to eat any food because of problems with your teeth?' The instructions given to the study participants should have been more explicit regarding focusing on the impact of the third molars alone on oral health alone. A further limitation of the study is that the OHIP-14 questionnaire was only completed by participants on one occasion, pre-operatively. It may have added significant value if it had been repeated at a date post–operatively to establish if there had been an improvement in perceived oral health. It must be acknowledged that this questionnaire was originally intended to assess the long-term effects on oral health related quality of life and may not be the ideal tool for assessing the effects of acute surgical intervention.

5.1.4 Intervention

Due to its safety-profile, low-cost, half-life and potency, dexamethasone has been described as an ideal corticosteroid (196). In our study we investigated an intervention of 4mg dexamethasone delivered as a 1ml submucosal injection buccal to the surgical site. Other potential routes of administration include oral, intravenous, intramuscular and oral. We focused our trial on the submucosal route as we wanted to avoid any potential systemic side-effects associated with oral or intravenous corticosteroids. Furthermore, for oral surgeons or dental practitioners, administration as a submucosal injection would be considered a safe and easy route as they are comfortable with intra-oral injections. With a submucosal injection administered buccal to the surgical site, the surgeon can target the delivery of the corticosteroid to a specified location.

Our study is consistent with others that report there is a direct association between duration of surgery and post-operative pain reported (197). Our post-hoc analysis comparing the dexamethasone receiving intervention site versus the control found some evidence that submucosal dexamethasone had a greater beneficial effect on the surgeries of longer duration although this did not reach statistical significance (Figure 4.10). Furthermore, the reduction in pain reported is estimated at 4.93mm on the visual analogue scale with a 95% confidence interval range of 2.26–7.60, which does not represent a clinically meaningful difference.

5.1.5 Post-operative complications

With respect to post-operative complications, a potential limitation of the study design is that the investigator did not review the patient and the surgical site in person following treatment. As such, we do not have an accurate or reliable measurement of the rate of post-operative complication such as dry socket or infection. Following the removal of third molars there is a wide ranging reported incidence dry-socket following treatment (198). Other more serious post-operative complications include temporary or permanent paraesthesia in the distribution of the inferior dental or lingual nerve (199). Indirectly, through our structured pain diary, we can estimate the incidence of complication using the question 'did you see a dentist for complications associated with your surgery today?'. Our pain diary records that a dentist was contacted on 13 occasions by our study population in the week following surgery. We are using this figure as a proxy to estimate a complication rate amongst our volunteers, however this is a flawed method of assessing complications. This figure presumes the assessing dentist confirmed a complication for each attending patient. Furthermore, the number calculated could account for the same patient returning to the dentist on multiple occasions. Ideally, each patient would have returned to the single investigator (MC) or a dedicated, suitably-qualified research assistant for review of any potential complications or post-operative concerns. Due to patient factors such as the distance required to travel and lack of funding for a research assistant this was not possible.

Through our Dental Visit Satisfaction Scale, we established that patients reported high levels of satisfaction following treatment. However, it must be noted

that we may have been able to improve on the psychological preparation of the patients. Approximately 20% of patients disagreed with the statement 'I have a good idea what to expect in the next few weeks'. Studies have demonstrated the importance of communication and explanation of the post-operative recovery period is associated with greater levels of patient satisfaction (200).

5.1.6 Patient Preference

On day 7 following surgery we asked the patients which treatment site they preferred. A very slight majority of respondents (33 patients) indicated preference towards the intervention side. The control side was preferred by 29 patients. Any intervention should have a benefit to the patient. The reasoning behind our study and the addition of a submucosal injection of dexamethasone to the protocol of surgical removal of impacted third molars is to reduce the pain experienced by the patient. This narrow margin of preference between the intervention and control sites indicates that the marginal difference in pain outcome was not clinically meaningful to the patient, further supporting the statistical comparisons of the VAS pain scores between intervention and control, where no sizeable difference in pain score was apparent.

5.1.7 Implications for practice

This study has shown a consistent, but very marginal reduction in pain reported at the dexamethasone-receiving site compared to the control site. Following regression analysis, the estimated mean reduction seen was -3.34mm on the 100mm visual

analogue scale. A reduction of this size does not indicate any meaningful clinical value. As a result, I would not change my current surgical protocol based on these results alone and would not advocate for the routine use of submucosal dexamethasone injections in the extraction of impacted third molars. In certain clinical scenarios, such as third molar surgery of long duration (15 minutes or greater), there is a greater reduction in pain reported at the intervention site by the patient and this may justify the intervention. We propose that each surgical site would be assessed independently by the treating clinician. Due to the drug administration close to the surgical site, low dosage of drug required for effect and low systemic absorption of the drug it is reasonable to recommend bilateral administration of submucosal dexamethasone if the clinical scenario required it. However, further research tasked specifically at answering this question is required before it can be recommended definitively.

5.2 Conclusion

Currently, due to the low quality research available, the medical literature reports mixed outcomes in the administration of submucosal dexamethasone for analgesic improvement in the extraction of impacted, third molar teeth. Our goal, through conduction of a randomised, double-blind, controlled trial using a split-mouth study design, was to determine whether there is patient benefit and greater analgesic effect when submucosal dexamethasone is administered prior to the extraction of impacted third molars. The null hypothesis states there is no difference in post-operative pain following surgical removal of lower third molars when a submucosal injection of 4mg dexamethasone is administered in the buccal vestibule pre-operatively. Consistently across days 1 to 7 post-operatively, this trial demonstrated a minor improvement in analgesic effect when submucosal dexamethasone was administered in comparison to control, supporting the alternative hypothesis. However, it must be considered the effect size detected was minimal (estimated 3% improvement) and not clinically meaningful for patients. Therefore, the routine use of submucosal dexamethasone injection in the extraction of impacted third molars should not be recommended. Post-hoc analysis suggested that for prolonged duration of extraction (>15 minutes), a greater analgesic effect may be seen with submucosal dexamethasone treatment. However, further, targeted studies are required to investigate this.

The secondary aim of the trial was to determine patients' post-operative preference and satisfaction with regard to a submucosal injection of dexamethasone

versus local anaesthetic alone during lower third molar extraction. Each patient was asked to indicate their preferred side of treatment on day 7 post-op. Of those who responded only a narrow majority of 54% indicated preference for the intervention receiving side. The lack of concordance between the patients preferred side of treatment and the side receiving dexamethasone casts further doubt on the utility or benefit of this treatment for removal of impacted third molars.

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Appendices

Appendix I

COISTE EITICE UM THAIGHDE CLINICIUIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

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:mail: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (b) 18/06/19

Date: 11th June 2019

Dr Catherine Gallagher
Specialist in Oral Surgery
Cork University Dental Hospital
Wilton
Cork

Study Title: Evaluation of the effect of submucosal dexamethasone injection in patients undergoing third molar removal in terms of pain experienced and impact on quality of life, a randomized control trial.

Approval is granted to carry out the above study at:

Cork University Dental School and Hospital.

The following documents have been approved:

Document	Approved	Version	Date
Cover Letter	Yes		5th May 2019
Application Form	Yes		14th May 2019
CV for Chief Investigator	Yes		
Evidence of Insurance	Yes		
Study Protocol	Yes		
Participant Information Leaflet	Yes		
Consent Form	Yes		
Study Questionnaire/Survey	Yes		

We note that the co-investigator(s) involved in this project will be:

Name	Occupation
Professor Duncan Sleeman	Consultant Oral and Maxillo-facial Surgeon
Dr Paul Brady	Consultant in Sedation
Dr Caroline McCarthy	Specialist in Oral Surgery
Dr Miriam Crowley	Specialist Registrar in Oral Surgery

Please note that the above study must be carried out in accordance with GDPR 2018 and clearance must be obtained from the Health Research Consent Declaration Committee if applicable. Information is available on the following link http://www.hrcdc.ie/

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)

2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study

3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.

4. Notify CREC of discontinuation of the study

5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix II

Consent for participation in research study

AGREEMENT

The research project and the procedures associated with it have been fully explained to me. I have had the opportunity to ask questions concerning all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at University Dental School and Hospital, Cork. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the Chief Investigator listed above. I understand that the study has been approved by the Cork Research Ethics Committee of the Cork Teaching Hospitals (CREC) and if I have further queries concerning my rights in connection with the research, I can contact CREC at Lancaster Hall, 6 Little Hanover Street, Cork, 021 4901901.

Please circle yes or no for the questions that follow:

I have read and understand the study: Yes / No

I agree to participate in this research: Yes / No

I grant permission for the data collected to be used in this research only: Yes / No

I understand that my anonymised data will be stored at University Dental School and Hospital, Cork for seven years: Yes / No

Chief Investigator Signature: _____

Signature of Study Participant: _____

Witness Signature (if applicable): _____

Date: _____

Appendix III

PATIENT INFORMATION SHEET FOR RESEARCH STUDY

Patient Name: _____

Study Title:

Evaluation of the effect of submucosal dexamethasone injection in patients undergoing third molar removal in terms of pain experienced and impact on quality of life, a randomised control trial.

Name of Chief Investigator: Dr Catherine Gallagher

Contact Number for Chief Investigator: 021 4901170

You are being asked to participate in a research study. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study. The Chief Investigator will also discuss the study with you in detail. When you are sure you understand the study and what will be expected of you, you will be asked to sign this form if you wish to participate.

Nature and Duration of the procedure: The aim of this research is to look at the effect of a localized steroid injection around the area the tooth had been removed. Specifically, does this improve quality of life in the recovery period for you as the patient. All other aspects of your treatment will be standard procedure. You will receive local anaesthetic on both sides of your mouth that lasts on average 2-3 hours. One side will receive an additional injection of a steroid, dexamethasone. Some pain is expected after wisdom tooth extraction despite being numb. We want to look at how satisfied you are following your extraction and if there is a difference in pain at either extraction site. You will be required to fill out a pain diary and questionnaire once daily for 1 week following surgery. A stamped addressed envelope will be provided for ease of returning the questionnaires to us. There will be no additional appointments required.
The surgery will be carried out by an experienced Oral surgeon. A single experienced oral surgeon will carry out both the right and left extraction.

Potential Risks and Benefits: There are no additional risks associated with taking part in this study, other than those already associated with wisdom tooth removal.

Possible alternatives: Your participation is entirely. Whether you agree to take part or not will not affect your treatment in any way.

Appendix IV

Hospital Anxiety and Depression Scale

NAME: **PATIENT NO.:**
Date: **PATIENT REF:**

Tick (√) the box of the answer that is most appropriate to you:

	Yes definitely	Yes sometimes	No, not much	No, not at all
1. I wake early then sleep badly for the rest of the night				
2. I get very frightened or have panic feelings for apparently no reason at all				
3. I feel miserable and sad				
4. I feel anxious when I go out of the house on my own				
5. I have lost interest in things				
6. I get palpitations, or sensations of "butterflies" in my stomach or chest				
7. I have a good appetite				
8. I feel scared or frightened				
9. I feel life is not worth living				
10. I still enjoy the things I used to				
11. I am restless and can't keep still				
12. I am more irritable than usual				
13. I feel as if I have slowed down				
14. Worrying thoughts constantly go through my mind				

Appendix V

PAIN CATASTROPHISING SCALE

Name: Patient CDS:
Date: Patient Ref:

Everyone experiences painful situations at some point in their lives. We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain.

Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0= not at all **1**=to a slight degree **2**=to a moderate degree **3**=to a great degree **4**=all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

Appendix VI

Oral Health Impact Profile – 14

NAME: **PATIENT NO.:**

Date: **PATIENT REF:**

Tick (V) the box of the answer that is most appropriate to you:

	Never	Sometimes	Often	Always
1. Have you had trouble pronouncing any words because of problems with your teeth and mouth?				
2. Have you felt that your sense of taste has worsened because of problems with your teeth and mouth?				
3. Have you had painful aching in your mouth?				
4. Have you found it uncomfortable to eat any foods because of problems with your teeth and mouth?				
5. Have you been self-conscious because of your teeth or mouth?				
6. Have you felt tense because of problems with your teeth or mouth?				
7. Has your diet been unsatisfactory because of problems with your teeth or mouth?				
8. Have you had to interrupt meals because of problems with your teeth or mouth?				
9. Have you found it difficult to relax because of problems with your teeth and mouth?				
10. Have you been a bit embarrassed because of problems with your teeth and mouth?				
11. Have you been a bit irritable with other people because of problems with your teeth and mouth?				
12. Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?				
13. Have you felt that life, in general, was less satisfying because of problems with your teeth or mouth?				
14. Have you been totally unable to function because of problems with your teeth or mouth?				

Appendix VII

Clinical Trial of Submucosal Dexamethasone Injection in Patients Undergoing Extraction of Bilateral Impacted Wisdom Teeth

Surgical Questionnaire

Date_____

Patient study number:

Surgeon's Name:

Patient Name:
Hospital Number:
Date of birth:
Male or female:

Surgical Information for Lower Right (Quadrant 4)

Duration of Procedure: ___:___mm: ss

State of eruption LR8 ***(Please circle ONE response)***

1. Erupted
2. Partially erupted
3. Unerupted

Extraction technique ***(please circle ONE response)***

1. Bone removal, tooth division and elevation
2. Bone removal and elevation
3. Elevation only

How would you describe the impaction?

Was it? (please circle ONE response)

1. Mesio-angular
2. Disto-angular
3. Horizontal
4. Vertical

How would you describe the extraction,

was it? (*please circle response*)

1. Routine
2. Complex
3. Highly complex

Surgical Information for Lower Left (Quadrant 3)

Duration of Procedure: __:___ mm: ss

State of eruption LL8 ***(Please circle one response)***

1. Erupted
2. Partially erupted
3. Unerupted

Extraction technique ***(please circle ONE response)***

1. Bone removal, tooth division and elevation
2. Bone removal and elevation
3. Elevation only

How would you describe the Impaction?

Was it? (please *circle ONE response)*

1. Mesio-angular
2. Disto-angular
3. Horizontal
4. Vertical

How would you describe the extraction,

was it? (*please circle response*)

1. Routine
2. Complex
3. Highly Complex

Additional notes (if required):

_____

Appendix VIII

Short Form McGill Pain Questionnaire

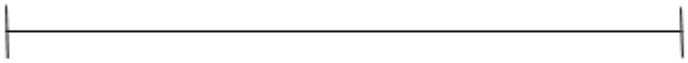
PATIENT NAME: _____ **DATE:** _____

PATIENT REF: _____ **PT NO.:** _____

Please tick (V) the circle for the amount of pain you are experiencing in relation to your mouth

	None	Mild	Moderate	Severe
Throbbing	○	○	○	○
Shooting	○	○	○	○
Stabbing	○	○	○	○
Sharp	○	○	○	○
Cramping	○	○	○	○
Gnawing	○	○	○	○
Hot-burning	○	○	○	○
Aching	○	○	○	○
Heavy	○	○	○	○
Tender	○	○	○	○
Splitting	○	○	○	○
Exhausting	○	○	○	○
Sickening	○	○	○	○
Fearful	○	○	○	○
Punishing	○	○	○	○

Please indicate present pain intensity:



No Pain Worst possible pain

Present pain intensity; *Please tick one*:

0. None___
1. Mild____
2. Discomforting___
3. Distressing___
4. Horrible___
5. Excruciating___

Appendix IX

Pain Diary

1. Did you have pain that you associate with your dental surgery today? (please tick)

   Yes □ No □

2. Did pain associated with your dental surgery affect what you could or could not do today?

   Yes □ No □

If yes, in what way? _____

3. Did pain associated with your dental surgery affect your speech today?

   Yes □ No □

4. Did pain associated with your dental surgery affect your diet today?

   Yes □ No □

5. Did you take painkillers today, to treat pain from your dental surgery?

Paracetamol ___ Tablets

Keral ___ Tablets

Oxynorm ___ Tablets

6. Did you need to see a dentist today for complications associated with the surgery?

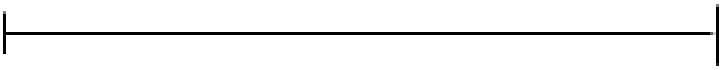
   Yes □ No □

7. Indicate how bad your pain is on the LEFT side of your mouth

0
No Pain

10
Worst possible pain

8. Indicate how bad your pain is on the RIGHT side of your mouth



0
No Pain

10
Worst possible pain

Appendix X

DENTAL VISIT SATISFACTION SCALE

NAME: **PATIENT NO.:**

PATIENT REF: **DATE:**

Please circle the most appropriate score for the statements below, using the following scale;

1- **Strongly disagree**
2- **Disagree**
3- **Neither agree or disagree**
4- **Agree**
5- **Strongly agree**

1. After talking with the dentist, I know what the purpose of my procedure is.

   1 2 3 4 5

2. After talking with the dentist, I have a good idea what to expect in the next few weeks.

   1 2 3 4 5

3. The dentist told me all I wanted to know about the procedure.

   1 2 3 4 5

4. I felt understood by the dentist.

   1 2 3 4 5

5. I felt that the dentist really knew how upset I was about the possibility of pain.

   1 2 3 4 5

6. I felt the dentist accepted me as a person.

   1 2 3 4 5

7. The dentist was thorough in doing the procedure.

   1 2 3 4 5

8. The dentist was too rough when he worked on me.

   1 2 3 4 5

9. I was satisfied with what the dentist did.

   1 2 3 4 5

10. The dentist seemed to know what he was doing during my visit.

    1 2 3 4 5

11. Thinking back at having your wisdom teeth removed, do you have a preference to the treatment you received?

    Right side□ OR Left side □ (Please √)

12. Please indicate any further comments on matters associated with your procedure in the box below.