The efficacy of Horizontal- Platelet Rich Fibrin (H-PRF) compared to Alveogyl in the treatment of alveolar osteitis: a randomised controlled trial

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Table of Contents

Declaration

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Maeve Cooney

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Abstract

Objectives:

To investigate the efficacy of treating alveolar osteitis with an autologous blood product, Horizontal Platelet Rich Fibrin (H-PRF) compared to Alveogyl, a conventional intra-alveolar dressing.

Materials and Methods:

Ethical approval to conduct this prospective, double-blind randomised controlled trial (RCT) was granted by the Joint Research and Ethics Committee (SJH/TUH). Thirty-eight patients presenting with alveolar osteitis following tooth extraction were recruited to participate. A blood sample was obtained immediately pre-operatively (T0) for all participants irrespective of study arm allocation, and H-PRF was prepared following published product protocol. Patients allocated to the treatment arm received H-PRF clot in the extraction socket whereas those allocated to the control arm received Alveogyl. Standardised surgical and analgesia protocols were followed for both study arms.

All patients received a virtual review by telephone on day three following intervention (T1) and were asked to return to the clinic for review, seven days following intervention when a second blinded assessor evaluated healing outcomes (T2). Patients kept a diary of their pain levels, analgesia consumption and changes in oral health related quality of life at three timepoints (T0, T1 and T2).

Primary outcome measure was Visual Analogue Scale (VAS) pain score data. Secondary outcome measures included analgesia use, socket healing and health related quality of life parameters (HRQoL) in the early postoperative period. Statistical analysis was performed using IBM SPSS ®29.0 software. Categorical variables were analysed using the Chi square test. The non-parametric Mann Whitney U test was used to analyse VAS pain scores and healing measurements. Median, interquartile range, effect size and p-values for appropriate tests of comparison between treatment groups were reported for HRQoL parameters.

Results:

The mean age of participants was 39.5 (21-78 range, 12.9 SD) with females accounting for 51.4% of the study sample. VAS scores were significantly lower for worst pain score at T1 (Z=2.49, (p= 0.011) and T2 (Z=2.76, p=0.006) in the H-PRF group following intervention in the absence of significant difference in pain scores between groups at baseline (T0, p=0.294). Significantly more Paracetamol was consumed by patients in the Alveogyl group at T1 (Z= 2.81, p=0.007) and T2 (Z=2.47, p=0.026). Socket healing, graded using a modified Landry healing index demonstrated clinically significant improved healing in patients treated with H-PRF at T2 (Z= 3.04, p=0.003). No significant differences were observed in the HRQoL subscales between groups overall, except for “sleep” being reported as improved at T1 in the H-PRF group (Z=0.71, p=0.029).

Conclusion:

The study concludes that there is a significant difference in the early alleviation of pain and improved healing outcomes where patients with alveolar osteitis are treated with H-PRF as opposed to Alveogyl. The difference in oral health related quality of life parameters was not significant for either group. This study has implications for clinicians deciding on how best to manage their patients with alveolar osteitis and suggests that the use of H-PRF is safe and could be considered as an alternative to current standard(s) of care in the management of alveolar osteitis.

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Finally thank you to my husband, Dáithí and my parents, Johanna and Denis, whose constant support and encouragement brought me through the more mundane days in the completion of this thesis while also being heavily pregnant. Your eternal belief in me pursuing my ambitions means the world to me!

Index of Tables

Index of Figures

Terms and Abbreviations

AO	Alveolar Osteitis
APC	Autologous Platelet Concentrates
CI	Confidence Interval
CHX	Chlorhexidine
DDUH	Dublin Dental University Hospital
DNA	Deoxyribonucleic Acid
GBR	Guided Bone Regeneration
GF	Growth Factor
HRQoL	Health Related Quality of Life
LLLT	Low Level Laser Therapy
MRONJ	Medication Related Osteonecrosis of the Jaws
NNT	Number Needed to Treat
NSAID	Non- Steroidal Anti-Inflammatory Drug
OCP	Oral Contraceptive Pill
PCR	Polymerase Chain Reaction
PHBA	Para-Hydroxybenzoic Acid
PRGF	Plasma Rich in Growth Factors
PRF	Platelet Rich Fibrin
PRP	Platelet Rich Plasma
RBC	Red Blood Cell
RCF	Relative Centrifugal Forces
RNA	Ribonucleic Acid
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organisation
ZOE	Zinc Oxide Eugenol

CHAPTER ONE

INTRODUCTION

1. Introduction

Alveolar osteitis (AO) remains one of the most common postoperative complications following the extraction of permanent teeth. It is referred to by the generic lay term “dry socket” and is known to result in severe postoperative pain, a decrease in quality of life and repeated dental visits (Noroozi and Philbert 2009). Despite a wide array of reported data available on all aspects of AO prevention and management, there remains no current evidence-based consensus or best practice guidelines for the condition. This likely reflects a lack of understanding of both the aetiology and pathophysiology of AO.

Enhancement of wound healing has been a concept applied across numerous surgical specialities for over thirty years. Platelet concentrates have evolved as highly biocompatible, autologous additives and their use in the context of third molar surgery was acknowledged in the 2020 Cochrane Review (Bailey et al., 2020). This process facilitates the development of an optimised blood clot, which can be applied to any wound site to optimise healing and promote tissue regeneration.

Application of platelet concentrates has since been explored in the context of alveolar osteitis prevention and management. The literature review provides a comprehensive review of alveolar osteitis along with a thorough analysis of the evolution of autologous platelet concentrates (APCs) currently available on the

market. Various treatment modalities used in the management of established alveolar osteitis are explored in detail. The review then looks at outcome measures, including both patient reported outcomes such as pain and quality of life parameters and clinician reported healing evaluation.

This trial aims to explore the efficacy of the most recently generated autologous platelet concentrate, Horizontal-Platelet Rich Fibrin (H-PRF), compared to the current standard of care, a medicated dressing known as Alveogyl. We hypothesise that the autologous concentrate, H-PRF will expedite the resolution of pain and show improved healing and quality of life outcomes compared to Alveogyl, a conventional sedative dressing.

CHAPTER TWO

LITERATURE REVIEW

2. Literature Review

2.1 Alveolar Osteitis

2.1.1 Nomenclature & Definition

Alveolar osteitis, often referred to colloquially as “dry socket” is one of the most commonly seen complications following tooth extraction. The term dry socket was originally coined by Crawford in 1896 and remains widely used in the literature today (Crawford 1896).

A variety of other terms have been used to describe the same condition including localised osteitis (Rutledge, 1984), postoperative alveolitis (Blondeau and Daniel, 2007), postextraction osteomyelitis syndrome (Alling, 1959), alveolalgia (Bjercke 1960) , septic socket (Goldman et al., 1973), alveolitis sicca dolorosa (Gersel-Pedersen, 1979) and fibrinolytic alveolitis (Birn, 1973). This heterogeneity in descriptive definitions across the literature ultimately leads to an inconsistency in diagnostic criteria and limits the ability to directly compare research. Furthermore, it likely reflects a lack of consensus on the pathophysiology of AO.

In 2002, Blum proposed a standardised definition for AO, which will be adopted throughout this thesis as diagnostic criteria: “*postoperative pain in and around the extraction site, which increases in severity at any time between one and three days after the extraction accompanied by a partially*

or totally disintegrated blood clot within the alveolar socket with or without halitosis" (Blum, 2002)..

2.1.2 Incidence of Alveolar Osteitis

The estimated incidence of AO (AO) varies from 1-5% for routine extractions, with an increase seen in third molar extractions of up to 38% (Blum, 2002; Bowe, Rogers, and Stassen 2011; Schow 1974). This wide range in reported incidence may result from the differences in diagnostic criteria, and methods of assessment as well as the large variation in individual pain thresholds across the population.

Some well executed studies report the incidence of AO after the removal of impacted third molars as 25-30% (Fridrich and Olson, 1990; Lilly et al., 1974; Afshin Haraji et al., 2012), which suggests that there is a ten-fold increase in AO following removal of third molars compared to other sites, especially where third molars are impacted. Given this reported incidence of AO following the surgical removal impacted third molars, Bailey et al. incorporated AO development as one of their primary outcome measures in their latest Cochrane review (Bailey et al., 2020).

2.2 Pathogenesis of Alveolar Osteitis

The pathogenesis of AO remains poorly understood but is believed to involve a series of events occurring within the extraction socket once the tooth has been removed. In normal healing, local alveolar blood supply facilitates the formation of a fibrin meshwork. This deposition of fibrin is a crucial step in the healing process as it forms a physical barrier to prevent the movement of bacteria into the socket (Nitzan, Sperry, and Wilkins, 1978).

Fibrinolysis, or degradation of the clot is postulated to occur with the release of tissue kinases, induced by the inflammation caused by the trauma of the extraction. Multiple in vitro and in vivo studies have shown the significance of locally increased fibrinolytic activity in the pathogenesis of AO, compared to normal healing sockets (Birn, 1970, 1972b; Birn and Myhre-Jensen 1972; Birn, 1973). Direct and indirect activators of plasminogen lead to the formation of plasmin which further disintegrates the clot. Direct activators include physiologic substances such as tissue plasminogen activator whereas indirect activators are nonphysiologic and include streptokinase and staphylokinase. These indirect activators are produced by bacteria and bind to plasminogen to form an activator complex that cleaves other plasminogen molecules to plasmin (Sheikh and Kiyani, 2010).

Birn claimed that AO develops from localised infection of the socket following extraction, resulting from the absence of a blood clot or when the initial clot is

lysed soon after formation due to alveolar bone inflammation (Birn, 1970). This partial or complete lysis is caused by tissue kinases liberated during inflammation by direct or indirect activation of plasminogen. More recently these have been further subclassified according to their origin as intrinsic and extrinsic activators (Vezeau, 2000). Intrinsic activators originate from components of plasma whereas extrinsic activators originate from outside plasma/blood. This process is summarised in the flowchart illustrated in Figure 1.

Birn also described the role of plasmin in the formation of kinins which induce a state of hyperalgesia by activating primary afferent nerves in the alveolar bone marrow, which may be a causative factor for the intense pain reported by patients with AO (Birn, 1972c). The presence of plasmin may therefore give rise to two of the most characteristic features of AO, neuralgic-type pain, and a disintegrated blood clot.

Many other aetiological factors have been suggested as having an effect in the development of AO but each of them can be linked to fibrinolysis, the loss of the blood clot which forms to protect the socket after extraction.

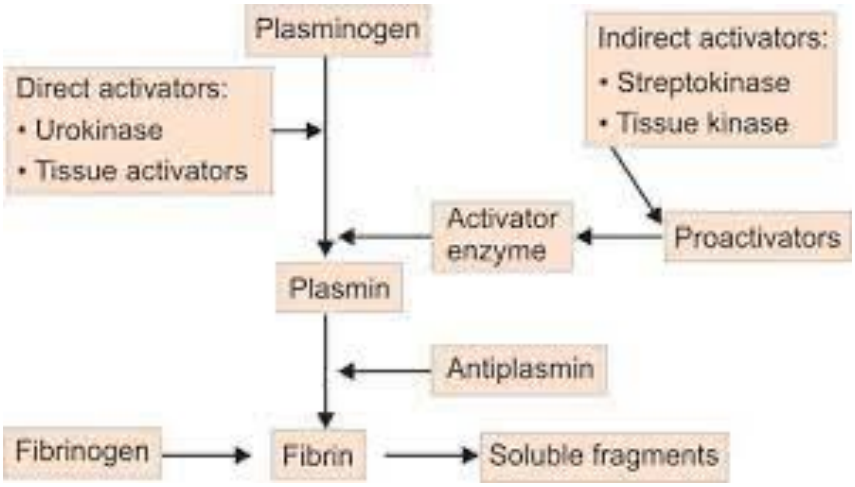

Figure 1: The pathophysiology of fibrinolysis (Gowda et al., 2013)

2.3 Aetiology of Alveolar Osteitis

There have been numerous aetiological factors described in the literature believed to play a role in precipitating AO. Though it is widely accepted that AO is multifactorial in origin, the following aetiological factors have been most implicated:

2.3.1 Oral Microorganisms

Bacteria are cited to play a role in clot lysis (Larsen, 1992). It is important to note that AO (AO) does not manifest with all the typical features of bacterial infection, therefore it has been suggested the bacteria present may be responsible for degradation of the blood clot and should be able to be isolated from the affected socket.

Although bacteria may play a role, there has been no direct cause-effect relationship established between bacteria and AO (Nitzan, 1983).

Nitzan et al. proposed the role of anaerobic bacteria, especially *Treponema denticola*, part of the red complex of periodontal pathogens, showed plasmin-like fibrinolytic *activity in vitro.* This red complex of bacteria includes *Porphyromonas gingivalis*, T*reponema denticola,* Tannerella *forsythia* which form a part of the flora in subgingival plaque and trigger periodontal disease initiation (How et al., 2016). Their virulence factors involve penetration of the periodontal tissue and can produce a fibrinolytic enzyme that can be found at sites distant to the bacterium itself. Healthy tissue in the vicinity of necrotic areas of periodontal disease can be occupied by treponemes, a finding that is relevant if considering a potential link between AO and poor oral hygiene. Patients with poor oral hygiene were found to have a threefold incidence of AO in third molar extractions (Peñarrocha et al., 2001). A prospective cohort study of 284 patients found that 100% of AO cases had developed in patients with poor oral hygiene (Parthasarathi, Smith and Chandu 2011). This theory is further supported by an increased incidence of dry socket in patients with poor oral hygiene and in the presence of pre-operative periapical infection, pericoronitis or advanced periodontal disease (Krekmanov and Nordenram 1986; Awang, 1989).

The potential role of bacteria in AO has also been explored in animal models. Rozanis et al. demonstrated the association between *Actinomyces*

viscosus and *Streptococcus mutans* causing delayed socket repair following injection of the organisms into extraction sockets (Rozanis, Schofield and Warren, 1977).

For prophylactic antibiotics to be effective in reducing AO, they must be administered before the beginning of the procedure to reduce the bacterial load, which likely shows that increased bacterial load can contribute to AO development. This causative relationship between bacteria and AO is further supported by the reduced incidence of AO when antibacterial measures such as chlorhexidine are employed pre- and postoperatively (Parthasarathi, Smith and Chandu 2011; Oginni, 2008; Shepherd, 2007).

2.3.2 Insufficient blood supply & anaesthetic agents

Various studies have suggested that poor local blood supply is correlated to an increased incidence of AO, especially in mandibular molar extractions where cortical bone may be thick and perfusion negatively affected (Kruger, 1973). This has been argued by Birn who demonstrated that the mandibular molar region is a highly vascularised region of the mandible with its blood supply being far superior to that of the anterior mandible. This also favours the fibrinolysis pathogenesis described by Birn where direct and indirect factors result in the activation of plasmin (Birn, 1973).

Another theory postulated relates to the use of repeated local anaesthetic injections, where the use of vasoconstrictors limits the local blood supply

to the socket (Meechan et al., 1987). Meechan et al. have also specifically found an increased incidence of AO where intraligamentary injections are used compared to block or infiltration injections. This increase has, however, also been attributed to the spread of bacteria when multiple injections are used around the affected site. This has also been disputed by other authors who found the PDL anaesthesia did not increase the incidence compared to block/infiltration techniques (Tsirlis, Iakovidis and Parissis 1992).

2.3.3 Physical dislodgement of the clot

This theory of physical dislodgement either by manipulation of the socket or by negative pressure, such as sucking on a straw, has not been substantiated as a causative factor in the development of AO (Blum, 2002).

2.3.4 Smoking

A study carried out among a smoking population with a total of 400 surgically removed mandibular third molars, who smoked a half-pack of cigarettes daily showed a four- to five-fold increase in AO (12% vs 2.6%) compared to non-smoking patients. The incidence increased to more than 20% in those who smoked more than a pack per day with incidence reaching up to 40% in those who smoked on the day of surgery, or on the first postoperative day (Sweet and Butler, 1978). In contrast to this, Parthasarathi et al. analysed 564 extractions and found no significant effects of smoking on the incidence of AO (Parthasarathi, Smith and Chandu 2011).

The significance of smoking and its relationship to AO may be related to introducing a potential contaminant to the surgical site. Smoking has been shown to decrease neutrophil chemotaxis and phagocytosis which in turn reduces immunoglobulin production (Unsal and Erbasar 2018). Nicotine absorbed through the oral mucosa acts as a vasoconstrictor. The hypothesis of the suction effect applied to the cigarette has not been substantiated. There is very little information correlating the effects of the contaminants, the heat produced or the systemic effects of the ingredients with the incidence of AO.

2.3.5 Trauma to Alveolar Bone

There is consensus in the literature that trauma combined with difficulty of surgery is a major causative factor in the development of AO (Birn, 1973; Bloomer, 2000).

Where surgical extractions are completed involving a mucoperiosteal flap with bone removal and with or without sectioning the tooth, there is a higher reported incidence of AO (Lilly et al., 1974). One study also reported an inverse relationship between the experience of the operator and the incidence of AO, postulating that more trauma is applied with less experience (Sisk et al., 1986).

Wound healing is known to be negatively impacted by excessive trauma (Brekke, Bresner and Reitman 1986). This is due to impaired vascular penetration when the bony walls of the socket are compressed. There is also a theory that trauma can result in thrombosis of the vessels supplying

the socket which results in reduced tissue resistance, leading to wound infection (Turner, 1982).

As previously referenced, Birn produced seminal papers on the role of fibrinolysis in AO. He proposed that trauma results in inflammation of alveolar bone marrow which results in release of direct tissue activators, which act to increase the levels of plasmin into the alveolus, leading to lysis of the blood clot (Birn, 1973).

2.3.6 A Female Predilection – Oral Contraceptive Pill

Oral contraceptive pills (OCPs) have been associated with an increased risk of AO in studies since the 1970s, likely due to their increased use from that time onwards (Cohen and Simecek, 1995; Sweet and Butler, 1977). A relatively recent prospective study of 267 women who had undergone third molar surgery showed that women taking OCPs were 2 to 3 times more likely to develop AO (Garcia et al., 2003).

The mechanism proposed is that oestrogens, like pyrogens, will activate the fibrinolytic system indirectly, and are believed to contribute to the incidence of AO by increasing lysis of the clot, further supporting Birn's fibrinolytic theory. Catellani et al. studied the relationship between increased incidence of AO with increased oestrogen dose in the oral contraceptive pill (Catellani et al., 1980).

The incidence of AO may be higher in females regardless of the contraceptive pill as proposed by the results of one prospective randomised controlled study. This study however was hampered by its small sample size of male participants (Chapnick and Diamond 1992). There is very little published evidence available on the effects of the various points in the menstrual cycle of the incidence of AO.

A summary of these proposed aetiological factors and the associated literature is presented in Table 1 below.

Table 1: The proposed aetiologies of alveolar osteitis and the associated literature. Modified from Kolokythas, Olech, and Miloro 2010

Risk Factors	Oral Microorganisms	Insufficient blood supply	Smoking	Trauma to Alveolar Bone	Inexperienced surgeon	Gender (Female)	Oral Contraceptives
Authors Supporting:	Birn, 1973 Rozanis et al., 1977 Nitzan, 1983 Krekmanov and Nordenram 1986 Awang 1989 Oginni 2008 Parthasarathi et al., 2011 Peñarrocha et al., 2001	Lehner, 1958	Sweet & Butler 1978 Meechan et al., 1987 Nusair & Younis, 2007	Birn, 1973 Fridrich & Olson 1990 Alexander, 2000 Torres-Lagaires et al., 2005 Nusaid & Younis 2007	Sisk et al., 1986 Alexander, 2000 Oginni et al., 2003	Field et al., 1985 Alexander, 2000	Sweet & Butler, 1977 Fridrich & Olson, 1990 Alexander, 2000
Authors refuting:	Martis et al., 1978	Birn, 1973 Alexander, 2000	Barclay, 1987	Krekmanov & Hallander, 1980 Field, 1985	Nusair & Younis, 2007	Catellani 1980 Nusair & Younis 2007	Barclay, 1987 Larsen, 1992

2.4 Diagnosis of Alveolar Osteitis

2.4.1 Clinical Examination

Alveolar osteitis simply means inflammation of the alveolar bone within the extraction socket. On examination, the alveolus is partially or completely denuded with very sensitive bony surfaces often covered by a greyish-yellow layer of detritus, necrotic tissue. Surrounding soft tissues often show inflammatory reactions (Birn, 1973). Patients commonly complain of intense continuous pain radiating from the socket to the ipsilateral ear and temporal region and occasionally have regional lymphadenopathy. Halitosis is often another symptom with the patient complaining of bad taste and/ or smell (Blum 2002). This combination of partial or total absence of a blood clot combined with moderate-severe pain is pathognomonic of AO.

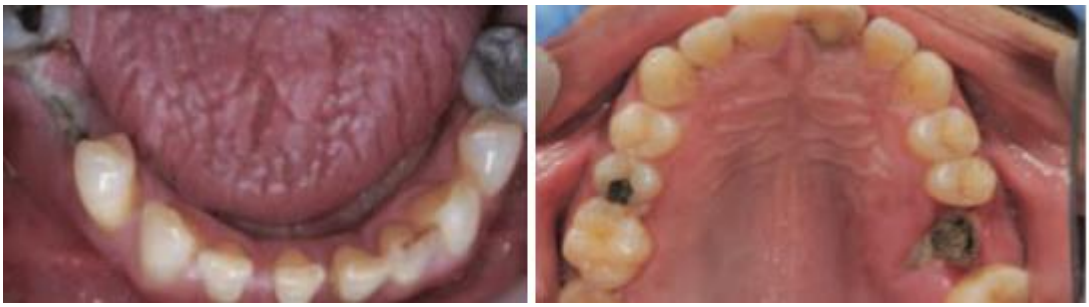

Figure 2a. (left) Clinical presentation of lower right molar socket at day 3 post-extraction shows the blood clot has been lysed. **b**. (right) Clinical presentation of alveolar osteitis at upper left first molar site, showing exposed necrotic bone and absence of any granulation tissue (Sharif et al., 2014).

Certain conditions where there may be pre-existing hypovascularity of alveolar bone must be distinguished from true AO. Such conditions include radiotherapy-induced osteonecrosis, osteopetrosis, Paget's disease and cemento-osseous dysplasia (Vezeau, 2000). These conditions may prevent initial formation of a coagulum whereas AO involves the premature loss of a formed coagulum in an extraction socket.

2.4.2 Onset and Duration of Symptoms

The onset of AO has been reported between one and three days post-extraction (Nitzan, 1983; Field et al., 1985; Fridrich and Olson, 1990), with between 95-100% of all cases of AO being registered within a week following extraction (Nitzan, 1983; Field et al., 1985). It has been postulated that AO is unlikely to develop before the first postoperative day as the clot must be consumed by plasmin for disintegration to occur (Blum 2002).

While AO is a self-limiting condition, the duration of the associated pain can vary, usually ranging from 5-10 days. This results in lost days at work, an economic burden and leads to return surgical practice or hospital visits. This has an implication on the treating clinician as patients who develop AO often require multiple visits to manage their postoperative pain (Osborn et al., 1985). It is for this reason, and to alleviate post-surgical pain, that finding an approach for best managing dry socket is a subject of interest.

2.4.3 Use of Radiology to Aid Diagnosis

AO is diagnosed through history and examination alone and there are few indications for further diagnostic aids. The use of radiology can provide clarity where there is ambiguity about whether there may be an infected retained root within the socket, resulting in the patient's presentation of severe postoperative pain. This is especially useful for a treating clinician who did not complete the extraction (Kolokythas, Olech, and Miloro 2010).

2.4.3 Histologic Examination to Aid Diagnosis

Much like the adjunctive use of radiology, histological findings are not extensively documented in the literature as diagnosis is based primarily on history and clinical evaluation. Biopsy of the affected socket is rarely undertaken.

Histologically, the focus is on the disrupted healing process, inflammation, and the absence of organised tissue repair (Syrjänen and Syrjänen, 1979). The histological features of AO primarily manifest due to clinical factors, such as the early loss or absence of the blood clot, rather than a distinct histopathological pattern.

2.5 The Microbiology of Alveolar Osteitis

There have been several methods established to analyse the composition of the oral microbiome including microscopy, immunoassays, culture testing, DNA sequencing, polymerase chain reaction (PCR) tests, DNA-DNA hybridisation and Sanger sequencing. In more recent studies, 16S ribosomal RNA gene sequencing has been employed to ensure less microorganisms are overlooked than while using

more traditional methods. Specific to AO, 16S rRNA sequencing is used to examine the microbiota of normal healing sockets compared to those with AO (Aguilar-Durán et al., 2019; Shen et al., 2019).

A recent systematic review carried out by Riba-Teres et al. in 2021 found that the spectrum of bacteria found in AO sites differed significantly from those that healed uneventfully. This suggests that bacterial infection may play a more important role in the development of AO than was heretofore believed (Riba-Terés et al., 2021). The most commonly found bacteria in sites with AO included *Prevotella* and *Fusobacterium*, the same as those implicated in pericoronitis which is a known risk factor for AO (Brescó-Salinas et al., 2006). Both *Prevotella* and *Fusobacterium* were found in high abundance in affected sockets when compared to normal sockets and therefore may be linked to the onset and evolution of the complication. *Paravimonas* and *Peptostreptococcus* are also commonly identified in sockets with AO (Riba-Terés et al., 2021). Future research is needed to investigate the fibrinolytic activity of various bacteria and this potentially infectious pathogenesis of AO.

2.6 Prevention of Alveolar Osteitis

There have been a multitude of studies examining ways to prevent AO. Despite the various measures that have been taken to prevent its occurrence, it is still a common postoperative problem. The primary aim with preventative measures as opposed to symptomatic management is to improve oral hygiene to reduce bacterial load and thus postoperative pain. The secondary aim, which has been

adopted by more recent preventative measures is to promote socket healing, expediting the process. Combining both of these modes of action, the economic burden of AO, including days off work and repeated visits to the treating clinician should be minimised (Poor, Hall and Poor 2002). Table 2 summarises the findings of published randomised controlled trials and systematic reviews focussing on the prevention of alveolar osteitis.

2.6.1 Preventative options:

2.6.1.1. Chlorhexidine

Chlorhexidine (CHX) is a biguanide antiseptic with antimicrobial properties and its preoperative and postoperative use has been shown to reduce the quantity of oral antimicrobials (Veksler, Kayrouz, and Newman 1991). In the same vein, myriad studies have examined how this may benefit patients having third molars removed with respect to AO and infection prevention.

A randomised controlled trial carried out by Halabi et al. compared use of 0.12% CHX mouthwash to placebo following dental extractions in 844 patients. They found a significant reduction of 63% in the number of patients developing AO when using CHX compared to those using placebo and a number needed to treat (NNT) of 21.88 (Halabi et al., 2018). This is supported by the findings of a Cochrane review by Daly et al. which included 39 studies looking at prevention of AO. They found that rinsing with chlorhexidine 0.12% or 0.2% before and 24 hours after tooth extraction probably results in a reduction in dry socket. Similarly they found

the chlorhexidine gel (0.2% strength) placed in an extraction socket probably results in a reduction in dry socket and that rinses and gels are equally effective, with there being less side effects when using gels (Daly et al., 2022).

It is worth noting that the authors described minor adverse reactions such as alteration in taste, staining and stomatitis in the latest Cochrane review associated with use of both 0.12% and 0.2% chlorhexidine mouthrinses (Daly et al., 2022). None of these adverse effects were reported when 0.2% chlorhexidine gel was used as an intra-alveolar medication, which was deemed to be as effective by multiple studies within the review (Canullo et al., 2020; Rodríguez Sánchez, Rodríguez Andrés and Arteagoitia Calvo, 2017).

2.6.1.2 Systemic antibiotics

There has been published evidence available for years to support the prescription of both antiseptic and antibiotics to reduce the incidence of AO (Ren and Malmstrom, 2007; Krekmanov and Nordenram 1986). Delilbasi et al., carried out a randomised controlled trial in 2002 and showed a marked reduction in AO where CHX was combined with amoxicillin and clavulanic acid compared to CHX alone. In the same trial, contrary to other findings, this group found that there was minimal difference in the incidence of AO where patients used CHX or control (saline) postoperatively (Delilbasi, Saracoglu, and Keskin, 2002).

Though there is some evidence that antibiotics may reduce the risk of AO, they carry mild and transient adverse effects. There is also the global public health risk of resistance and the unnecessary destruction of host commensals. Lodi et al., reported that 46 patients would require antibiotic prescription in order for one person to prevent getting AO, while the NNT is 19 for postoperative infection (Lodi et al., 2021). These findings would suggest that the evidence supporting prophylactic antibiotic prescription in healthy patients does not exist if aiming to prevent AO. These should be reserved for patients with a history of multiple episodes of AO and those who are immunocompromised (Fazakerley and Field, 1991; Lodi et al., 2021). Interestingly it has been reported that if given antibiotics, they are more effective for decreasing AO if given pre-operatively compared to post-operatively (Laird, Stenhouse and Macfarlane, 1972). If an infectious aetiology of AO is established within future research, prevention and management guidelines should be modified to reflect these changes.

2.6.1.3 Antifibrinolytic agents

Following initial publications from Birn et al. exploring the fibrinolytic nature of AO, early investigations began to examine the topical use of para-hydroxybenzoic acid (PHBA) in extraction sockets. Early publications showed the incidence of AO decreased in a dose-dependent fashion (Birn 1972a; Ritzau and Therkildsen 1978; Schatz, Fiore-Donno and Henning, 1987).

It should be noted that PHBA is available on the market as a component of Apernyl (Bayer AG, Germany), an alveolar cone containing the ingredients of 32 mg acetylsalicylic acid, 3mg propyl ester of PHBA and 20mg of unknown mass. It is therefore not possible to distinguish the efficacy of PHBA alone as the anti-inflammatory properties of acetylsalicylic acid may have a role. PHBA has also demonstrated some antibacterial properties which may also contribute to the reported findings (Vezeau, 2000). Histological studies carried out in vitro on rat subjects subsequently showed that acetylsalicylic acid in contact with bone produces a local irritation with inflammation, which may in fact result in AO development (Carroll and Melfi, 1982).

Tranexamic acid is another antifibrinolytic agent investigated as an agent to prevent AO when applied to the socket following exodontia. Controlled studies in patients undergoing third molar extractions have failed to show a significant reduction in AO compared to placebo subjects (Gersel-Pedersen, 1979).

Overall, there remains no confirmed scientific advantage in using these agents in the prevention of alveolar osteitis.

2.6.1.4. Autologous blood concentrates (APCs)

Most recently, the use of autologous platelet concentrates has been advocated to expedite postoperative healing and used in both the prevention and treatment of AO (Del Fabbro, Panda and Taschieri, 2019). Particular emphasis has been placed on platelet rich fibrin (PRF) and its successors which is extracted from plasma through centrifugation of autologous blood, resulting in production of a fibrin matrix containing concentrations of platelets, leukocytes and growth factors (Unsal and Erbasar, 2018).

In a split-mouth randomised study by Unsal and Erbasar including 50 patients, partially erupted, symmetric third molars were extracted and PRF was placed by random allocation in one socket while the other was left empty. A significant difference in AO incidence was observed amongst smokers ($P < 0.05$) with the incidence notably higher within the control group when compared to the PRF group (Unsal and Erbasar, 2018). PRF did not significantly change the AO incidence in non-smokers, but it positively affected pain levels.

Many authors have noted that the properties of PRF and its three dimensional structure facilitate cell migration and the organised fibrin matrix supports clot formation, while also preventing mechanical dislodgement (Eshghpour et al., 2015; Hoaglin and Lines, 2013). A single-

centre retrospective analysis in 499 patients and 904 third molar extractions showed a 62.1% lower incidence of AO in those sockets treated with PRP (Rutkowski et al., 2007). The authors failed to disclose any diagnostic criteria they may have used with respect to AO.

Haraji et al. (2012) conducted a split-mouth RCT on 40 patients and demonstrated a statistically significant difference in the incidence of AO in PRGF-treated third molar sides compared to control sides. It was noted that their cohort was split between maxillary (n=20) and mandibular third molar removal which had a likely impact on the accuracy of their results due to the higher propensity for AO development in mandibular sites (Afshin Haraji et al., 2012).

A systematic review by Del Fabbro et al. aimed to determine whether adjunctive use of plasma rich in growth factors (PGRF) in extraction sockets could improve both postoperative pain and healing. They concluded by qualitative analysis of the studies that PRGF could result in improved hard and soft tissue healing, patient discomfort and adverse events. Due to the heterogeneity in outcome assessment, he was unable to perform a quantitative analysis however and therefore the benefits of PRGF in pain control and healing were unquantifiable (Del Fabbro, Panda and Taschieri 2019).

Table 2: Randomised controlled trials and systematic reviews related to prevention of alveolar osteitis

Author	Study Type	Intervention	Sample Size	Results
Halabi et al., 2018	RCT	CHX mouthwash (0.12%) vs placebo in post-extraction sockets	744	CHX reduced incidence vs placebo (absolute RR, 4.57; 95% CI, 1.5-7.1; NNT, 21.88); AO incidence, 4.97% (placebo, 7.26%; CHX, 2.69%)
Daly et al., 2022	Cochrane systematic review	CHX mouthwash (before and after procedure); CHX gel (0.2%) after extraction	MW: 6 trials, 1547 participants Gel: 7 trials, 753 participants	CHX mouthwash substantially reduced risk of AO with RR, 0.38 (95% CI 0.25 to 0.58; P<0.00001 CHX gel intrasocket after extractions reduced the odds of AO with RR, 0.44 (95% CI 0.27 to 0.71; P=0.0008. CHX rinse was not superior to CHX gel in reducing risk of AO
Eshghpour et al., 2014	RCT	PRF	78	PRF resulted in statistically significant decreased risk of developing AO vs non-PRF sockets (RR,0.44; 95% CI 0.1480-989; P=.042
Coulthard et al., 2014	Cochrane systematic review	Surgical flap type (triangular vs envelope flap); primary vs secondary wound closure	3 studies (94 pts); 3 studies (375 pts)	Triangular flap showed reduced risk of AO (RR, 0.29; 95% CI, 0.41-2.40; P=.98

Delilbasi et al., 2002	RCT	0.2% CHX with amoxicillin + clavulanic acid vs CHX	177	Significant reduction in AO in CHX with amoxicillin + clavulanic acid group (P= .001, x^2 test
Lodi et al., 2021	Cochrane systematic review	Pre- and postoperative antibiotics	13 studies (1882 pts)	Antibiotics may reduce the risk of dry socket by 34% (RR 0.66, 95% CI 0.45 TO 0.97: NNT, 46 patients
Guazzo et al., 2018	RCT	Topical amino acid and sodium hyaluronate gel	106	No significant difference

2.7 Treatment of Alveolar Osteitis

The management of established AO focuses on the alleviation of symptoms rather than intervening with the pathological process. Though treatment of the affected extraction socket may provide symptom relief, some management strategies are directed towards the relief of pain until normal healing can take place. A reduction in the time taken for patients to return to normal function, such as eating and sleeping, is also important. There have been over twenty treatment modalities described in the literature including (Table 3).

Table 3: Remedies & their properties used for treatment of dry socket in publications between 2000-2020 (modified from Kamal, 2020)

	ANALGESIA	ANTI-INFLAMMATORY	ANTIMICROBIAL	SEDATIVE	ANTIOXIDANT	REGENERATIVE	REFERENCE
SALINE	x						Blum, 2002
HONEY	x	x	x		x	x	Soni et al., 2016
TURMERIC	x	x	x		x		Lone et al., 2018
ALOE VERA/ ACEMANNAN	x	x	x		x	x	Mangaiyarkarasi et al., 2015
VITAMIN C	x	x			x	x	Halberstein & Abrahnsohn, 2003
COLLOIDAL SILVER	x	x	x				Helei et al., 2019
LIDOCAINE OINTMENT	x			x			Burgoyne et al., 2010
METRONIDAZOLE	x	x	x				Helei et al., 2019; Silva, 2006
CLINDAMYCIN	x	x	x				Cebi 2020
ZINC OXIDE EUGENOL	x		x	x			Chaurasia et al., 2017
EUGENOL/ OIL OF CLOVE	x		x	x			Kamal et al.,2020
ALVOGYL (SEPTODONT)	x		x	x			Faizel et al., 2015; Supe et al., 2019
ALVEOGYL (SEPTODONT)	x		x	x			King et al., 2018
SALICEPT	x	x	x	x			Kaya 2011
OZONE GEL	x	x	x	x			Khanand Abid, 2015
NEOCONE	x	x	x	x			Faizel et al., 2015
OZONE THERAPY			x			x	Azarpazhooh and Limeback., 2008
LOW LEVEL LASER THERAPY (LLLT)	x	x	x			x	Jovanovic et al., 2011; Kamal et al., 2020
LOW INTENSITY-PULSE ULTRASOUND (LIPUS)	x	x	x			x	Muragod et al., 2016
PLASMA RICH IN GROWTH FACTORS	x	x	x			x	King et al., 2018
PLATELET RICH FIBRIN	x	x	x			x	Yuce et al., 2019

2.7.1 Treatment Options

2.7.1.1 Topical and Local Anaesthesia

The use of topical anaesthetic containing 2.5% lidocaine or 2.5% prilocaine are commonly employed in the symptomatic treatment of AO. Burgoyne et al. carried out a randomised controlled trial in 2010 investigating the use of topical anaesthetic compared to eugenol and found no significant difference in the pain reduction between groups (Burgoyne et al., 2010). Lidocaine 2% viscous gel had previously been shown to be effective compared to placebo in short-term pain reduction within the first hour of placement into the socket (Betts et al., 1995). Though topical gels may provide short-term symptomatic relief, long-acting local anaesthesia such as bupivacaine administered by regional blocks or infiltrations can be helpful for immediate symptomatic relief when used alongside regular systemic analgesia.

2.7.1.2 Systemic analgesia

There is very limited evidence available for standardised analgesia regimens in relation to treating AO. Guidelines have been proposed by the World Health Organisation (WHO) in the form of following an analgesia ladder consisting of nonopioid medications to start followed by weak opioids with or without adjuvant therapy and a strong opioid with adjuvant therapies. Analgesics should be

consumed regularly, orally and given relative to the individual's experience of pain (Azevedo São Leão Ferreira, Kimura and Jacobsen Teixeira, 2006).

Therapeutic guidelines from the Oral and Dental Expert Group have reported that paracetamol in combination with a nonsteroidal anti-inflammatory drug (NSAID) have repeatedly been shown to be effective to control post-extraction pain (Oral and Dental Expert Group 2012). This is further acknowledged by the grade A recommendation by the WHO analgesic ladder (Azevedo São Leão Ferreira, Kimura and Jacobsen Teixeira, 2006).

Systemic oral opioids affect the pain pathway on multiple levels and are the final step on the WHO drug ladder. Their disadvantages lie within their side effects profile, including nausea, vomiting, constipation and dependency (Frydman, 2010).

No studies have examined neuropathic agents such as pregabalin, an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid for their efficacy in AO. It has however been shown to have superior analgesic properties to placebo in the setting of elective molar extraction by a single-centre randomised controlled trial (Hill et al., 2001).

2.7.1.3 Medicated Dressings

Therapeutic, medicated dressings can be analgesic and/or antibacterial and have been used for decades. Alveogyl and SaliCept remain two commonly used dressings, acting as a physical barrier against food debris entering the socket. Alveogyl was reformulated in 2014 and now contains eugenol as its only active ingredient. It previously contained a local anaesthetic, antiseptic and analgesia (25.7% butamben, 15.8% iodoform and 13.7% eugenol) respectively. The former ingredients were removed due to potential allergic reactions and a risk to patient safety (Kalsi, Major, and Jawad 2020).

SaliCept patches are also commonly used and contain acemannan hydrogel which is found in aloe vera. Acemannan hydrogel is believed to have properties that promote healing by isolating the wound site and providing a moist barrier for healing (Oginni, 2008). This dressing also has the ability to induce macrophage infiltration which is critical to initiate the process of repairing damaged tissue (Thomas et al., 1998).

2.7.1.4 Phototherapy with Low Level Laser Therapy

Phototherapy through the use of low level laser therapy (LLLT) is a relatively novel form of treatment for AO, having previously been used in other aspects of oral surgery such as treatment of MRONJ

(Vescovi et al., 2012). The subtypes of lasers used include Er:YAG, Nd: YAG, ErCrYSGG and Nd: YAP. It has been a source of interest in the literature due to its combined benefit of alleviating symptoms and hastening the healing process through its bio-stimulant effect. On a cellular level it increases the inorganic content of bone matrix, inducing osteoblastic differentiation and neo-angiogenesis (Vescovi et al., 2012). With regards to the mechanism of pain relief, LLLT is believed to reduce inflammation by inhibition of prostaglandin-2 and cyclooxygenase-2 production, both of which are inflammatory mediators, though this has not been fully elucidated. Additionally, it is reported to be user-friendly, efficient and has a good safety profile (Smigiel and Parks, 2018).

Compared to medicated dressings, it does not involve multiple visits for removal or re-application and the onset of pain relief has been reported to be more efficient than other conventional dressings (Kaya et al., 2011).

2.7.1.5 Autologous Platelet Concentrates (APCs)

Autologous platelet concentrates (APCs) have evolved in their formulation and applicability of use across multiple fields of medicine and dentistry. These concentrates are derived from the patient's blood through a process involving centrifugation, making them highly biocompatible. This centrifugal force separates the blood into layers, creating a fibrin meshwork where platelets,

cytokines, growth factors and white blood cells become embedded (Kobayashi et al., 2016; Cabaro et al., 2018). Systematic reviews have shown that APCs provide stability in haemostasis, improve epithelialisation of sockets and promote bone graft healing (Marenzi et al., 2015).

Various platelet concentrates have been used in the management of AO, such as platelet rich in growth factors, concentrated growth factor and platelet rich fibrin but there remains a lack of clarity due to a relative paucity in the literature regarding their benefits compared to more conventional treatments (Puidokas et al., 2019; Kamal et al., 2020; Kamal et al., 2020).

King et al. carried out a clinical trial to compare pain scores and clinical parameters (exposed bone, inflammation, dysguesia, halitosis) in 38 patients with 44 sockets with established alveolar osteitis. Patients either received treatment of their alveolar osteitis with PRGF (n=22) or Alvogyl dressing (n=22). Though the authors demonstrate a reduction in pain scores following the use of PGRF in sockets with AO, they failed to implement valid instruments for evaluation of QoL outcomes, instead listing generic outcomes such as pain, swelling, dysgeusia and healing as QoL parameters (King et al., 2018). Another weakness of this trial was the failure to blind study participants.

Yuce et al. (2019 carried out a randomised controlled trial on 40 patients to assess the efficacy of Advanced- Platelet Rich Fibrin (n=20) as opposed to saline placebo (n=20) on patient's who met Blum's diagnostic criteria for alveolar osteitis in third molar sockets only. Outcomes measured included postoperative pain measured by VAS at five timepoints and healing using Landry's soft tissue index at three timepoints. They found that pain scores on postoperative days 1,3 5 and 7 were significantly lower following A-PRF application compared to the control group. The control group also had significantly higher analgesia usage compared to the A-PRF group. With regards to healing, the A-PRF group showed significantly expedited healing compared to the control group though it was difficult to decipher how the second assessors were blinded. A weakness of this study for generalisability however is the extensive list of exclusion criteria including the presence of inflammation, anti-inflammatories 7 days prior to extraction, smokers and any third molar that would require raising a flap or removing bone (Yüce and Kömerik, 2019).

In contrast to the above two trials concluding that autologous platelet concentrates show superiority to conventional dressings, Keshini et al. (2020) found that use of Alvogyl (old formulation) was

comparable rather than superior to PRF (Keshini et al., 2020). Both treatment options showed positive results in reduction of pain and improved healing, Yuce et al notwithstanding.

Overall, it is notable from exploration of the literature that research to date has focussed on the use of APCs in the prevention of AO, rather than on its treatment, especially in the setting of third molar extractions.

2.7.2 Comparison of conventional treatment modalities

Multiple studies have compared different treatment options used in the management of AO (see Table 4). Supe 2018 & Lenka 2019 both compared the efficacy of Alveogyl/ Alvogyl respectively to zinc oxide eugenol impregnated cotton pellets in the treatment of dry socket and had a primary outcome of pain relief measured on visual analogue scales. Both studies found that Alveogyl/Alvogyl was more effective than ZOE for providing timely pain relief (Supe et al.,2018; Lenka et al., 2019). Prior to that however in 2017 Chaurasia, who had a larger sample size of 88 patients found ZOE to be the superior material for achieving complete pain relief sooner than Alveogyl (Chaurasia, Upadhyaya, and Dixit 2017).

In 2011, Kaya ran a prospective randomised controlled trial of 104 patients and allocated them to four groups curettage and irrigation

alone (C+I), C+I and Alvogyl, C+I and SaliCept Patch and C+I and low-level laser therapy (LLLT). Though he found LLLT more effective than the other form of treatments, there were no significant differences between Alvogyl and SaliCept (Kaya et al., 2011).

Though symptoms of AO are debilitating, the process is self-limiting and does not result in long term morbidity. Despite the continued lack of evidence to advocate the prescription of antibiotics, they continue to be commonly prescribed for prophylaxis and treatment purposes. Given the lack of consensus regarding the pathophysiology, it is therefore not surprising that ambiguity remains regarding optimal management.

Table 4: Randomised controlled trials related to treatment of Alveolar Osteitis

Author & Year	Study Type	Intervention	Sample Size	Outcome	Results
Burgoyne 2010	RCT	Topical anaesthetic gel (prilocaine-lidocaine) versus eugenol	35	Pain (VAS)	Efficacy of both materials comparable but topical anaesthetic easier to use
Chaurasia 2017	RCT	Zinc Oxide Eugenol vs alveogyl	88	Pain (VAS)`	ZOE > Alveogyl in early and complete pain relief
Faizel 2015	RCT	Neocone vs. zinc oxide eugenol vs. Alveogyl	117 sockets	Pain and healing	Alveogyl is superior to neocone and ZOE in initial pain relief but neocone showed faster complete pain relief and healing

Kaya 2011	RCT	Curettage and irrigation alone (C+I) ; C+I vs Alvogyl ; C+I vs SaliCept ; C+I vs low level laser therapy	104	Pain	Low level laser therapy was superior to both SaliCept and Alveogyl
Keshini 2020	RCT	Alvogyl vs PRF	30	Pain (VAS), wound healing	PRF was comparable to Alveogyl in both pain and wound healing
King 2018	RCT	Alvogyl vs PGRF	38 patients (44 sockets)	Pain, exposed bone, inflammation, halitosis, patient reported outcomes	PGRF showed faster bone coverage and decreased inflammation. No difference for pain, exposed bone or QoL factors
Lenka 2019	RCT	Alvogyl vs Zinc Oxide Eugenol (ZOE)	30	Pain (VAS)	Alvogyl > ZOE for providing pain relief
Mitchell 1984	RCT	Metronidazole in orabase vs orabase alone	55	Absence of pain, no of visits	Topical metronidazole > placebo at reduction of treatment time
Supe 2018	RCT	Alvogyl vs Zinc Oxide Eugenol (ZOE)	50	Pain (VAS scale), healing	Alvogyl > ZOE for shorter time to complete pain relief and faster healing
Yuce 2019	RCT	Advanced PRF vs placebo (saline)	40	Pain, soft tissue healing	A-PRF might result in improved healing and pain compared to placebo

2.8 Control Material: Alveogyl

2.8.1 Ingredients and its Evolution

The most commonly used intra-alveolar dressing material for dry socket is Alveogyl (Septodont, Inc, Wilmington, DE), which provides pain relief and a soothing effect to the alveolar bone (Chaurasia, Upadhyaya, and Dixit 2017). It has a fibrous consistency and good bony adhesion from the Penghawar fibers within the dressing. It is a user-friendly, single step procedure and the dressing is advertised as “self-eliminating” thereby

requiring no follow up (Supe et al., 2018). It was reformulated and renamed in 2014, formerly known as Alvogyl, and now the only active ingredient is eugenol which provides an analgesic effect. Both other active ingredients, butamben (anaesthetic) and iodoform (antimicrobial), were removed from the original dressing ingredient list as they were believed to pose an allergy risk and a concern for patient safety. Some researchers using the product may have been unaware of the ingredient changes as the packaging is almost identical (Kalsi, Major, and Jawad 2020).

There remains controversy about the placement of a physical dressing into the alveolus and there is no available literature investigating the incidence of side effects or tissue damage that may arise from placement of an intra-alveolar dressing. Case reports have described local complications such as foreign body reactions and it is generally accepted that dressings result in delayed healing of the extraction socket (Sotorra-Figuerola et al., 2019; Moore and Brekke, 1990).

2.8.2 Evidence supporting its efficacy in treatment of alveolar osteitis

Supe et al. carried out a prospective randomised controlled trial in 2018 and compared the efficacy of old formulation Alvogyl to ZOE over a ten-day period from the day of presentation with AO. Their primary outcome was pain reduction as measured by visual analogue scale. They found that the mean time required for complete pain relief was 6.52 ± 1.88 days for Alvogyl and in the ZOE group, 9.06 ± 2.14 days. The difference between the

two groups was statistically significant (P=0.0003) (Supe et al., 2018). Similar observations were made by Faizel et al. in their study who found the mean time to complete pain relief was 6.47 days in the Alvogyl group compared to 8.64 days in the ZOE group (P< 0.0001) (Faizel et al., 2015). In another randomised study carried out by Lenka et al. in 2019, these findings were further supported. At seven days following intervention, Alvogyl (2.90 +.738) showed a statistically significant difference in relieving pain compared to ZOE (4.10 + .315) (Lenka et al., 2019).

Interestingly all three authors compared the mean number of dressings required across both test and control groups. They all found that Alvogyl also required fewer dressing changes and less healing time compared to ZOE. While Supe and Lenka compared two materials, Alvogyl and ZOE, Faizel also included Neocone as a third material. They found that although Alvogyl was superior for providing initial pain relief, achieving complete pain relief was faster with Neocone (Faizel et al., 2015; Supe et al., 2018; Lenka et al., 2019).

A prudent approach needs to be taken when interpreting the applicability of these results to the efficacy to the current formulation of Alveogyl however, as the composition has since changed. This is demonstrated by the clinical trial run by Chaurasia and his colleague in 2017 who tested the efficacy of new formulation Alveogyl versus ZOE in a sample of 88 patients.

Pain reduction, measured by VAS, was their primary outcome and they concluded that there was an immediate and sustained improvement in VAS scores with ZOE compared to Alveogyl (p=0.0001 at 30 minutes, p=0.006 at 7 days). A notable pitfall in this study, however, is their lack of inclusion and exclusion criteria, and though Blum's definition is used for establishing a diagnosis of alveolar osteitis, there are no other criteria applied (Chaurasia, Upadhyaya and Dixit 2017)..

2.9 Test Material: Horizontal Platelet Rich Fibrin

2.9.1 The Evolution of Platelet Concentrates

Platelet concentrates are regenerative surgical additives which have been in use in medicine because of their ability to rapidly secrete autologous growth factors and ultimately optimise wound healing. They have gained popularity over the last two decades across many medical fields due to being a regenerative agent from an autologous source (Dohan Ehrenfest et al.,. 2014).

The original concept of manipulation of wound healing using a regenerative material was introduced by Matras in 1970, when they used fibrin glue to expedite skin wound healing in rat models (Matras 1985). The concept behind this was based on the understanding that the fibrin formed the first matrix in the healing process. Fibrin glues remain in use as surgical adjuvants, especially in the context of haemostasis.

Between 1975-1979, scientists proposed to upgrade the concept for use of blood extracts to “gelatin platelet-gel foam” mixtures where fibrin glues included a high contraction of platelets within their final preparation (Rosenthal et al., 1978). Rosenthal et al. recognised the importance of platelets in the initial healing process and sought to use their biological properties. These gel foams were the first platelet rich plasma concentrates (cPRP) that led to the development of the concentrates we know today.

Specific to dentistry, platelet concentrates were introduced to the oral cavity following the pioneering work of Whitman and Marx in the 1990s (Whitman, Berry and Green 1997; Marx et al., 1998). In the early days of platelet concentrates, it was proposed that by concentrating platelets using a centrifugation device, growth factors from blood could be collected by a variety of separation techniques and used in surgical sites to promote wound healing. All of these products were termed “first generation” cPRPs. Platelet-rich plasma (PRP), as its name implies, was designed to accumulate platelets within the plasma layer following centrifugation. Initially protocols typically ranged in duration from 30 minutes to 1 hour and therefore anticoagulants were added to the blood collection tubes, typically in the form of concentrated bovine thrombin or sodium citrate. Despite its success and continued use, several limitations existed with this initial formulation of PRP including that anticoagulants were hindering healing potential (Kobayashi et al., 2016). PRP is credited for having exponentially

grown the entire field of platelet concentrates including its subcategories, such as PRF.

In 2001, Choukroun was responsible for developing a new type of platelet concentrate, platelet rich fibrin (PRF) (J. Choukroun et al., 2001). Due to the differences in both biological and structural properties from cPRPs, these were deemed “second generation” platelet concentrates, and they focused on avoiding the need for anticoagulants. High g-force centrifugation protocols were adopted to separate blood layers prior to clotting, and this resulted in a plasma layer composed of a fibrin clot which acts as a scaffold with entrapment of platelets and leukocytes. The main advantage of this new generation concentrate was its ability to release growth factors over time during fibrin degradation. The working time for PRF products was found to be much more conducive to dentistry workflow and avoided the need for dual-spin protocols which required pipetting or specialised tube compartments (Dohan Ehrenfest et al., 2010).

Over the years, PRF has been termed L-PRF (leukocyte- platelet rich fibrin) due to the discovery that leukocytes remain incorporated in PRF, and white blood cells are pivotal in both tissue regeneration and healing. The inclusion of leukocytes facilitates the phagocytosis of debris, microbes and necrotic tissue and directs the future regeneration of these tissues through the release of cytokines and growth factors while orchestrating communication

between different cell types. Concentrated leukocytes in PRF have been well documented as jet regulators of tissue healing and formation (Adamson 2009; Dohan et al., 2006a).

From 2014-2018, further discoveries were made in basic research laboratories and while using the original L-PRF protocol, Dr Ghanaati found that when centrifugation is carried out at high speeds (700g), leukocytes are located either at the buffy coat zone or at the bottom of centrifugation tubes (Ghanaati et al., 2014). He also found that increasing the centrifugation time exaggerated this effect. His research led to development of advanced PRF (A-PRF) whereby lower centrifugation speeds (200g) resulted in a higher concentration of platelets and leukocytes in the upper PRF layers (Kobayashi et al., 2016). These newer protocols led to a higher release and concentration of growth factors over a 10-day period when compared to PRP or L-PRF. The A-PRF protocol was also modified from 14 minutes at 200g to 8 minutes (Kobayashi et al., 2016). Table 5 below outlines the development of second-generation platelet rich concentrates in chronological order.

Table 5: Preparation protocol for 2nd generation platelet concentrates

Platelet concentrate	**Developed by**	**Revolutions per minute (RPM)**	**G-force**	Time (minutes)
PRF	Choukroun et al., (2001)	3,000	700g	10
L-PRF		2,700	400g	12
A-PRF (i)	Ghanaati et al., (2013)	1,500	200g	14
A-PRF (II)	Ghanaati et al., (2014)	1,300	60g	8
H-PRF	Fujioka- Kobayashi (2021)	2,200	700g	8

2.9.2 The Advance of Horizontal Platelet Rich Fibrin

Up to 2019, most centrifugation was performed on fixed-angle centrifuges. Though horizontal centrifugation did exist, its use was confined primarily to research laboratories and medical hospitals but it demonstrated a superior ability to separate cell layers based on their density (Lourenço et al., 2018).

In research by Miron et al. it was found that leukocytes, lymphocytes, monocytes and platelets had a more even distribution throughout the PRF layers in horizontal centrifugation when compared with fixed-angle centrifugation. The other advantage over previous generations of platelet concentrates, namely L-PRF and A-PRF, was that cellular concentrations

increased with horizontal centrifugation, with a 2.4-fold increase in platelets and a 2-fold increase in leukocytes compared to L-PRF. This method ensures that >99% of platelets and 53% of leukocytes are found within the plasma layer (Miron et al., 2019).

There were two distinct advantages of horizontal centrifugation noted in the above study regarding cell separation. Due to the mechanism produced by a swing-out bucket creating a completely horizontal tube, greater differentiation between minimum and maximum radius can be found within the centrifugation tube. This allows for an improved ability to separate cell layers based on the disparities between minimum and maximum relative centrifugal forces (RCF) within a tube. In addition to this, there is less trauma to individual cells within horizontal centrifugation. In fixed-angle centrifuges, cells are pushed toward the outer distal wall and cell layer separation is observed in an angulated fashion and migrate up or down based on density. Larger cells can entrap smaller cells, such as platelets and prevent them from staying with the superior layers of the PRF membrane. Centrifugal g-forces create shear stress on cells as they separate along the back wall of a centrifugation tube. In contrast to this, horizontal centrifugation facilitates the free mobility of cells and separation into their appropriate layers based on density without the friction produced along the back wall in fixed-angle centrifuges (Miron et al., 2019). Figure 3

presents a visual representation of how fixed-angle compares to horizontal centrifugation.

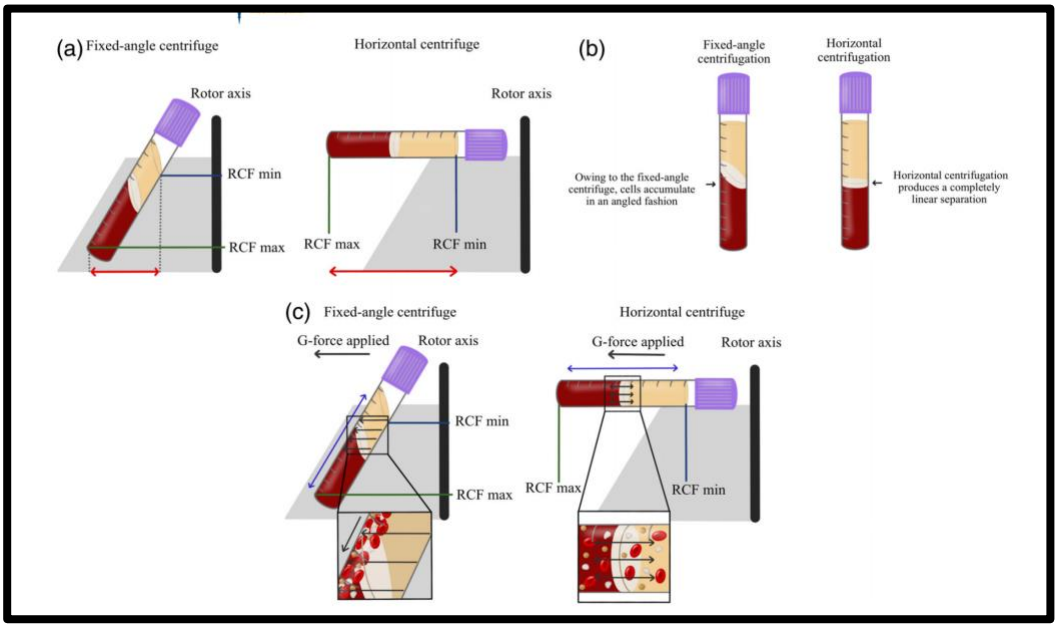

Figure 3: Illustrations comparing fixed-angle and horizontal centrifugation.

(a) With fixed angle centrifuges, a greater separation of blood layers based on density is achieved due to the greater difference in RCF-min and RCF-max.

(b) With fixed-angle centrifuges, blood layers do not separate evenly and as a result, an angled separation is observed whereas horizontal centrifugation produces an even separation.

(c) With large RCF values (～200-700g), cells are pushed towards the outside and downward based on cell density. These g-forces produce shear stress on cells as they separate in fixed-angle centrifugation. In horizontal models, there is free mobility of cells to separate into their appropriate layers which provides more optimal separation and less trauma to cells

Reprinted with permission from (Miron et al., 2019)

2.9.3 Preparation of Horizontal Platelet Rich Fibrin membranes

In order to produce solid H-PRF membranes, the protocol is described extensively by Miron et al. in his book entitled *"Understanding Platelet Rich*

Fibrin" (Richard John Miron, 2021). The aim of the protocol is to concentrate cells with a high yield in the upper four to five 1ml layers of PRF. Following venipuncture, the whole blood samples are collected in hydrophilic plain glass tubes and are centrifuged using a 700g protocol for 8 minutes. Using this protocol, a maximum yield of platelets and leukocytes is achieved with a relatively even distribution of cells.

Box 1: Clinical Indications for PRF membranes in dentistry (Glavina et al., 2017)

- Soft tissue healing in extraction sockets
- Soft tissue healing around implants or soft tissue defects, leaving to restoration of keratinised mucosa
- Promotion of root end closure/ apexification in immature teeth requiring endodontic treatment
- Management of recurrent aphthous stomatitis (RAS) and refractory oral lichen planus
- Guided bone regeneration (GBR) procedures: to mix with bone grafting particles or as outer barrier membrane over collagen
- Sinus grafting: alone or in combination with bone graft
- Arthroscopy for management of temporomandibular joint dysfunction, with conflicting results

2.9.4 Normal Healing Process following extraction

The following events take place during the healing process as outlined in Figure 4 (Avila-Ortiz and Zadeh, 2019).

a) The socket fills with blood from the disrupted blood vessels, which contain protein and growth factors. Cells initiate events that lead to formation of a fibrin network, along with platelets forming a coagulum within the first 24 hours (Amler, 1969).

b) The coagulum acts as a physical matrix, directing the migration of cells. Neutrophils followed by macrophages enter the wound site and digest bacteria and tissue debris within the wound. They release cytokines and growth factors that amplify the migration of mesenchymal cells (Lin, McCulloch and Cho 1994).

c) Within days, the coagulum begins to break down by fibrinolysis. Mesenchymal proliferation leads to granulation tissue replacing the coagulum (2-4 days) (Araújo and Lindhe 2005).

d) By day 7 the vascular network has formed and by day 14 the extraction socket is covered with early connective tissue rich in vessels and inflammatory cells (Cardaropoli, Araújo and Lindhe 2003).

e) By 4-6 weeks, the alveolus is filled with woven bone while the soft tissue becomes keratinised (Lin, McCulloch, and Cho 1994; Araújo and Lindhe 2005).

f) At 4-6 months the mineral tissue within the socket is reinforced with layers of lamellar bone that has been deposited into previously woven bone (Lin, McCulloch and Cho 1994; Araújo and Lindhe, 2005).

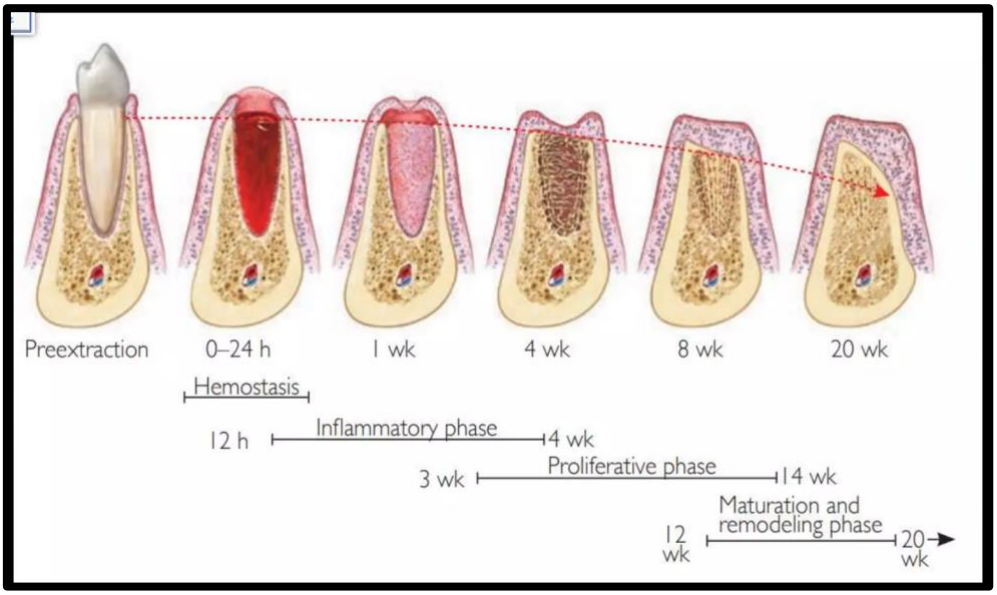

Figure 4: The healing process following tooth extraction

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2.9.5. The Cellular Content of Horizontal Platelet Rich Fibrin

The three main cell types found in all autologous platelet concentrates are platelets, leukocytes, and red blood cells (RBCs). The objective of producing a platelet concentrate was of course to concentrate platelets and because they are the lightest of all cells in blood, it was possible to use a

centrifugation device to separate these layers based on their density. Lighter cells, such as platelets, could be accumulated on top, followed by leukocytes and because RBCs are the densest, they tend to migrate downwards. In optimal circumstances, the final H-PRF product should be composed of platelets, leukocytes and fibrin. It has been shown that initially developed PRF concentrates contained greater than 90% platelets and more than 50% leukocytes within a high density fibrin network when compared to whole blood (Dohan Ehrenfest et al., 2010).

With more recently developed methods of cell quantification, researchers have been able to harvest leukocytes more specifically. The lower yield of leukocytes relative to platelets is as a result of their similar density to RBCs, making them difficult to separate and accumulate in the upper layers of PRF. Shorter centrifugation time and lower centrifugation forces have been proposed to favour the accumulation of cells (Ghanaati et al., 2014).

2.9.5.1 Platelets:

Platelets are anuclear, discoidal cell fragments derived from megakaryocytes within the bone marrow (Yadav and Storrie 2017) with an average lifespan of 9-10 days (Ogundipe, Ugboko, and Owotade 2011). They are the smallest of the blood cells with mean diameters of 2-5µm with a thickness of 0.5µm and quantity of 150-

400 x 10^9 in the average individual (Gremmel, Frelinger and Michelson 2016).

The role of platelets in haemostasis was first recognised by Bizzozero in 1882, who described their adherences to sites of blood vessel injury with formation of a platelet aggregate which marks the beginning of the repair process (de Gaetano and Cerletti, 2002).

The internal structure of platelets has been studied using electron microscopy, cell fractionation and platelet release studies (Yadav and Storrie, 2017). Platelets contain many of the cytoplasmic organelles found in most eukaryotic cells including mitochondria, endoplasmic reticulum (termed dense tubular system), endosomes and lysosomes as seen in Figure 5. These organelles are mainly secretory in function and release their contents in response to collagen, thrombin and thromboxane A2. Two additional platelet-specific secretory organelles were identified, α- granules and dense (δ) granules were identified in the 1960s for playing a central role in the process of haemostasis, thrombosis, angiogenesis and host defence.

Granule formation occurs in the megakaryocyte precursor, with maturation continuing in circulating platelets.

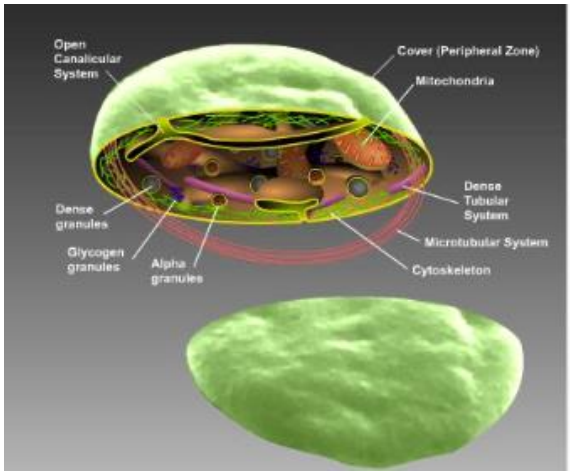


Figure 5. Internal platelet structure http://wwww.platelet-research.org/

2.9.5.2 Leukocytes:

Leukocytes play an integral role in PRF therapy and comprises at least 50% of the regenerative material, its predominant benefit being in wound healing (Dohan Ehrenfest et al., 2010). Studies from animal research and basic sciences demonstrated the impactful contribution of leukocytes in tissue regeneration by comparing PRP/PRF therapy with and without white blood cells (WBCs) (Perut et al., 2013; Pirraco, Reis and Marques 2013). In these split design studies, the contralateral side receiving leukocytes performed better and this encouraged further research to further incorporate and harvest leukocytes.

Though it has been well described that leukocytes contribute to host defence against pathogens, they also play a central role in immune modulation due to their ability to secrete inflammatory

cytokines such as IL-1β, IL-6 and TNF- α as well as healing cytokines such as IL-4.

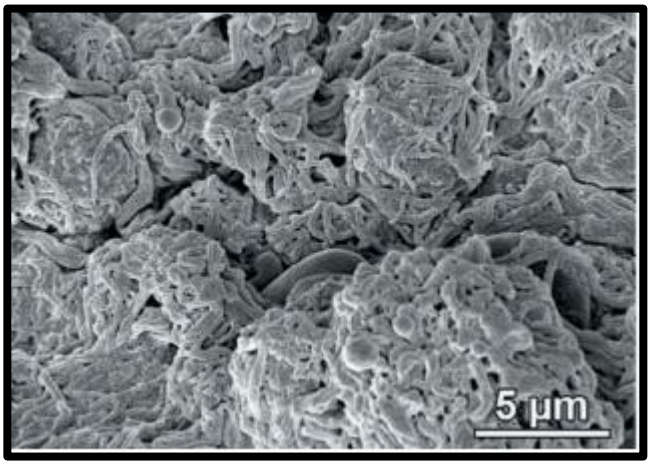


Figure 6: Spectrum electron microscopy examination of the fibrin clot revealing a dense and mature matrix with various cell types entrapped within its matrix

2.9.5.3: Growth Factors:

Growth factors (GFs) are critical to wound healing and are primarily responsible for the migration of cells while playing a critical role in their adhesion, proliferation, and differentiation. Though they exist in all tissues, blood acts as the main reservoir for numerous cytokines and GFs. Certain GFs may exist as inactive or partially active precursors that require proteolytic activation, or require binding to matrix molecules for activity or stabilisation (Kobayashi et al., 2016). GFs typically have very short half-lives ranging to only a few minutes (Clark, 2001). Unlike recombinant human GFs that usually consist of only a single GF, platelet concentrates create the

opportunity to deliver many autologous GFs simultaneously (Shaik et al., 2008). The GFs most accumulated and utilised in PRF include VEGF, PDGF, TGF-β1, EGF and IGF as discussed below.

Vascular Endothelial Growth Factor (VEGF)

VEGF is secreted by activated platelets and macrophages to sites of damage, promoting angiogenesis. It has previously been isolated and used as a recombinant GF and is believed to be the most potent GF for angiogenesis, stimulating increased blood flow to injured sites as well as stimulating blood vessel formation. It enables remodelling of tissues and when incorporated with bone biomaterials, it demonstrates regenerative properties (Shamloo, Xu and Heilshorn 2012).

Platelet Derived Growth Factor (PDGF)

These are essential regulators promoting the migration, proliferation and survival of mesenchymal cell lineages (Davis et al., 2014) and are believed to be the first growth factor detected in a wound, responsible for initiating connective tissue healing (Marx et al., 1998). Platelets are the major source of PDGFs, specifically in the α-granules. PDGF has an extremely short half-life (～2 minutes) and the ability of PRF scaffold to act as a reservoir by protecting PDGF

from matrix metalloproteinases improves the release profile dramatically when compared to PRP.

Transforming Growth Factor (TGF-β1)

TGF-β is part of a large collection of growth factors that mediate tissue repair, immune modulation, and extracellular matrix synthesis (Bowen, Jenkins and Fraser 2013). TGF-β1 is the predominant isoform and supports cell proliferation of multiple cell types (Clark, 2001). It plays a role in angiogenesis, re-epithialisation and connective tissue formation (Clark, 2001). Platelets are again the major source to produce this growth factor. Specific to bone healing and remodelling, TGF-β is also heavily released from autogenous bone (Clark, 2001).

Epithelial Growth Factor (EGF)

This group of growth factors are responsible for chemotaxis and angiogenesis of endothelial cells and mitosis of mesenchymal cells. When administered in its recombinant form, it has been shown to markedly shorten the overall healing process. It plays a role in increasing the tensile strength of wounds, as they exist on most human cell types including fibroblasts, endothelial cells and keratinocytes (Babensee, McIntire and Mikos, 2000).

Insulin-like Growth Factor (IGF)

IGFs regulate the proliferation and differentiation of most cell types. It is found in high concentrations in PRF because it is released from platelets during their activation and degranulation, facilitating differentiation of mesenchymal cells. It also constitutes the major axis for programmed cell apoptosis regulation by inducing survival signals protecting cells from apoptotic stimuli (Giannobile et al., 1996).

2.9.5.4: Fibrin

Fibrin is the activated form of a plasmatic molecule called fibrinogen that converts into fibrin with thrombin and it becomes one of the first key components to wound healing, Once a fibrin clot is formed within the centrifugation cycle, cells and growth factors are able to be trapped inside the 3D fibrin matrix, which enables the gradual release of GFs from PRF over time (Kobayashi et al., 2016).

Fibrin is a soluble fibrillary molecule that is present in high quantities in plasma itself as well as in the α granules of platelets and therefore plays a secondary role in platelet aggregation during haemostasis. The use of fibrin alone has been shown to lead to matrix stabilisation favouring tissue stability, cellular invasion and tissue regeneration (Mazzucco, Borzini and Gope 2010; Nguyen et al., 2012). Despite this, PRF has numerous advantages in that during

fibrin clot formation, a supraphysiologic concentration of platelets, leukocytes and growth factors are also present This comprises an intimate assembly of cytokines, glycanic chains and structural glycoproteins in a slowly polymerised fibrin network (Burnouf et al., 2013).

The fibrin scaffold produced following centrifugation is a three-dimensional biologic network, whereby the micropores support cell migration, proliferation and differentiation of growth factors. It also gives the matrix flexibility and strength which facilitates membrane adaptability into surgical sites and allows them to be sutured. This PRF scaffold is typically broken down within 2-3 weeks (Dohan et al., 2006b), as opposed to only a few hours, as observed with PRP (Kobayashi et al., 2016).

2.9.6 Clinical Effects of Horizontal Platelet Rich Fibrin on Tissue Healing

H-PRF facilitates three aspects in wound healing, namely angiogenesis, immunity, and epithelialisation.

2.9.6.1 Angiogenesis:

Neovascularisation necessitates a three-dimensional matrix that facilitates cellular migration, division and a change in phenotype of endothelial cells (Choukroun et al., 2006). H-PRF emulates physiologic fibrin polymerisation, and the efficacy of neovascularisation is significantly influenced by the rigidity of the

matrix as demonstrated in in-vitro models (Nehls and Herrmann, 1996). It is reasonable to infer that a system replicating physiological conditions would be more conducive to neovascularization than rapidly polymerized fibrin found in PRP (platelet-rich plasma) and fibrin glues.

Factors promoting angiogenesis are embedded within the fibrin matrix, including fibroblast growth factor-basic (FGFb), VEGF (vascular endothelial growth factor), angiopoietin, and PDGF (platelet-derived growth factor). Fibrin can induce the expression of αvβ3, another crucial step in angiogenesis. Endothelial cells expressing this factor can effectively bind to fibronectin, fibrin and vitronectin (Choukroun et al., 2006).

2.9.6.2 Biologic activity on immune cells

Strauss et al. carried out an extensive systematic review investigating the biologic properties of PRF in which 53 studies were included. They found that because PRF is capable of improving angiogenesis in vivo, it was reported that PRF enhanced the proliferation, migration, adhesion and osteogenic differentiation of various cell types along with the activation of cell signalling pathways (Strauss et al., 2020).

Furthermore, there have been recent studies showing the effects of PRF on macrophage polarisation from proinflammatory M1 to

proresolving M2 phenotypes. It is therefore thought that PRF has anti-inflammatory properties and can shift macrophage polarisation (Nasirzade et al., 2020). This may work in part to explain the observed decreases in postoperative pain on a clinical level.

2.9.6.3 Wound coverage and epithelialisation

The fibrin matrix plays a crucial role in promoting wound coverage at injury sites by influencing the metabolism of epithelial and fibroblast cells. Epithelial cells at the wound edge undergo a loss of basal and apical polarity, resulting in lateral extensions that project towards the wound edge to cover the defect. Additionally, factors like fibrinogen, fibronectin, tenascin, and vitronectin contribute to this process (Choukroun et al., 2006).

Fibrin, fibronectin, PDGF (platelet-derived growth factor), and TGF-β (transforming growth factor-beta) play pivotal roles in integrin expression, as well as the proliferation and migration of fibroblasts. The movement of fibroblasts within the fibrin clot is facilitated by their proteolytic activity. Cells can migrate within this transient matrix, a process enhanced by cross-linked α-chains between the fibrin fibrils. This feature is not shared by rapidly polymerized fibrin glue and PRP. The initiation of collagen formation occurs following fibrinolysis in the sequential healing process.

These properties, coupled with PRF's ability to trap stem cells, create an optimal environment for wound healing. Mesenchymal cells derived from circulating blood serve as a source of undifferentiated cells capable of developing into various cell types (Choukroun et al., 2006). Many studies, such as the prospective cohort study by Pinto and colleagues have demonstrated the beneficial effects of L-PRF. Pinto and his group examined the adjunctive benefit of topical L-PRF application in the management of forty-four patients with refractory leg ulcers (Pinto et al., 2018). Changes in wound area were examined postoperatively as well as patient reported outcomes such as pain levels and all wounds showed significant improvements, having previously been unresponsive to conventional treatment modalities. Caution should be taken when applying these findings to intraoral sites and it is essential to note that many studies examining wound coverage are conducted in vitro, with further in vivo research is needed to comprehensively assess tissue responses to PRF

2.9.7 Comparison of Centrifugation Devices

There remains ongoing debate about the influence of various centrifugation devices on the production of PRF. While it is acknowledged that there are quality differences between different devices, the more important factor to consider is how to optimise the centrifugation system.

In 2018 research was conducted to compare three commercially available centrifuges at high (700g) and low (200g) centrifugation forces. The machines used were IntraSpin (Intra-Lock), Duo Quattro and Salvin devices. Each of the tested groups was compared for cell numbers, GF release and by using scanning electron microscopy (SEM) for differences in morphology and clot size (weight and length/width) (Miron et al., 2020).

Findings revealed that PRF clots produced using lower speeds and less time contained a higher concentration of evenly dispersed platelets and secreted higher concentrations of GFs over a ten-day period, irrespective of the device. The protocol utilised led to the greatest difference. It was also found that when centrifugation was carried out at lower speeds, a less dense fibrin mesh was produced with more space to allow cellular migration.

Arguably the most important finding revealed in this 2018 study was that the choice of centrifugation tube has a large impact on the final size of the PRF clots compared to the centrifugation device, which has since led to a large volume of research on that specific topic (Miron et al., 2020).

2.10 Outcomes

This section explores the potential outcomes expected to be found during the trial based on similar studies found in the literature. The evaluation of these outcomes and justification for chosen scales is discussed in detail.

2.10.1 Evaluation of Pain

Several methods for evaluating pain have been developed in the literature, including both scales and inventories. Such scales for measuring pain intensity include the visual analogue scale (VAS), numeric scale, the verbal rating scale (VRS) and Faces Pain Scale-Revised (FPS-R) (see Figure 7) are employed widely in both clinical research and in pain surveys (Raspe and Kohlmann, 1994; Lund et al.,2005).

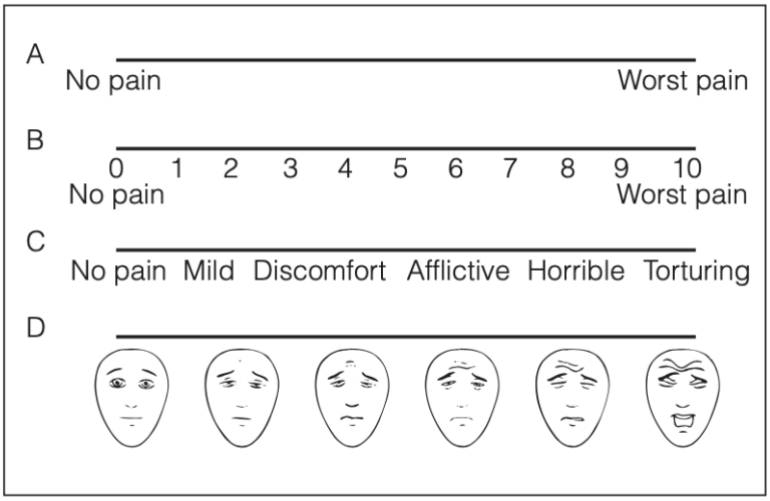


Figure 7: Pain scales employed for evaluation of pain. A. Visual Analogue Scale B.Numeric Scale C. Verbal Rating Scale and D. Faces Pain Scale- Revised. Printed with permission from (Hicks et al., 2001)

Dos Santos and her colleagues in 2012 investigated the concordance amongst different pain scales and found that each of them were highly correlated, demonstrating both validity and reliability for use in clinical dental practice but they are not interchangeable with each other (dos Santos Calderon et al., 2012). There has been no proven ideal pain scale, but any scale used should consider the patient's preference, age, and general characteristics.

The validity of the VAS was established by Lara-Mūnoz et al. who tested the VAS, VRS and NS in experimental conditions using a sound stimulus as a variable (Lara-Muñoz et al., 2004). Though it was concluded that the VRS provides more reliable scientific information, most investigators consider the VAS more sensitive as it has the ability to detect smaller variations in the intensity of pain (Hjermstad et al., 2011; Ohnhaus and Adler, 1975). Holdgate et al. showed correlation between the VAS and NS but also claimed that the minimum difference of 4mm is required to determine clinical changes in pain, which signifies that these scales cannot be used interchangeably and is in line with other studies (Holdgate et al., 2003; dos Santos Calderon et al., 2012).

2.10.2 Evaluation of Healing

There are three well described intraoral healing scales or indices used in the evaluation and monitoring of early wound healing in oral and maxillofacial surgery settings. These scales focus on assessment of healing in the inflammatory and proliferative phases. These include Landry's healing index, a modified version of Landry's Healing Index and the Early Wound Healing Index.

Landry's healing index included five clinical outcome parameters: tissue colour (percentage of pink vs red gingivae), presence of bleeding on palpation, presence of suppuration, incision margin (epithelisation and connective tissue exposure) and the presence of granulation tissue. The final score ranged from zero (very poor healing) to five (excellent healing). Modified versions of this index have been employed by multiple authors whereby the incision margin parameter may have

been replaced by AO (present/absent) or swelling, for example (Panneerselvam et al., 2016; Pippi, Santoro and Cafolla 2015).

Applications of this index to surgical site healing is particularly relevant in autologous platelet product interventional studies, as many authors have contributed accelerated wound healing to their use. These indices have been used in the context of randomised controlled trials evaluating the effectiveness of autologous blood products as adjuncts to healing. One study by Marenzi et al. studied the effect of treatment with L-PRF in 26 patients following 2-8 extractions. Wound healing was assessed at 3-, 7-, 14- and 21-days post-surgery in a split mouth design. The results of their study showed superior epithelisation on the side treated with L-PRF (Marenzi et al., 2015).

The Early Wound Healing Index (EHI) is more specifically used to evaluate mucoperiosteal flap healing and closure and again divides the quality of healing into five levels from 1 (complete flap closure) to 5 (incomplete flap closure - complete necrosis). Table 6 below summarises how various oral surgery articles have used different versions of the healing indices in their research.

Table 6: Use of Intraoral healing scales for oral surgery procedures (modified from (Hamzani and Chaushu 2018)

Study	Year	Study Design	No of Pts	Wound healing scale	Oral Surgery Procedure	Results
Yelamali et al.	2015	Split- mouth	20	Landry's Healing Index	Third molar extractions	PRF> control
Panneerselvam et al.	2016	Split- mouth, double blind	50	Modified Landry's Healing Index	Local anaesthesia	Lignocaine plain> lignocaine with adrenaline
Pippi et al.	2015	Split-mouth	20	Modified Landry's Healing Index	Tooth extraction	Wound healing improved with HemCon Dental Dressing
Mozzati et al.	2014	Split-mouth	34	Modified Landry's Healing Index	Tooth extraction	PRGF sockets > control
Marenzi et al.	2015	Randomised, single-blind, split mouth	26	Modified Landry's Healing Index	Tooth extraction	L-PRF > control
O Sullivan et al.	2022	Randomised, single-blinded, parallel group	74	Modified Landry's Healing Index	Third molar extractions	No statistically significant difference between PGRF and control
Farina et al.	2013	Parallel group	35	EHI	Intraosseous defect	Single flap approach alone leads to wound close in 2 weeks

2.10.3 Evaluation of Quality-of-Life Implications

Many instruments have been proposed to measure the impact of oral health on the quality of life. A plethora of specific quality of life assessment tools have been developed specific to dentistry and their psychometric properties evaluated (Slade, 1997). The Oral Health Impact Profile (OHIP) and its shortened form OHIP-14 are widely used as well as more specific oral surgery scales such as the Postoperative Symptom Severity Scale (PoSSe) and condition-specific Health-Related Quality of Life (HRQOL). These tools aim to gauge the subject's perception of the social impact of oral disorders on his or her wellbeing. Measuring quality of life outcomes can also aid in evaluating the process of treatment in a research context in cohort studies and randomised control trials as the views of patients are incorporated.

Condition-specific Health-Related Quality of Life (HRQOL) instruments were first introduced to evaluate short-term outcomes of third molar surgery. These instruments were based on the original work of Torrance (Torrance, 1987) and developed into a questionnaire by Shugars et al. (Shugars et al., 1996). Emphasis is placed on four patient-centred outcome measures which include oral function, general function, pain and any other symptoms.

Though the limitation of this questionnaire is that it is not validated for use in cases of AO, it is more readily applicable to patients with this postoperative complication compared to other quality of life tools. No single outcome tool exists to satisfy the multidimensional and subjective components of quality of life. As a result,

clinicians must carefully select an outcome assessment tool which is best suited to the outcomes of interest in their specific population.

2.11 Aims, Research Question and Null Hypothesis

The purpose of this trial is to assess the efficacy of Horizontal Platelet Rich Fibrin (H-PRF) compared to Alveogyl in the treatment of alveolar osteitis. This study is the first in the literature to assess the efficacy H-PRF in the context of alveolar osteitis.

2.11.1 Aims:

1. To compare the efficacy of Alveogyl (control) to H-PRF (test) for pain reduction in the treatment of alveolar osteitis
2. Investigate whether the choice of material (Alveogyl vs H-PRF) influences postoperative clinical outcomes

2.11.2 Research Questions

1. Is there a clinically significant difference in pain relief achieved by patients with AO who receive H-PRF compared to Alveogyl at day three and day seven following treatment?
2. Is there a clinically significant difference in soft tissue healing at the AO site at day seven in patients who are treated with H-PRF compared to Alveogyl?
3. Do patients report significant differences across various quality of life parameters at day three and day seven when treated with H-PRF as opposed to Alveogyl?

The research questions were investigated using the following primary and secondary outcomes:

Primary outcomes:

- VAS pain score measured on day 0, day 3 and day 7 following intervention, with worst pain on day 3 being the primary outcome

Secondary outcomes:

- Analgesia consumption
- Socket healing using modified Landry et al., healing index
- Health Related Quality of Life measurements

2.11.3 Null hypothesis

The use of H-PRF in the treatment of alveolar osteitis has no effect on pain or other postoperative clinical outcomes compared to Alveogyl in the immediate postoperative period.

CHAPTER THREE

MATERIALS AND METHODS

3. Materials and Methods

3.1 Trial Design

3.1.1 Study Design

The study design took the form of a double-blind superiority randomised controlled trial using a parallel-group design with a seven-day follow-up period. The 2010 CONSORT statement was applied in the reporting of the study (Schulz et al., 2010).

3.1.2 Ethical Approval

Ethical approval was obtained from Trinity College Dublin, Tallaght Hospital/ St James' Hospital Joint Research Ethics Committee with full approval granted in August 2022 (Appendix 1).

3.1.3 Registration of Trial

This trial was registered as a randomised clinical trial on ClinicalTrials.gov in September 2022 before recruitment commenced (NCT05615272).

3.2 Participants

3.2.1 Patient Sample

The sample was recruited from a cohort of patients referred to the Accident and Emergency Department of Dublin Dental University Hospital (DDUH) either by their general dental or medical practitioners. Those patients who self-referred to Accident and Emergency and were internally referred from colleagues within the Dublin Dental Hospital were also assessed for suitability. The Irish Association of

Oral Surgery committee and the Dental Lead of the National Coagulation Centre at St James' Hospital were also invited to refer any suitable patients for inclusion in the study.

Recruitment of subjects began in September 2022 and ceased in February 2024 (18-month total period). The house officers in the Accident and Emergency Department of DDUH were trained as gatekeepers of the study through two dedicated hours of teaching. They provided potential study patients with information leaflets, which explained the study, and the benefits and risks of treatment (See Appendix 2). The lead investigator was notified, and the patient asked to participate once all inclusion and exclusion criteria were fulfilled. Written consent to participate was attained in all cases (Appendix 3).

There was no interval between receiving study information and providing written informed consent in this research as AO requires immediate intervention to alleviate pain in a timely manner. Although each subject was given appropriate time to consider participation with all options clearly explained, for optimum results treatment started on the day the patient presented to DDUH with AO.

3.2.2 Selection Criteria

The following inclusion and exclusion criteria applied to the sample population:

Inclusion Criteria	Exclusion Criteria
Male and female adults at least eighteen years of age with capacity to give informed consent	Pregnant or breastfeeding women
A diagnosis of AO following tooth extraction as per Blum's definition (Blum 2002).	Current or previous use of drugs predisposing to Medication Related Osteonecrosis of the Jaw (MRONJ) or history of radiotherapy to the jaws
Good command of the English language	Current systemic antibiotic use
Willingness to keep a diary of symptoms and travel for the review appointment on day seven (T2) following intervention	Allergy or intolerance to study materials
	Patients who do not want to participate in the study or who are unwilling to follow the study protocol as well as those lacking capacity to give informed consent

3.2.3 Location

All aspects of the study were completed in the Department of Oral and Maxillofacial Surgery at Dublin Dental University Hospital (DDUH).

3.3 Data Collection

The initial assessment and recruitment of patients for the study was completed by the team of house officers in the Accident & Emergency department of Dublin Dental Hospital. They made the principal investigator aware of the patients presenting with both history and examination findings consistent with AO. They also provided all potential participants with verbal and written information about the study.

The gatekeepers ensured that all recruited patients met the selection criteria.

Once accepted into the study and before intervention, the following information was recorded:

1. A detailed history which included medical history, social history, and history of presenting complaint, with a specific focus on the timing of onset of these symptoms and the presentation for treatment
2. Details surrounding the indication for extraction were noted along with the surgical approach for removal (simple, flap +/- bone removal and tooth sectioning).
3. Specific details of smoking or vaping were recorded in the postoperative period.

4. The presence of any facial asymmetries, cervical lymphadenopathy, pain, and paraesthesia was recorded.
5. The site of AO was recorded, and a clinical photograph was taken.
6. Where applicable in cases where the history was ambiguous surrounding the extraction completed external to DDUH, a periapical radiograph was taken to assess for the presence of retained roots or bony sequestrae.
7. All patients were given oral hygiene and analgesia instructions as well as smoking cessation advice if required.

3.4 Interventions

All patients were treated by a single skilled operator, the principal investigator. Venipuncture was performed on all patients, with blood collected into two 10ml plain glass tubes without anticoagulant (Figures 8 & 9). Performing venipuncture on both groups facilitated patients to be blinded to subsequent group allocation.

Figure 8: Illustrates venipuncture

Figure 9: Collection of whole blood with a 21-gauge butterfly needle

Local anaesthetic was administered using 2% Lidocaine 1:80,000 adrenaline via inferior alveolar nerve block and/ or infiltrations as applicable to the affected site. Each socket was irrigated gently with twenty millilitres of sterile saline.

For the subjects allocated to H-PRF, their whole blood sample was centrifuged for eight minutes at 700 RCF according to the Bio-PRF protocol. If the patient was taking an anticoagulant, the blood was centrifuged for an additional 4 minutes. This process was performed efficiently to prevent the initiation of the clotting cascade.

Figure 10: Demonstrates the H-PRF in the superior layer with the red blood cells at the base of the tube

The H-PRF was then transferred and prepared using the FDA/CE approved Bio-PRF centrifuge and kit as per protocol (Bio-PRF EU, Puredent, 4000 Roskilde Denmark). Due to the size and shape of the sockets, H-PRF clots were prepared into plugs using the Expression kit. The socket was then sutured with 4-0 Mersilk to ensure retention of the study material.

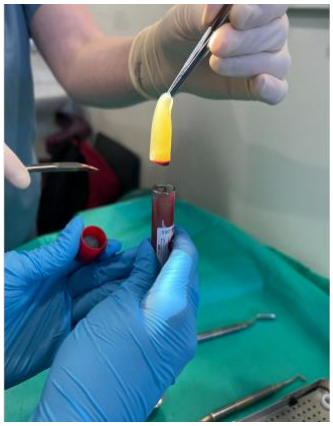


Figure 11

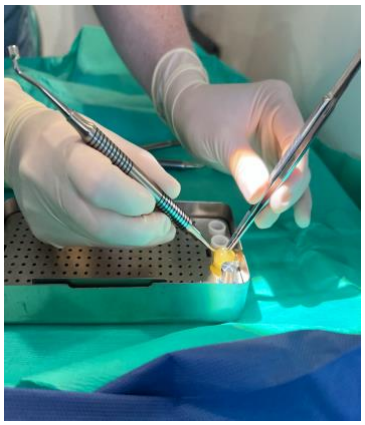


Figure 12

Figure 13

Figures 11-13: Demonstration of the clot being removed from the tube with fine forceps using an aseptic technique with most red cells being removed. A piston and cylinder assembly is then used to make H-PRF plugs in the Expression kit.

For the subjects allocated to Alveogyl group, though venipuncture was performed for blinding purposes, these subjects did not have their whole blood sample placed into the centrifuge. Instead, their socket was irrigated with 20 millilitres of saline and 0.2g was placed into the socket as per manufacturer's instructions. The socket was sutured with 4-0 Mersilk to ensure retention of the study material. The rationale for choosing Alveogyl as the control intervention material was based on the outcome of a questionnaire distributed to dental practitioners (see Appendix 4).

All patients received standard postoperative instructions and were advised on analgesia regimen including paracetamol 1g four hourly and ibuprofen 400mg six-hourly, while encouraged to rinse with warm saline three times daily. Patients were asked to record both the frequency and quantity of analgesia taken on the

provided pain diary, on day of presentation (T0), and on day 3 (T1) and day 7 (T2) following intervention.

All patients received a virtual follow-up appointment by the treating clinician by telephone on day 3 postoperatively (T1). Patients were asked to return to the clinic for review on day 7 (T2) postoperatively. An inspection was performed by the original treating clinician with removal of sutures and remaining Alveogyl if applicable, followed by saline irrigation. A second blinded assessor thereafter graded socket healing using a modified version of the healing index devised by Landry et al. Quality of life scores, pain scores and analgesia consumption were also documented at day 3 (T1) and day 7 (T2) following intervention and clinical photographs were taken of the sockets at day 0 (T0) and day 7 (T2).

3.5 Outcome Assessment

3.5.1 Primary Outcome:

3.5.1.1 Evaluation of Pain

Pain was measured objectively at days 0, 3 and 7 of treatment using a validated Visual Analogue Scale (VAS) questionnaire as part of a pain diary (Appendix 5). The VAS was represented with a 100mm horizontal line between two verbal descriptors at either end. This VAS was used to record patients' average pain and worst pain in the previous twenty-four hours. The participant was asked to mark the point of this line with an "X" where their pain is best represented at each timepoint pre- and post-surgical intervention, and this was

measured by the primary investigator in millimetres. Of note, these evaluations were done in person on day 0 (T0) and day 7 (T2) but virtually by telephone consultation on day 3 (T1). The patients returned the day 3 pain diary at their in-person follow up appointment on day 7.

The worst pain score at day 3 (T1) was the primary outcome for subjects who received control and test materials. This was verbally explained to the patient as the worst pain experienced in the previous twenty-four hours, without any analgesia whereas average pain was to be considered when analgesia was taken.

3.5.2 Secondary Outcomes

3.5.2.1 Analgesia Consumption

Patients were asked if they were using any form of analgesia from the day of presentation until trial cessation (T0, T1, T2) and this analgesia consumption (number of tablets and frequency of consumption) was recorded within a 24-hour period (Appendix 5). Patients were given a standardised DDUH postoperative instruction leaflet and asked to take a combination of Paracetamol 1g 4 hourly and Ibuprofen 400mg 6-hourly as required, where there were no contraindications. Those who had previously started on variations of analgesia including codeine use were also included.

3.5.2.2 Evaluation of Healing

All patients were assessed on the seventh day (T2) following intervention for suture removal and irrigation by both principal investigator and one of three calibrated second blinded assessors. Clinical photographs were taken at each appointment. A modified version of the Landry Healing Index (see Appendix 6) was used by each of the three assessors.

This modified version of Landry's healing index included four clinical outcome parameters: tissue colour (percentage of pink vs red gingivae), presence of bleeding on palpation (yes/no), presence of suppuration (yes/no) and presence of exposed bone (yes/no). The assessors were asked to circle the finding most appropriate under each subheading and then select the most accurate representation of the socket's healing. The final score ranged from one (very poor healing) to five (excellent healing).

Resolution of the AO was classified as the presence of granulation tissue within the alveolus and no visual or probable exposed bone. The evaluation of healing at Day 7 (T2) was a secondary outcome of the study.

3.5.2.3 Quality of Life Assessment

A condition-specific Health-Related Quality of Life (HRQOL) instrument for evaluating short-term outcomes of third molar surgery was used in this study. It describes different aspects of the patients' overall wellbeing. Four quality of life parameters are explored to represent different dimensions of dental outcomes which include oral function, general function, pain and any other symptoms. Versions of this questionnaire had previously been used at our institution by other investigating authors (see Appendix 5).

This self- administered questionnaire consisted of seven items representing the 4 dimensions of dental outcomes: chewing foods, mouth opening, talking, sleeping interference with work/school attendance, interference with regular daily routine and social life. Five-point Likert-type scales were used as the response format. For the HRQOL, each outcome was scored: 'none' - score 1, 'a little'- score 2, 'some'- score 3, 'quite a bit' - score 4 and 'a lot' -score 5. A high HRQOL score represents poor quality of life.

A VAS, similar to those described for pain assessment, was used to record interference with daily activities. Each patient was given a questionnaire to fill out on the initial day of assessment and was instructed to complete another on day 3 post-intervention when

they received their virtual review. This also facilitated the patients to inquire about any problems or difficulties they had with the diary. At their postoperative review on day 7, each patient again completed a questionnaire.

3.6 Sample Size Calculation

Initially effect size was based on Cohens as there were no previous studies available to provide additional information. A second interim power calculation was done by a biostatistician on the first 10 participants. Blinded, de-identified data on the first ten participants was used to assess the effect size of the primary outcome of the worst pain score on Day 3 (T1) following intervention. Sample size calculation was performed in G*Power v3. 1.

Based on data from the first 10 participants an r^2 of 0.24 was observed, producing an effect size of 0.32. Using 3 independent variables (treatment, age, and gender) with 5% alpha and 90% power, a sample size of 29 was required to detect significant differences in worst pain score at Day 3 (T1). Anticipating a 10% drop out rate the sample size was increased to 33 participants.

3.7 Randomisation:

3.7.1 Sequence generation

The patients were allocated into one of two study arms, Horizontal-Platelet Rich Fibrin (H-PRF) or Alveogyl via computer-generated randomisation. Patients were assigned to the experimental and control groups in a 1:1 ratio, using randomly permuted blocks of size 10. All patients allocated to

the experimental group received the H-PRF “clot” or “plug” into their dry socket prior to wound closure. Those allocated to the control group received Alveogyl medicament into their socket prior to wound closure.

3.7.2 Allocation Concealment

Study arm allocation was made available only to the principal investigator via concealed allocation. Brown sealed opaque envelopes were consecutively numbered and were used for all participants. Within each envelope a card with a number (1 or 2) was contained and written instructions for the operating surgeon, “PRF-yes” or “PRF-No”. Each envelope was labelled with the study code number. After reviewing the instructions within each envelope, the card was discarded immediately in the confidential waste by the operating surgeon.

3.7.3 Implementation

The random sequence allocation was computer-generated, and assembly of the envelopes was done by a third party, who otherwise had no affiliation with the study. Enrolment of participants and all interventions were done by the principal investigator with the house officers in the Accident & Emergency department acting as gatekeepers, alerting the operating surgeon to patients presenting with AO.

3.8 Blinding:

All study participants and the second blinded assessor doing the examination on day 7 (T2) were blinded to the study arm allocation. Patient blinding was achieved

by obtaining blood from all subjects irrespective of study arm allocation and not disclosing whether they had been assigned test or control materials.

The second blinded assessors were three experienced oral surgeons working within the Oral & Maxillofacial department. Their first encounter with any participant was at day 7 (T2) following intervention following suture removal and irrigation by the principal investigator which ensured there was no residual material visible within the sockets. Each patient's electronic record did not disclose which of the materials the patient received in order to meet blinding requirements.

3.9 Training & Calibration:

Teaching was carried out by the principal investigator for both the house officers staffing the Accident & Emergency Department who would act as gatekeepers for the study as well as for the second blinded assessors of healing. Teaching the gatekeepers comprised of a two-hour dedicated teaching session via Powerpoint to ensure that each of the NCHDs understood the value of carrying out the study as well as potential benefits and risks. Further information was distributed by email and all house officers were given copies of the patient information leaflets, pain diaries and written consent forms. A refresher teaching session was carried out the principal investigator biannually and any queries about eligibility criteria were resolved in person or by email.

A separate one-hour teaching session on how to clinically apply the modified version of Landry's Healing Index was conducted by the principal investigator with all three second assessors before study commencement. The assessors were then

sent twenty images of sockets via SurveyMonkey with various grades of healing at two separate timepoints. Assessors were calibrated against one another to ensure high inter- and intra-examiner reliability. A Kappa coefficient was calculated by the statistician which resulted in showing an inter-examiner reliability score of 0.776 and a mean intra- examiner reliability score of 0.76 (0.858, 0.814, 0.608)) thereby demonstrating good inter-and intra-examiner reliability. Each socket was photographed pre- and postoperatively in case there was any ambiguity in assessment outcomes and to facilitate reassessment at any timepoint, if necessary.

3.10 Statistical Methods:

All data collected was transferred onto an Excel (Microsoft Corporation) spreadsheet before analysis. Data analysis was performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

For the randomised controlled trial, descriptive statistics were used to describe patient demographic characteristics, ASA status, smoking status, site of AO (maxilla/mandible), tooth type (premolar/molar/third molar), reason for extraction and difficulty of extraction. Number and percentage of participants within each group of demographic variables were reported. Mean and standard deviation (median and interquartile range, where appropriate) of outcomes were reported. A chi-square test was used to study the potential association between demographic variables and treatment groups. Subsequent analyses examined the differences in outcomes between groups at day 3 post-intervention and at day 7 post-intervention.

The primary outcome was the worst pain score at day 3 measured by 100mm VAS. For this analysis and other continuous variables, a non-parametric test, Mann-Whitney U test was used for comparison. The significance level was determined as $P<0.05$.

The difference between treatment groups was also analysed for worst pain day 7 post-intervention as well as the average pain across all timepoints using Mann-Whitney U test. The pain reduction between day 0 and 3 as well as between day 0 and 7 was analysed between treatment groups using a t-test.

The secondary outcomes included analgesia consumption, healing outcomes and quality of life outcomes. Analgesia consumption was presented both for Paracetamol, Ibuprofen and codeine. Paracetamol and Ibuprofen consumption were reported by the number of tablets consumed in a 24-hour period and the difference between treatment groups was analysed using Mann Whitney test at all timepoints. Codeine consumption, however, was recorded as a binary variable (yes/no) and therefore the difference between treatment groups was analysed using chi square test.

Healing was reported as an ordinal variable (5-point Likert scale) and therefore the difference between groups was analysed using a Mann Whitney test.

For the health-related quality of life parameters, the difference between treatment groups in terms of the improvement between day 0 and day 3 as well as between day 0 and day 7 were analysed. Median, interquartile range, effect size and p-values for appropriate tests of comparison between treatment groups are reported.

CHAPTER FOUR

RESULTS

4. Results

Results from Randomised Controlled Trial

4.1 Participant Flow

A total of fifty-seven patients were assessed for inclusion in the study by gatekeepers. Fifteen of those patients were excluded from the study as they did not meet inclusion criteria: postoperative antibiotics prescribed (n=7), diagnosis of postoperative infection made (n=5), pregnant (n=1), history of oral bisphosphonates (n=1), retained root in socket (n=1). A further four patients were excluded for other reasons; the principal investigator unavailable to treat (n=2), did not want to return for follow-up (n=2).

Thirty-eight patients with thirty-eight disease sites were enrolled in the study. An attrition rate of 2.7% meant that a total of thirty-seven patients completed all stages of follow up to the endpoint. A total of thirty-seven patients with thirty-seven affected extraction sockets completed all stages of follow-up to the endpoint.

One patient was excluded from the study due to admission to hospital with an acute exacerbation of cystic fibrosis, which meant she could not return for follow-up (see Figure 14).

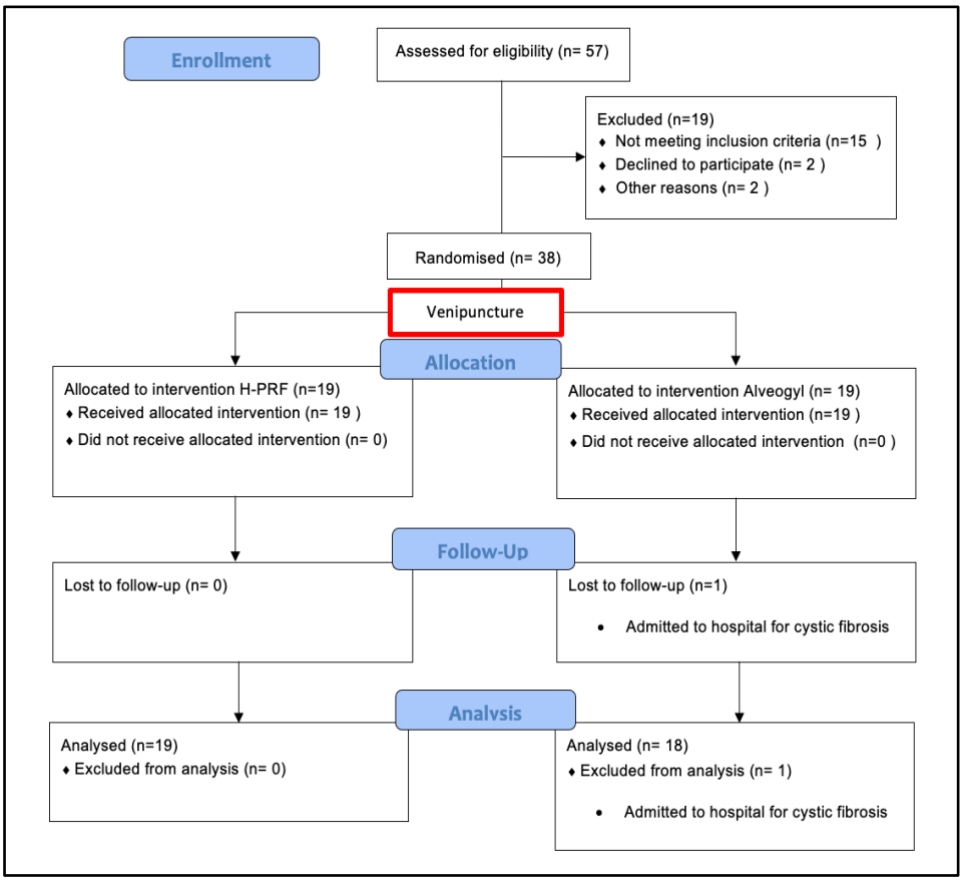


Figure 14: Consolidated Standards of Reporting Trials **(**CONSORT) 2010 Flow Diagram representing how participants were enrolled, randomised, and followed up and analysed in this randomised controlled trial.

It should be noted that venipuncture was performed on all patients for the purposes of blinding.

4.2 Recruitment

Recruitment of subjects began in September 2022 and ceased in February 2024 (i.e., 18-month total period). The trial was ceased by the principal investigator when the appropriate sample size was achieved to allow adequate time to disseminate the trial's findings. The mean time from tooth extraction to the onset of alveolar osteitis symptoms was 2 days (+/- SD 0.8) whereas average time to present for treatment in Dublin Dental Hospital was 4.6 days (+/- SD 1.4).

4.3 Subject Demographics

The first set of analyses of the data generated summarises patient demographics, clinical characteristics, and surgical data. It was assumed that groups are balanced at the outset due to randomisation and as a result no formal statistical comparisons were made.

4.3.1 Patient Age

A total of 37 patients enrolled in the study with a mean age of 39.5 years (+/- 12.9 SD) ranging from 21 to 78 years. The mean age of patients in the experimental (H-PRF) group was lower than that of the control (Alveogyl) group at 37.2 and 41.9 years, respectively. Summary statistics for age among the groups are displayed in Table 7. There was no significant difference in participant's ages between both groups (t= 1.11, df=35, p-value= 0.277).

Table 7. Age profile of study population

Age (years)	**Total (n= 37)**	**H-PRF group (n=19)**	**Alveogyl group (n=18)**
Mean	39.5	37.2	41.9
Standard deviation	12.9	12.2	13.4
Range	21-78	21-70	24-78

4.3.2 Patient Gender

Of the 37 patients who participated in the study, the number of males and females was very similar with 18 males (48.6%) recruited compared to 19 females (51.4%). Gender stratification was achieved between the two study arms with 7 (38.9%)

males and 12 (63.2%) females in the experimental group and 11 (61.1%) males and 7 (36.8%) females in the control group.

A chi-square test was performed to examine the relation between gender and treatment group allocation and these variables were found to be not significant; $\chi 2$ = 2.18 and p= 0.145. Gender data are presented in Table 8.

Table 8. Gender distribution amongst the study population with stratification for gender between study arms.

Gender	**Total (n=37)**		**H-PRF Group (n=19)**		**Alveogyl Group (n=18)**	
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
Male	18	48.6	7	38.9	11	61.1
Female	19	51.4	12	63.2	7	36.8
Total	37	100	19	51.4	18	48.6

4.3.3 Patient Ethnicity

Amongst those participants recruited the majority were White Irish, accounting for 30 of the total 37 (81.1%). The remainder included White Romanian (n=2), White Italian (n=2), Middle Eastern (n=2) and Black Nigerian (n=1). The distribution of nationalities was relatively consistent between H-PRF and Alveogyl groups (Table 9)

Table 9. Ethnicity of study participants, with stratification for study arm allocation.

Ethnicity	**Total (n=37)**		**H-PRF group (n=19)**		**Alveogyl Group (n=18)**	
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
White Irish	30	81.1	15	78.9	15	83.3
White Italian	2	5.4	0	0	2	2.4
White Romanian	2	5.4	1	5.3	1	5.6
Middle-Eastern	2	5.4	2	10.5	0	0
Black Nigerian	1	2.7	1	5.3	0	0

4.3.4 Smoking

All patients were questioned on their smoking status specifically in the postoperative period and this was quantified on their patient record. Eighteen patients (48.7%) were smokers with an additional two patients vaping (5.4%). Seventeen patients were non-smokers (45.9%). There was a very slightly higher proportion of smokers in the control group (50%) compared to the experimental group (47.4%).

A chi-square test of independence was performed to examine the relation between smoking and treatment group allocation, and this was found not to be significant; $\chi 2$ =0.032, p=0.984.

Table 10. Smoking status of participant with stratification for study arm allocation.

Smoker	Total (n=37)		H-PRF Group (n=19)		Alveogyl Group (n=18)	
	Frequency	%	Frequency	%	Frequency	%
Yes	18	48.7	9	47.4	9	50
No	17	45.9	9	47.4	8	44.4
Vaping	2	5.4	1	5.3	1	5.6
Total	37	100	19	100	18	100

4.4 Clinical characteristics

4.4.1 ASA Status

The American Society for Anaesthesiologists classification was used to assess and communicate each participant's medical comorbidities. Of the 37 study participants, 21 (56.8%) participants were graded ASA I which signifies overall good health. 14 (37.8%) were classified as ASA II signifying mild systemic disease and 2 (5.4%) were ASA III. ASA III represents patients with "a severe disease process which limits activity but is not incapacitating". This status was given to one patient with a history of myocardial infarction, chronic thrombocytopenia and asthma and another patient who reported having hypertension, type II diabetes and a history of unstable angina previously treated with stents. The distribution of these patients was even between both experimental and control groups.

A chi-square test was again used to assess the relationship between ASA classification and treatment group allocation, and this was not found to be significant; $\chi 2$ = 0.021 and p=0.990.

Table 11. ASA Status of study participants, with stratification for study arm allocation.

ASA Grade	Total (n=37)		H-PRF Group (n=19)		Alveogyl Group (n=18)	
	Frequency	%	Frequency	%	Frequency	%
I	21	56.8	11	57.9	10	55.6
II	14	37.8	7	36.8	7	38.9
III	2	5.4	1	5.3	1	5.6
Total	37	100	19	100	18	100

4.4.2 Site & Tooth Location

Twenty-nine cases arose in the mandible (78.4%), with eight in the maxilla (21.6%). There was a relatively even distribution of these cases between treatment groups and a chi-square test was used to analyse this relationship, returning as not significant; $\chi 2$ = .007, p=0.931.

Premolar and molar sites were the only affected sites in this study, with no patient presenting with AO from an incisor or canine extraction. Third molar sites were examined as a separate entity to first and second molar sites.

Of the 37 extraction sockets, 6 were premolar sites (16.2%), while 15 (40.5%) were molar (first & second molars) and 16 (43.2%) were third molar sites. There was no

significant difference between tooth number and treatment group allocation; $\chi 2$ = 4.910, p= 0.086.

4.4.3 Reason for Extraction

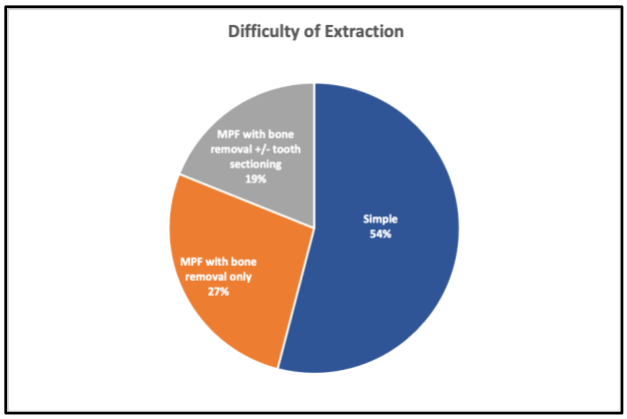
The justification for removal of each tooth was recorded from the patient's history and divided into caries (including retained roots), irreversible pulpitis, pericoronitis and periodontal disease. The predominant reason for extraction was caries (64.8%), followed by pericoronitis (18.9%). Patients with irreversible pulpitis represented 13.6% of the sample and one patient had periodontal disease affecting the extracted tooth (2.7%).

4.4.4 Difficulty of Extraction

Complexity of extraction was classified as 1) Simple forceps extraction with no bone removal required; 2) Mucoperiosteal flap raised with bone removal only and 3) Mucoperiosteal flap with tooth sectioning +/- bone removal.

20 patients had a simple extraction (54%), 10 patients had a flap raised with bone removal only (27%) and the remaining 7 patients had a flap raised with bone removal and/or tooth sectioning (19%).

Figure 15: A pie chart representing the patient-reported difficulty of extraction leading to a diagnosis of alveolar osteitis



4.5 Numbers analysed

The numbers analysed in each group were consistent throughout all variables at all timepoints (T0, T1, T2), with one exception, resulting in 18 participants analysed Alveogyl group compared to 19 participants in the PRF group.

The exception to this in the measurement of quality-of-life parameters. Five participants in the study were neither in work or school and answered this question as “not applicable (N/A)”. This resulted in 16 patients allocated to each treatment group for this question only.

4.6 Outcomes

In both treatment groups, all clinical outcome measurements improved during the study. For patients treated with both H-PRF and Alveogyl, improvements were progressive for all measures, with the best outcomes observed at the review appointment on day 7 (T2).

4.6.1 Primary Outcome- Pain

4.6.1.1 Day Three Worst Pain

For the purposes of the sample size calculation, the primary outcome for the study was chosen to be the worst pain score at day 3 following intervention on day 0. Non parametric Mann Whitney U Test was performed to compare groups for "worst pain" experienced at Day 3 (T1). The analysis showed that the worst pain score was significantly improved in the H-PRF group. The mean worst pain score for control group patients at T1 was 64.11 millimetres as compared to 46.95 millimetres in H-PRF patients (Z=2.49, p=0.011).

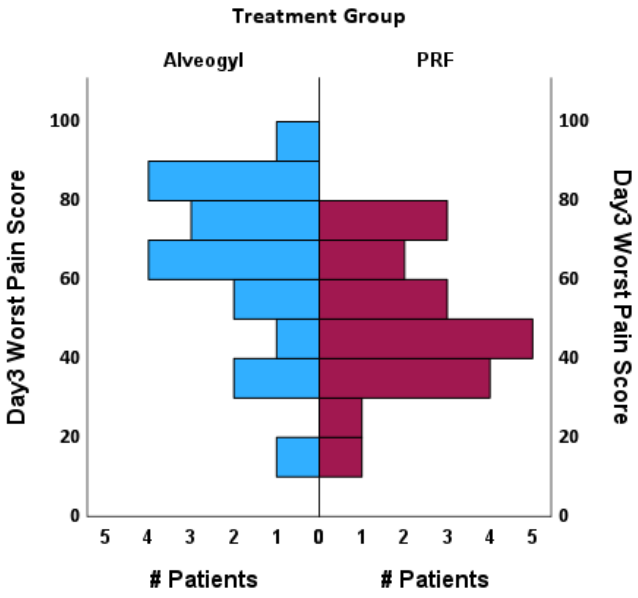


Figure 16: A bar chart representing worst pain score in both control and test groups at day 3 (T1) following intervention

4.6.1 2 Day Seven Worst Pain

Non parametric Mann Whitney U Test was performed to compare treatment groups for “worst pain” experienced at Day 7 (T2). The analysis showed that pain reduction was significantly better in the H-PRF group (Z= 2.76, p=0.006). The mean worst pain score for control group participants was 23.67 millimetres compared to 9.42 millimetres for those in the H-PRF group.

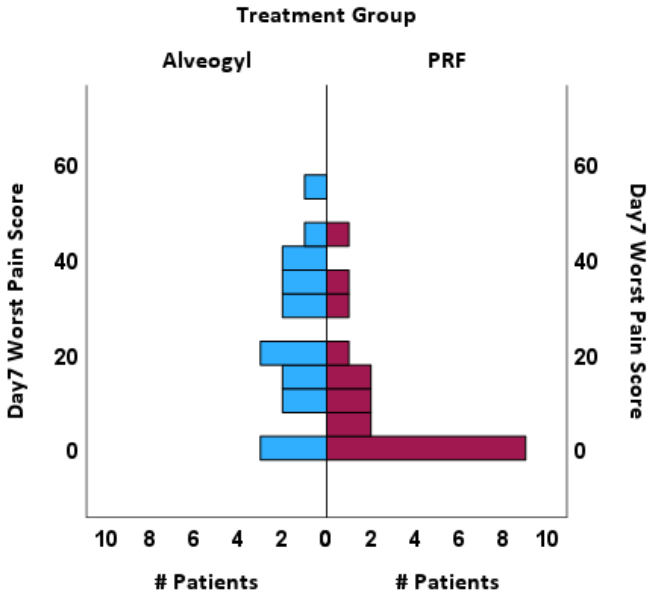


Figure 17: A bar chart representing worst pain score in both control and test groups at day 7 (T2) following intervention

4.6.1.3 Evaluation of Worst Pain over Timepoints

The regression analysis showed that pain at baseline (T0) was not the significant predictor of pain at Day 3 (T1) for any of the treatment groups ($p>0.05$). It was therefore decided to run a generalised linear model for repeated measures of worst pain instead of ANCOVA.

The analysis showed that worst pain scores reduced both significantly and progressively over the seven days ($p=0.001$) post-intervention in both treatment groups. There was no significant difference in mean worst pain scores between groups at baseline (T0).

Though there is progressive improvement in both treatment groups, pain reduction happens sooner in the H-PRF group and by post-intervention day 3, these participants have a lower worst pain score compared to the control group.

The mean scores for different groups across the three postoperative days (T0, T1, T2) are presented in Table 12.

Table 12: The mean of worst pain scores (VAS, 100mm line) represented at baseline, day 3 and day 7 post-intervention with 95% confidence intervals (CI)

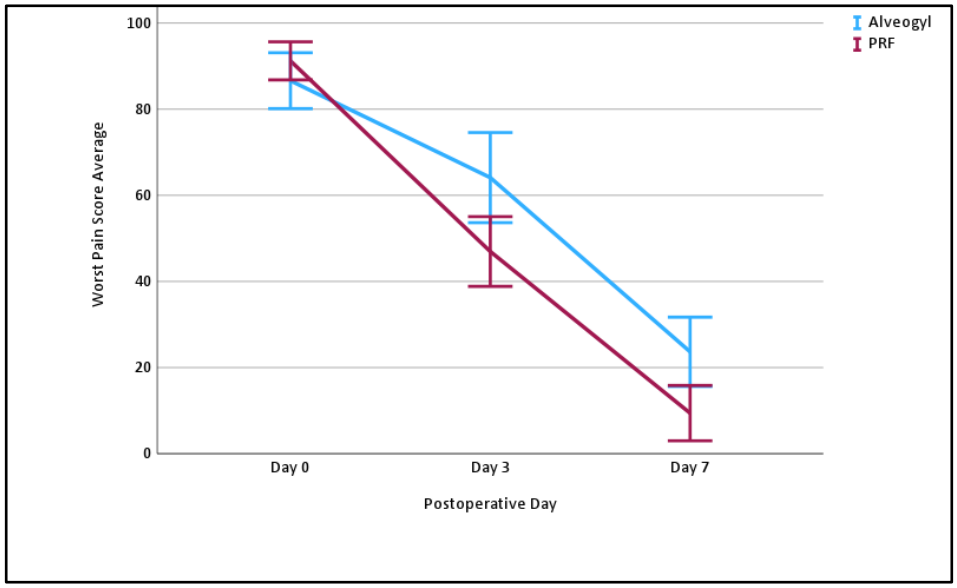
			95% Wald Confidence Interval		p- value
Day	**Group**	**Mean**	**Lower**	**Upper**	
0	Alveogyl	86.81	80.87	92.47	0.294
	H-PRF	91.21	87.2	95.22	
3	Alveogyl	64.11	54.66	73.56	0.011*
	H-PRF	46.95	39.59	54.3	
7	Alveogyl	23.67	16.41	30.92	0.006*
	H-PRF	9.42	3.6	15.25	
*p-value as reported by Mann Whitney test *p<0.05*					

4.6.1.4 Evaluation of Pain Reduction over Timepoints

An analysis was performed to assess pain reduction amongst groups between T0 and T1 as well as between T0 and T2. Data distribution was tested using a Kolmogorov-Sminov test which proved the data had parametric distribution and a t-test was used to compare pain reduction between the groups.

This analysis showed that mean pain reduction between T0-T1 was significantly better in the H-PRF group compared to control (p=0.005) and this was again found to be true when measured from T0-T2 (p=0.001). Data is tabulated in Table 13 below.

Table 13: Analysis of reduction in pain on 100 mm VAS scale reported between Day 0-3 (T0- T1) and Day 0-7 (T0-T2) with stratification for study arm allocation



Day	Group	Mean (SD)	Median (Q1-Q3)	p-value
0-3	Alveogyl	22.5 (26.76)	28.5 (5-33)	0.005*
	H-PRF	44.2 (16.9)	42 (29-54)	
	Combined groups	**33.67 (24.5)**	**33 (24-47)**	
0-7	Alveogyl	62.9 (17.7)	69 (48-78)	0.001*
	H-PRF	81.7 (13.9)	81 (70-96)	
	Combined groups	**72.6 (18.3)**	**76 (63-83)**	
p-value as reported by t-test *p<0.05 (HA: diff=0)				

Figure 18: A confidence interval graph representing the mean worst pain scores for both Alveogyl and H-PRF treatment groups with lower pain scores in the H-PRF group at Day 3 and Day 7 following intervention

4.6 1.5 Day Three Average Pain

Non parametric Mann Whitney U Test was performed to compare groups for “average pain” experienced at Day 3 (T1). The analysis showed that the average pain score was significantly improved in the H-PRF group. The mean average pain score for control group patients at T1 was 51.61 millimetres as compared to 33.10 millimetres in H-PRF patients (p=0.012).

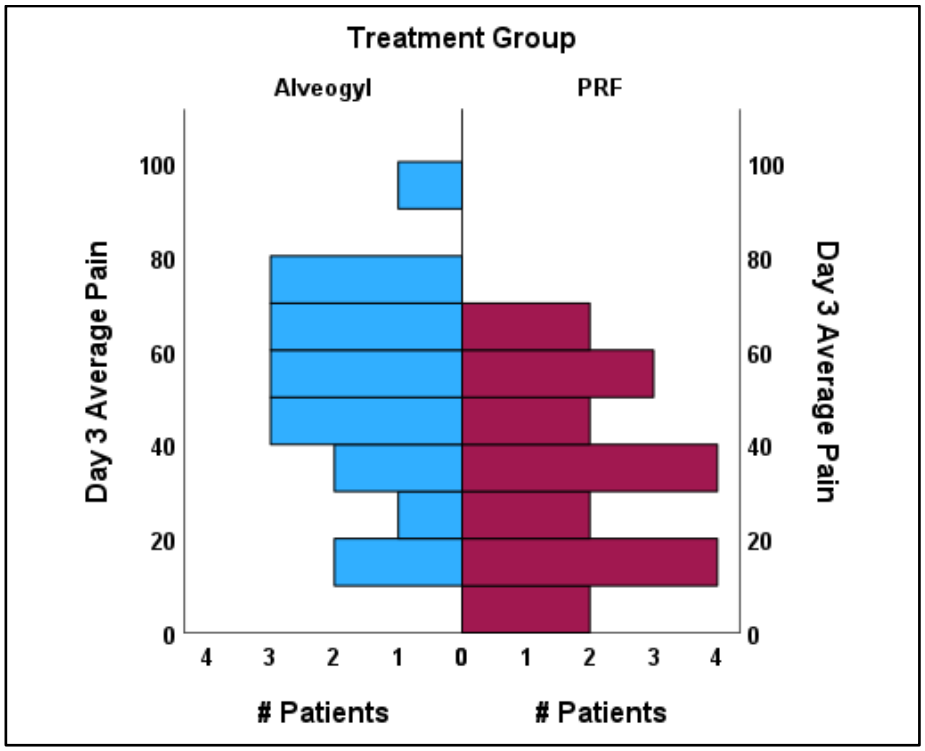


Figure 19: A bar chart representing average pain scores in both control and test groups at day 3 (T1) following intervention

4.6 1.6 Day Seven Average Pain

Non parametric Mann Whitney U Test was performed to compare groups for “average pain” experienced at Day 7 (T2). The analysis showed that the average pain score was significantly improved in the H-PRF group. The

mean average pain score for control group patients at T2 was 17.33 millimetres as compared to 5.89 millimetres in H-PRF patients (p=0.017).

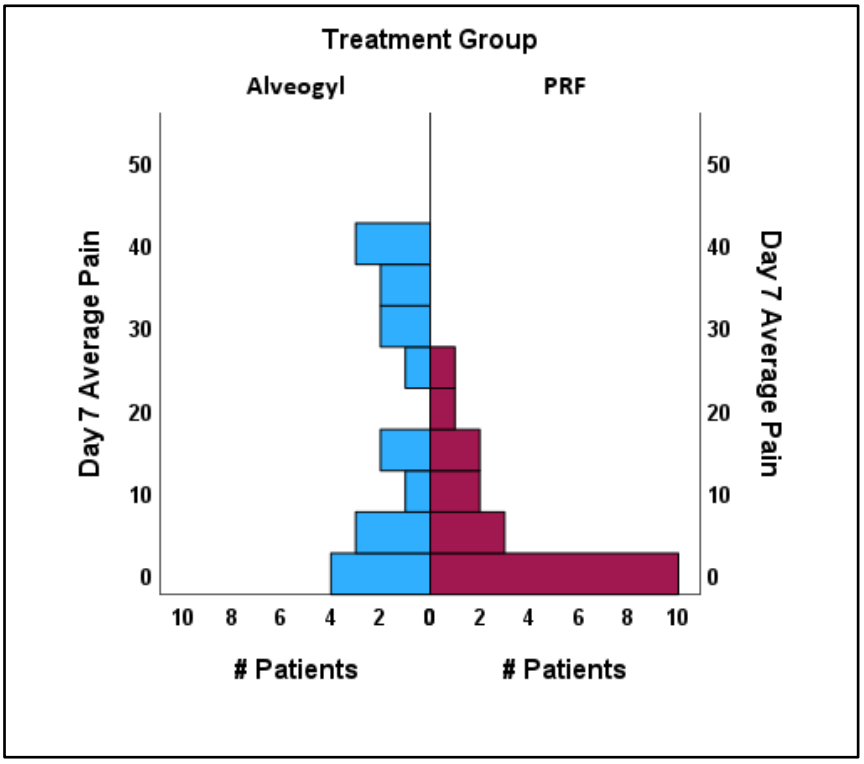


Figure 20: A bar chart representing average pain scores in both control and test groups at day 7 (T2) following intervention

4.6.2 Secondary Outcomes

4.6.2.1 Analgesia Consumption

The use of over-the-counter analgesics decreased progressively in both treatment groups over the course of the study period. The use of each recommended analgesic product was analysed over each study timepoint to determine any significant differences between treatment groups.

4.6.2.1.1 Paracetamol

Non parametric Mann Whitney U Test was performed to compare treatment groups for Paracetamol usage at Day 3 (T1). The analysis

showed that significantly more 1g Paracetamol tablets were consumed by the control group patients (Z= 2.81, p=0.007). This same analysis was performed at Day 7 (T2) and again showed that significantly more Paracetamol was being used by patients in the control group compared to those in the H-PRF group (Z= 2.47, p=0.026)

4.6.2.1.2 Ibuprofen

Non parametric Mann Whitney U Test was performed to compare treatment groups for Ibuprofen usage at Day 3 (T1) and Day 7 (T2). The analysis failed to show any significance in the quantity of Ibuprofen 400mg tablets used by participants in either treatment group at both timepoints (p=0.753 at T1, p=0.159 at T2).

4.6.2.1.3 Codeine

Codeine was being used for analgesia by 10/37 participants on the presentation (27%) but this number reduced to 2/37 participants (5.4%) by T1 and remained the same at T2.

Due to the very low number of codeine users, consumption was analysed as a binary variable using chi square test of association and did not show significance between treatment groups at either Day 3 or Day 7 (p>0.95).

4.6.2.2 Evaluation of Healing

Non parametric Mann Whitney U Test was performed to compare the healing of all sockets at Day 7 (T2) post intervention. The analysis showed significantly improved healing scores for the patients treated with H-PRF compared to Alveogyl (Z= 3.05, p=0.003).

Table 14 gives a numerical comparison of the healing scores between treatment groups and represents the same data as Figure 22.

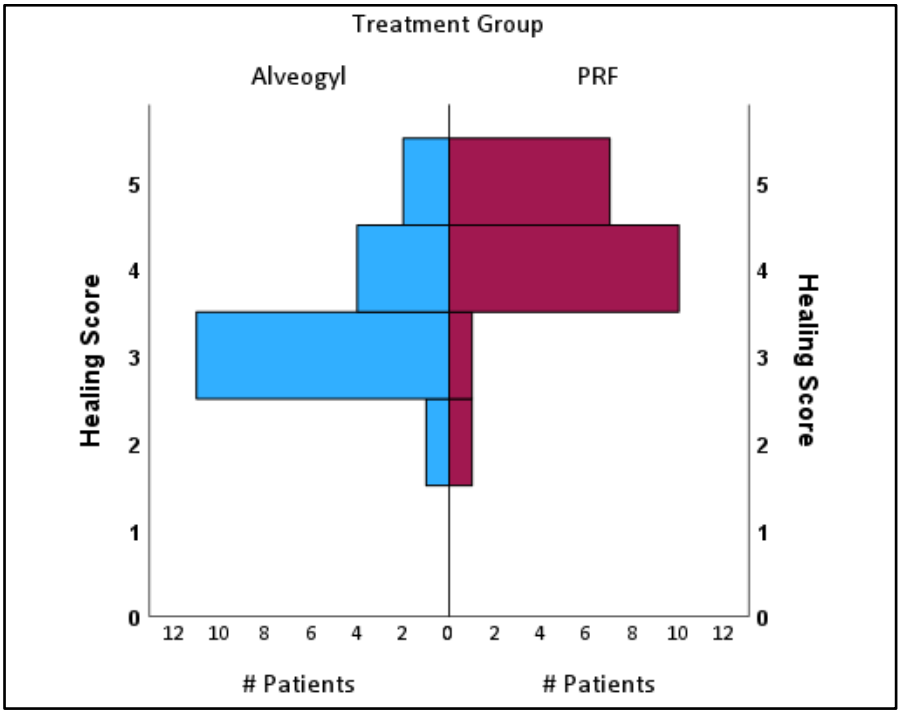


Figure 21: A bar chart representing the healing scores at Day 7 (T2) following assessment by one of three calibrated and blinded second assessors. Healing scores (y-axis, 1-5) are explained in words in the box adjacent to the bar chart. This bar chart reflects that superior healing at T2 was seen in H-PRF (test) patients. Healing Scores: 1= Very poor, 2= Poor, 3= Good, 4= Very good, 5= Excellent.

Table 14: Joint frequency table reporting healing score and treatment group

Healing	Group (n %)	
	Alveogyl (n=18)	**H-PRF (n=19)**
Very Poor	0 (0)	0 (0)
Poor	1 (50)	1 (50)
Good	11 (91.67)	1 (8.33)
Very Good	4 (28.57)	10 (71.43)
Excellent	2 (22.22)	7 (77.78)

4.6.2.3 Quality of Life (QoL) Assessment

No significant differences between treatment groups for any patient-reported QoL parameter was detected from screening through to study completion, except for sleep being reported as improved on postoperative day 3 (T1) in the H-PRF group (Z= 0.71, p=0.029).

Table 15: Health Related Quality of Life (HRQOL) outcomes on postoperative day 3 (T1)

HRQOL outcome	Treatment	No of patients	Score, median (IQR)		Effect size (95% CI)	P-value
			Baseline	3 days post-op		
Chewing	Alveogyl	18	5 (3-5)	3 (3-4)	0.46	0.904
	H-PRF	19	5 (4-5)	3 (3-4)		
Trismus	Alveogyl	18	4 (3-4)	2 (2-4)	0.46	0.892
	H-PRF	19	4 (2-5)	3 (2-4)		
Talking	Alveogyl	18	3 (2-4)	3 (2-3)	0.54	0.420
	H-PRF	19	4 (3-4)	2 (2-3)		
Sleeping	Alveogyl	18	5 (4-5)	4 (3-5)	0.71	0.029*
	H-PRF	19	5 (4-5)	3 (2-4)		
Attending work/school	Alveogyl	18	5 (4-5)	4 (3-4)	0.62	0.253
	H-PRF	19	4 (4-5)	2 (2-4)		
Routine activities	Alveogyl	18	4 (3-5)	3 (3-4)	0.60	0.418
	H-PRF	19	4 (3-5)	2 (2-4)		
Social Life	Alveogyl	18	5 (4-5)	3 (3-5)	0.64	0.640
	H-PRF	19	4 (3-5)	3 (2-4)		

Table 16: Health Related Quality of Life outcomes on postoperative day 7 (T2)

HRQOL outcome	Treatment	No of patients	Score, median (IQR)		Effect size (95% CI)	P-value
			Baseline	7 days post-op		
Chewing	Alveogyl	18	5 (3-5)	2 (1-3)	0.5	0.408
	H-PRF	19	5 (4-5)	2 (2-3)		
Trismus	Alveogyl	18	4 (3-4)	2 (1-2)	0.47	0.370
	H-PRF	19	4 (2-5)	1 (1-2)		
Talking	Alveogyl	18	3 (2-4)	1 (1-1)	0.43	0.417
	H-PRF	19	4 (3-4)	1 (1-2)		
Sleeping	Alveogyl	18	5 (4-5)	2 (1-3)	0.63	0.948
	H-PRF	19	5 (4-5)	1 (1-2)		
Attending work/school	Alveogyl	18	5 (4-5)	1 (1-2)	0.50	1
	H-PRF	19	4 (4-5)	1 (1-2)		
Routine activities	Alveogyl	18	4 (3-5)	1 (1-2)	0.46	0.754
	H-PRF	19	4 (3-5)	1 (1-3)		
Social Life	Alveogyl	18	5 (4-5)	1 (1-2)	0.52	0.866
	H-PRF	19	4 (3-5)	1 (1-2)		

4.6.2.3.1 Interference with Daily Life

Progressively less interference with daily life is seen in both H-PRF and Alveogyl groups at T1 and T2 following intervention but there is no significant difference between groups at any postoperative timepoint.

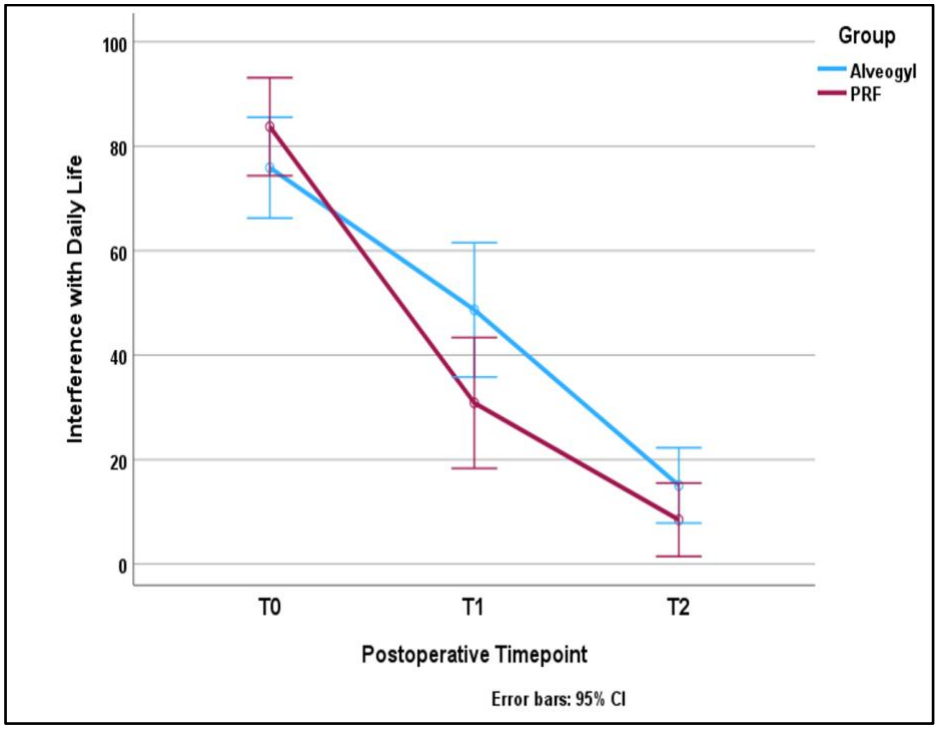


Figure 22: A confidence interval graph representing interference with daily life for both Alveogyl and H-PRF treatment groups.

(H-PRF, horizontal platelet rich fibrin; T0, day of treatment; T1, 3 days postoperative; T2, 7 days postoperative)

CHAPTER FIVE

DISCUSSION

5. Discussion

5.1 Statement of Principal Findings

This trial was conducted as a prospective double-blinded superiority randomised controlled trial using a parallel-group design with a seven-day follow up period.

The hypothesis under investigation was to assess whether H-PRF was more effective as a treatment for alveolar osteitis compared to Alveogyl and whether the choice of material had any effect on postoperative clinical outcomes in the immediate postoperative period. The main study findings were that H-PRF resulted in expedited pain resolution in patients with AO when compared to Alveogyl, as well as improved healing outcomes.

5.1.2 Trial Population Demographics

Though both treatment groups were well balanced with respect to baseline demographics and clinical characteristics without the need for stratified randomisation, there were several demographic characteristics worth noting.

5.1.2.1 Gender & Alveolar Osteitis

There was no gender preponderance amongst our study population with relatively equal numbers of males (n=18, 48.6%) compared to females (n=19, 51.4%). It has been reported in the literature that female gender has been shown to increase the incidence of alveolar osteitis, especially those on the oral contraceptive pill due to hormonal imbalances (Catellani et al.,

1980; Garcia et al., 2003). This finding was not notable in our, albeit relatively small, study population.

When it came to stratifying into each study arm, the distribution was not as balanced however, with more females in the experimental group (11/19) and more males in the control group (11/18). It has been reported in many studies across the literature that compared with men, women report more pain and have a lower pain threshold and tolerance to experimental pain stimuli (Myers, Riley and Robinson 2003; Fillingim et al., 2009). This was examined in the context of postoperative discomfort following third molar removal and females were twice as likely as males to experience severe post-operative pain (Grossi et al., 2007).

It is unclear whether this slight imbalance had an influence on postoperative outcomes in either of our study groups. The authors propose, however, that it is unlikely to have had a significant influence because the pre- and postoperative pain outcomes were consistent from baseline to day seven in both groups. If females reported more pain at baseline, it could be assumed this finding would be consistent if the AO intervention had not worked. This finding has not been previously examined in the literature within a patient cohort with alveolar osteitis.

5.1.2.2 Smoking & Alveolar Osteitis

The relationship between smoking, degree of smoking and the development of alveolar osteitis is also reported by the literature

(Bortoluzzi et al., 2012; Sweet and Butler, 1978). Though there was a marginally higher number of smokers (n=18, 48.7%) compared to non-smokers (n=17, 45.9%) amongst our study population, it is unlikely that this marginal imbalance had any tangible clinical influence on the postoperative outcomes. There were two additional patients reporting a vaping habit (n=2, 5.3%).

It is worth noting that many randomised controlled trials focusing on both prevention (Babar et al., 2012) and treatment (Yüce and Kömerik, 2019) exclude smokers from participation, due to the presumed interference with healing.

5.1.2.3 Site of Alveolar Osteitis

Within our study population, 78.4% (n=29) of alveolar osteitis presentations were in the mandible as opposed to 21.6% (n=8) in the maxilla. Though the prevalence rate of AO cannot be calculated from this study, our data corroborates with that of previous findings where the most commonly affected sites are mandibular molar sockets, especially third molars (n=16, 43.2%) (Fridrich and Olson, 1990; Haraji et al., 2013; Vezeau, 2000). The reason why mandibular third molar sites are more predisposed to alveolar osteitis remains unclear and early speculation that it is attributable to decreased vascularity in dense posterior alveolar bone was challenged by work done by Birn who showed greater posterior alveolar blood vessel density than the anterior alveolar regions (Birn, 1966). One

hypothesis to explain posterior site predisposition to AO is that the bone in these sites may experience more trauma during extraction (Turner, 1982).

5.1.2.4 Difficulty of extraction

In our study, most patients presenting with AO reported simple forceps extractions (n=20, 54%) rather than surgical extractions involving bone removal and/or tooth sectioning (n=17, 46%) as demonstrated in Figure 15. This finding is at odds with many studies in the literature where surgical extractions, particularly in the context of third molars, show a significant increase in incidence of AO compared to non-surgical extractions (Chow et al., 2020). Interestingly, a prospective community based study examining factors affecting the incidence of AO in 284 patients with 564 extractions found that the surgical removal of teeth did not increase the risk of AO development, while intraoperative crown or root fracture did (Parthasarathi, Smith and Chandu 2011). This finding, along with our study's findings, may imply that surgical removal of a tooth may be less traumatic than the use of excessive force to remove a tooth in a non-surgical manner. Further research is merited to fully elucidate the potential influence of extraction approach and its effect on the incidence of AO.

5.1.3 Primary and Secondary Outcome Findings

5.1.3.1 Pain

Pain relief remains the primary goal in all cases of AO management. The results of our study have demonstrated that pain alleviation is significantly improved in patients who were randomised to the H-PRF treatment arm of the trial. VAS scores were significantly lower for worst pain score at T1 (Z=2.49, p= 0.011) and T2 (Z=2.76, p=0.006) in the H-PRF group following intervention in the absence of significant difference in pain scores between groups at baseline (T0, p=0.294). The positive analgesic effect of H-PRF is further augmented by our finding that patients needed to consume significantly less Paracetamol at T1 (Z=2.81, p=0.007) and T2 (Z=2.47, 0.026) in the H-PRF group.

Due to our trial being the first in the literature to report on H-PRF as a treatment modality in AO, we cannot directly compare our findings to other trials. Arguably similar to our study, however, is an RCT of forty patients in a single centre in Turkey where the effect of advanced platelet rich fibrin was evaluated for the acceleration of wound healing in AO, with saline as their control. This group found positive secondary benefits of A-PRF in pain reduction, attributing this to coverage of the denuded bony walls by day seven following intervention (Yüce and Kömerik 2019). Platelet concentrates have also been shown to be effective at decreasing inflammation (El-Sharkawy et al., 2007) and because pain is a symptom of inflammation, its eradication should thereby lead to a decrease in pain

severity. In the study by Yuce and Kömerick, like ours, there were no significant difference in VAS scores between groups pre-operatively (T0, p=0.310) but pain scores had significantly reduced in the A-PRF group every post-operative day thereafter (day 3 and day 7, p: 0.000*). They however chose to evaluate pain scores more frequently than our group i.e., at days 1, 3, 5 and 7.

Keshini and colleagues carried out another similar RCT in India comparing Alvogyl (old formulation) to PRF in a group of 30 patients in a single centre (Keshini et al., 2020). In their study they use VAS to measure pain at three time intervals post intervention, namely day 1, 3 and 10. They found that there was a statistically significant difference in pain reduction in both groups and by day 10 postoperatively both groups showed a similar decrease in pain. They concluded that PRF and Alvogyl were comparable as materials in the treatment of alveolar osteitis both from a pain and healing perspective. This contrasts with the findings of our study as we saw a statistically significant difference in pain reduction in the H-PRF group at each post-intervention timepoint. It remains unclear if the superiority of H-PRF is attributable to its therapeutic advantages over its platelet concentrate predecessors or whether the reformulation of Alvogyl played a greater role.

There are myriad studies using platelet concentrates in third molar surgery for their perceived ability to decrease postoperative pain and reduce the

number of analgesics taken by patients. In one such study by Bilgnaylar and Uyanik, patients were divided into four groups and assessed for pain, analgesia consumption, trismus and swelling on days 1, 2, 3 and 7 following removal of eighty impacted third molars. The third molars in this study were removed using either traditional osteotomies with rotary drills or with piezosurgery, an ultrasound-driven osteotomy device believed to reduce trauma to hard tissues due to its selective cutting action (Ruga et al., 2011). The results of their study showed significant reduction in pain on days 1, 2 and 3 and in the quantity of analgesia consumed on days 2 and 3 in the PRF groups irrespective of osteotomy technique. There were also significantly less cases of AO reported in the PRF groups (Bilginaylar and Uyanik, 2016). This ability of PRF to decrease postoperative pain as a prophylactic adjunct to third molar surgery has been reported across other numerous studies ((Unsal and Erbasar 2018; Ritto et al., 2019; Sharma et al., 2020).

Aside from our study being the first to examine the effect of H-PRF on AO treatment, the heterogeneity in the literature amongst methods of pain evaluation makes it difficult to directly compare our study to other similar studies. In the recently published Cochrane review (Daly et al., 2022), pain was one of the main outcome measures in all included studies focusing on treatment of AO, but the method of measuring pain varied hugely. Faizel et al., 2015 measured time (in minutes and days) to achieve initial pain relief and complete resolution of pain following medicament placement. Mitchell 1984 looked at the duration of treatment from initiation until the patient

had complete resolution of pain. Seven studies (Burgoyne et al., 2010; Chaurasia, Upadhyaya and Dixit 2017; Keshini et al., 2020; King et al., 2018; Lenka et al., 2019; Supe et al., 2018) measured pain on subsequent days following placement of a medicament using VAS scales, however these scores were taken on different days across the various studies.

These discrepancies in reporting pain outcomes between studies highlighted some outstanding questions regarding the use of the VAS. The reliability of VAS measurements as a measure of pain intensity (Baños et al., 1989) has been demonstrated in postoperative patients, as well as differences in VAS measurements as a gauge of change in pain sensation for patients experiencing mild to severe acute pain (Myles and Urquhart, 2005). These differences between groups in their VAS scores may have no or trivial clinical relevance, even if they achieve statistical significance. Moreover, a patient's perception of meaningful change in pain may depend on their baseline level of pain. In the same vein, several analgesic studies have reported that the proportion of patients achieving a desired level of pain relief is more clinically relevant than the average fall in VAS in studies evaluating pain interventions. Some authors have suggested a 50% reduction in baseline VAS represents a meaningful analgesic effect (Moore et al., 1997), while others have argued a change of 20mm represented satisfactory pain relief in patients following surgery (DeLoach et al., 1998). In our study, patients in the H-PRF group had a mean reduction in pain of 51.4% between days 0 and 3 following intervention, which would

thereby suggest a clinically relevant reduction on the basis of aforementioned studies.

Limitations when using VAS include that participants may intuitively believe that the VAS is a linear scale and may attempt to reduce their scores based on recollection of their prior assessment. We sought to minimise this risk and source of bias by clear explanation of the scale and concealment of their previous responses. There is evidence available that suggests patients are not necessarily influenced by previous ratings when asked for repeated measurements (Bodian et al., 2001). The VAS is also a unimodal measurement of pain which is often described as a multidimensional experience and therefore it does not represent all aspects of pain perception. The extremes of pain- “no pain” and “worst imaginable pain”- may not truly represent the limits of perception. Despite this, the simplicity of its application for patients, clinicians and researchers, as well as its reliability and reproducibility make it a widely used and validated pain assessment tool.

5.1.3.2 Healing

Socket healing was a secondary outcome in our trial and was graded using a modified version of Landry et al. healing index (Appendix 6), demonstrating significantly improved healing in patients treated with H-PRF on day 7 following intervention (p=0.003) as assessed by one of three calibrated, blinded assessors. There have been major advancements in the

literature specifically studying the positive effects of platelet concentrates on promoting soft tissue healing as well as limiting dimensional changes post-extraction (Temmerman et al., 2016; de Almeida Barros Mourão et al., 2020). Parallel to our study findings, with the exception of our study not reporting on bone healing, a recent systematic review found that PGRF may bring advantages both clinically and radiographically with improved soft tissue healing and bone density while reducing adverse events, complications and patient discomfort (Del Fabbro et al., 2019).

Within the Cochrane review of local interventions for the management of AO (Daly et al., 2022), four RCTs focusing on the treatment of alveolar osteitis used healing as an outcome measure (Faizel et al., 2015; Keshini et al., 2020; King et al., 2018; Supe et al., 2018). The heterogeneity of their healing assessments, including changes to signs of AO, makes it very difficult to compare our trial to any of these studies. Changes reported included empty sockets, exposed sockets, number of socket walls exposed, redness around sockets and inflammation as well as patient-rated healing scores. King (2018), for example, investigated the efficacy of PGRF and Alveogyl in the treatment of AO and concluded that PGRF appears to be more beneficial from a healing perspective. Her outcome measures for healing however included a host of unvalidated measures including exposed alveolar bone (present/ absent), inflammation assessed on a scale of 0 to 3 and patient rated outcomes including their interpretation of "speed of healing" using VAS. Not only are the majority of these outcome

measures unvalidated and unique to her study, but they are also ambiguous and difficult to assimilate or interpret by the reader.

Further ambiguity arises when evaluating whether previous studies made use of an impartial, blinded second assessor to measure their chosen healing outcomes, or whether it was in fact the principal investigator or a non-blinded second assessor examining the socket healing following intervention. Studies have shown that where non-blinded assessors of subjective binary outcomes are used in randomised clinical trials, substantially biased estimates of treatment effects are generated. It appears that this may be the case with two of the trials (Supe et al., 2018; Keshini et al., 2020) in the aforementioned Cochrane review (Daly et al., 2022). The other pair of trials reporting on healing outcomes (King et al., 2018; Faizel et al., 2015) stated that a second blinded assessor was involved in determining healing in the follow up period, with the principal investigator doing the initial assessment which is similar to our trial. Our trial differs as there were multiple clinicians involved in the post-operative healing assessments, thereby necessitating education and calibration to optimise intra- and inter-examiner reliability scores.

Retardation of healing and persistent inflammation has been reported in the literature when sockets were packed with Alvogyl (Syrjänen and Syrjänen, 1979). An increased risk of developing a foreign body reaction has also been reported (Sotorra-Figuerola et al., 2019). Studies focusing on

treatment of AO where healing was a reported outcome frequently outlined any complications during their study period such as delayed healing, abscess, fascial space infections and foreign body reactions. Fortunately, in our study we experienced no reports of side effects from either group nor did we experience any secondary bacterial infections that required the use of antibiotics.

5.1.3.3 Quality of Life

Quality of life parameters were assessed as a secondary outcome in our trial to strengthen clinical relevance of the study and to provide more patient centred outcomes. No significant differences were observed in the health-related quality of life (HRQoL) subscales between groups overall, except for "sleep" being reported as improved at T1 in the H-PRF group ($p=0.029$). This finding corroborates with multiple studies that have shown a bidirectional relationship between sleep and patient pain experience (Lautenbacher et al., 2006; Onen et al., 2001). In one longitudinal study of 971 patients, the magnitude of this effect was stronger in the sleep to pain direction than the opposite direction, implying that decreased sleep on a given day predicted increased pain on the subsequent day (Edwards et al., 2008). In our study, there were significant improvements in both worst pain scores and sleep at day 3 following intervention with H-PRF which is likely attributable to this bidirectional relationship. "Interference with daily life" was also analysed with quality-of-life parameters by means of VAS at

Days 0, 3 and 7 but there was no significant difference between the treatment groups.

Though the use of psychometrically tested instruments such as HRQoL scores are used to explore patient-reported outcomes in areas such as third molar surgery (O'Sullivan, Gallagher, and Ní Ríordáin 2022), they have never been applied, to the best of our knowledge, in the treatment of AO. IIncreased use of validated quality of life outcomes measures would prove useful to clinicians and would likely guide management of this painful postoperative condition. In her trial, King analysed functional patient reported outcomes including swelling, bleeding bruising and speed of healing measured by VAS and categorised these as quality-of-life parameters in her results. She did not however explore any aspect of the patients' general wellbeing or their perception of the impact of AO on their sleep or daily work and social lives. Another weakness of this study was the failure to blind her study participants.

Patient satisfaction with treatment is another aspect of quality of life that may have ameliorated our study and has yet to be explored in any previously published studies focussed on treatment of AO.

5.2 Trial Design

This study was conducted as a prospective randomised controlled clinical trial (RCT). In a paper entitled "How to Design a Randomised Controlled Trial" by Brocklehurst and Hoare in 2017, they described RCTs as *"the only research designs that can demonstrate causality, that is that an intervention causes a direct change in a clinical outcome"*. The use of randomisation also provides validity to statistical tests of significance. In other words, incorporating an element of randomness into the trial forms a basis for using statistical methods to draw inferences from the data (Itani and Reda, 2017). Our study was designed as a superiority or head-to-head trial between the two treatment modalities to answer our research question. Figure 24 describes the characteristics of various types of study design.

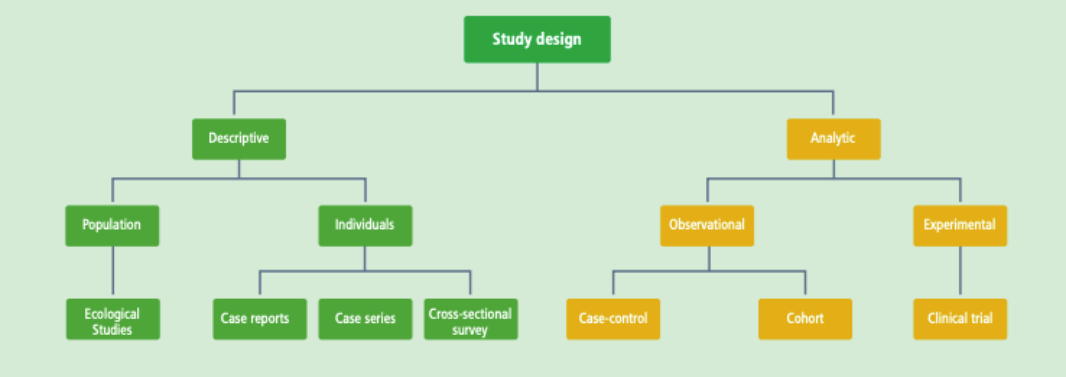


Figure 23: Trials in context ((Brocklehurst and Hoare 2017)

5.2.1 Parallel Group Design

The most frequently used clinical trial design is the two-parallel-group design which was adopted for this study. In this basic design, participants are randomised to one of two treatment groups and then followed over time for assessment of

outcomes (Itani and Reda, 2017). The null hypothesis is that there is no difference between the two treatment groups in the outcomes, with the two-sided alternative hypothesis being the opposite.

By contrast, split-mouth design studies can be used where patients act as their own controls and this design has been used in multiple third molar interventional studies (Ritto et al., 2019; Kapse et al., 2019). This design has also been adopted in a number of randomised controlled trials looking at the prevention of alveolar osteitis with PRF and chlorhexidine in third molar surgery as their primary outcome (Afshin Haraji et al., 2012; Eshghpour et al., 2018; Unsal and Erbasar, 2018) This study design is not feasible to adopt in the case of treatment of alveolar osteitis, however due to the infrequency and lack of predictability of patients presenting with multiple affected sites. Though split-mouth studies offer advantages over parallel-design studies as they allow direct comparisons between intervention and control sides of the same mouth, they have limitations for accurate assimilation of patient- reported outcomes which was critical to evaluate in our study outcomes.

5.3 Trial Strengths

Our trial was conducted as a prospective, double-blinded RCT, which was the chosen type of study for data analysis in the recent Cochrane Review on "Local interventions for the management of alveolar osteitis" (Daly et al., 2022) and continues to be the gold standard for interventional clinical trials.

5.3.1 Single operator

The lead investigator took responsibility for the treatment of all patients at baseline, data collection at all timepoints and undertook the virtual phone reviews for the purposes of this study. The only outcome that involved other personnel was the healing assessment at Day 7 to conform with the double-blinding requirement of the study. This involved ensuring these assessors were calibrated against one another.

Minimising the number of operators involved in the treatment of the study population ensured both accuracy and consistency of the data was maintained which is a strength of this trial.

5.3.2 Blinding

A strength of our study is the robustness of the blinding methodology, especially compared to other similar randomised controlled trials where it is difficult to elucidate how they implemented or maintained the blinding of participants and/ or outcome assessors. There was no timepoint throughout our study where patients or outcome assessors were unblinded and this was controlled by the unblinded lead investigator.

This sets our study apart from similar previous published trials adopting a parallel-group design where blood was obtained only from patients allocated to the experimental group of the study (King et al., 2018; Yüce and Kömerik 2019) or where patient and outcome assessor blinding was unclear (Keshini et al., 2020; Chaurasia, Upadhyaya and Dixit 2017). Failure to implement and sustain the blinding methodology leads to both performance and detection bias, which reduces the reliability of the results.

5.3.3 Calibration of assessors

Another strength of our study compared to similar previously published trials, involved the calibration of the clinicians who carried out the healing assessments on day 7 postoperatively. To our knowledge, ensuring these clinicians were both blinded to treatment group allocation and calibrated against one another makes this study the first of its kind in the context of treatment of alveolar osteitis. We believe our methodology for calibration is accessible and reproducible for future research in this area and should be adopted to add rigour where healing is an outcome of choice.

5.3.4 Precision of outcome measures

All the outcome measures evaluated within our study were analysed using validated instruments. Visual analogue scales have a long track record of validity and sensitivity to evaluate pain and is by far the most cited pain measurement instrument used in alveolar osteitis studies, facilitating comparison between our trial and other similar trials (King et al., 2018; Keshini et al., 2020).

Healing outcomes were evaluated using a modified version of Landry's Healing Index at day seven following intervention. Applications of this index to surgical site healing is particularly relevant in autologous platelet product interventional studies, as many authors have used this index when reporting the benefits of APCs as adjuvants to healing (Del Fabbro, Panda and Taschieri, 2019; Yüce and Kömerik 2019). Incorporating this instrument into our study provides ease of comparison between other studies and facilitates reproduction of the same methodology in future studies.

Ideally, we would have implemented an in-person rather than virtual review appointment at day 3 following intervention, both to eliminate any ambiguity with pain diary responses and to evaluate healing at two timepoints however we felt that enforcing this would have resulted in higher attrition rates. Time off work, access to childcare and travel arrangements and cost were all potential barriers for patients to attend in person. Physical attendance was considered more important at day 7 to ensure resolution of symptoms and assessment of healing before the termination of the trial.

Quality of life outcomes were assessed by means of a Health-Related Quality of Life (HRQoL) questionnaire at the three timepoints which has been used in our institution in many different studies. Though the limitation of this instrument is that it is not validated for use in cases of AO, it is more readily applicable to patients with this postoperative complication compared to other quality of life tools.

5.4. Trial Limitations

5.4.1 Sample size

This study is limited by the relatively small nature of the sample which may impact the generalisability of the findings. This shortfall was due to the relatively small number of patients presenting to DDUH with AO, especially where postoperative antibiotics had not been prescribed. In addition, there were considerations around time constraints of the postgraduate training duration, gaining ethical approval and being available to treat patients who presented in an emergent fashion. These factors resulted in a relatively small sample size which negatively affects the power of the study, introduces bias and makes it difficult to statistically analyse.

Notwithstanding this, the sample has reached power and is comparable to other similar previously published studies. This study offers an insight into the superiority of H-PRF in comparison to conventional dressings such as Alveogyl for expedited pain resolution and improved healing outcomes.

5.4.2 Oral hygiene status

Though poor oral hygiene status has been noted as a risk factor for increasing the incidence of AO and pain following third molar removal (Peñarrocha et al., 2001), it is regretful that this information was not formally recorded at baseline for our study population nor does it appear to be incorporated in the methodology of other similar studies.

This information may be more useful in studies examining AO prevention rather than treatment of the condition, as there is a stronger emphasis on reduction of intraoral bacterial load prior to surgery with use of antiseptic mouthrinses.

Nonetheless it would remain valuable to examine whether there is a correlation between poor oral hygiene status and AO.

5.4.3 Comparability to other studies

Our study is relatively limited in its ability to be compared to other previously published randomised controlled trials as it is the first study that compares the new formulation of Alveogyl against H-PRF, an autologous platelet concentrate that has not yet been evaluated in available published literature for the treatment of alveolar osteitis.

In the recently published Cochrane review (Daly et al., 2022), there was cause for confusion surrounding which formulation of Alveogyl was being used by authors and whether the authors themselves were in fact aware of this change. One trial published in 2020 reported comparing old formulation Alvogyl to platelet rich fibrin, despite postdating formula change (Keshini et al., 2020). Within this Cochrane review, any study using new formulation Alveogyl (Chaurasia, Upadhyaya and Dixit 2017) was excluded from the meta-analysis.

5.4.4 Practicalities of H-PRF treatment in practice

There are practical parameters for consideration such as the possibility to use these techniques in daily practice as well as the cost and ergonomics of the preparation procedure for H-PRF. Within the questionnaire distributed to dental practitioners as part of this study (Appendix 8), one question explored the availability of access to APC equipment such as a centrifuge. Of 107 respondents, only 10 clinicians (9.3%) responded reporting frequent use of these products, while

4 (3.7%) additional respondents admitted to having access but wishing for further training before use.

With this low number of APC users in mind, lack of confidence and the financial constraint of acquiring a Bio-PRF machine at a cost of $3,450.00, it may be assumed it is unlikely for practitioners to purchase a machine if the sole purpose is for treatment of alveolar osteitis. These clinicians may be more motivated by the numerous other indications for use of H-PRF in their dental practice, especially if surgically inclined but likely need further education.

Alveogyl has been used for decades by clinicians in the treatment of dry socket, and despite its inferiority to H-PRF in this study, it has still been shown to provide symptomatic relief. The argument may be put forward that investing in a centrifuge may be financially rewarding in the long term. One can acquire free autologous venous blood samples from patients as opposed to buying tubs of Alveogyl at a cost of €45- 56 per item with the risk of repeated visits and lost chairtime. Factors such as chairtime, preparation time of H-PRF and ergonomics would need to be considered for full evaluation.

5.5 Future Research

There have been several areas of potential future research have been highlighted by in this study. One of the most pertinent areas where knowledge is limited falls within the aetiology of this common and debilitating postoperative condition. Though Birn's theory of fibrinolysis leading to clot breakdown is widely accepted (Birn, 1973), this theory has very seldom been explored in a clinical context where

bacteria are hypothesised to play a role. Nitzan found that Treponema denticola demonstrated fibrinolytic activity independent of other factors (Nitzan, 1983); however, this research was completed in vitro. This void in the literature should be further explored by means of a multi-centre prospective case-control study where the bacterial profile of healthy control sockets are compared to sockets diagnosed with AO to assess whether there are differences between groups, similar to the work done on a small scale by a research team in Barcelona (Aguilar-Durán et al., 2019). If differences are noted, this may lead to further exploration of the general and fibrinolytic properties of the individual bacteria and further management strategies for AO elucidated.

Development of a validated quality of life outcome assessment instrument for alveolar osteitis, could be useful rather than adopting an assessment tool specifically designed for another area of research. This would facilitate consistency amongst different patient groups and jurisdictions, making it useful to directly compare patients undergoing the same procedure.

Another area of future research could encompass a qualitative study examining the beliefs and attitudes of dentists in the context of APC use in their practice and a cost-effectiveness analysis considering both Alveogyl and H-PRF as potential treatment options for dry socket.

We have conducted a robust randomised controlled clinical trial examining the efficacy of Alveogyl against H-PRF in the treatment of AO, two materials that have not previously been compared to each other. We believe our methodology is

comprehensible enough to be replicated anywhere across the world with the same or a variant in choice of study materials and as such our study could provide a template from which researchers could work from.

CHAPTER SIX

CONCLUSION

6. Conclusion

This study concludes that there is a statistically significant difference in the early alleviation of pain and improved healing outcomes where patients with alveolar osteitis were treated with H-PRF as opposed to Alveogyl. The null hypothesis is therefore rejected.

Although this study failed to show any significant difference in oral health related quality of life parameters between groups, it must be acknowledged that these variables were not specific to alveolar osteitis and were more applicable to patients following oral surgery procedures, such as implant surgery or third molar removal. The reason the authors adapted this tool was due to the lack of an alternative validated quality of life assessment tool for alveolar osteitis. This is an area that would benefit from further research, especially bearing in mind that going forward it is likely additional materials will be added to the armamentarium for treatment of alveolar osteitis. Without a validated instrument to assess quality of life outcomes, direct comparison of treatment modalities will continually be inhibited.

This study has implications for clinicians deciding on how best to manage their patients with alveolar osteitis. It is the authors' opinion that this study should set a benchmark for future randomised controlled trials exploring treatment options for AO due to the reproducibility of the methodology. Though our study is the first of its kind to examine H-PRF in the context of alveolar osteitis, the quality of

available studies using PGRF and A-PRF to treat AO have not been deemed sufficiently high to draw any conclusions about the efficacy of these biomaterials (Daly et al., 2022). It is therefore the authors' suggestion that future researchers would adopt this study's methodology to examine the effects of any proposed treatment option for AO. It is also hoped that there will be further development examining the perceived superiority of H-PRF over previous generations of autologous platelets concentrates as we cannot confirm its superiority from our study alone.

To conclude, this study suggests that the use of H-PRF is safe, and that it could be considered as a superior alternative to current standard(s) of care in the management of alveolar osteitis and has an important role in oral surgery.

CHAPTER SEVEN

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7. References

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CHAPTER EIGHT

APPENDICES

8. Appendices

Appendix 1: Ethical approval

Project ID: 0733

Dr Maeve Cooney,

Dublin Dental University Hospital

Dr Anna Beattie, Dublin Dental University Hospital

Approval Date: 19 September 2022

Submission Number: 2106

Submission Title: A clinical investigation of the efficacy of Platelet Rich Fibrin (PRF) compared to Alveogyl in the treatment of Alveolar Osteitis
Submission Date: 16.Aug.2022 17:16

Dear Dr Cooney,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL.** Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Principle Investigator C.V.	Updated CV Maeve	08.Mar.2022	1
Survey/Questionnaire	Patient Diary of Symptoms	08.Jun.2022	2
Default	Amedments to Ethics	08.Jun.2022	1
Participant Information Leaflet	Patient Information Leaflet copy	16.Aug.2022	3
Participant Consent Form	Research Consent Form	16.Aug.2022	3

Please note that ethical approval for this study is only active under the following conditions:

Page 1 of 2

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics & Clinical Trials Manager,

SJH/TUH Joint Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 2: Patient Information Leaflet

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

DUBLIN DENTAL HOSPITAL

Patient Information Leaflet

Title of Research: A clinical investigation of the efficacy of Platelet Rich Fibrin compared to Alveogyl in the treatment of alveolar osteitis

Investigators:

1. Dr. Maeve Cooney, Postgraduate Student in Oral Surgery, Dublin Dental Hospital, Lincoln Place, Dublin 2
2. Dr. Anna Beattie, Specialist Oral Surgeon, Dublin Dental Hospital, Lincoln Place, Dublin 2
3. Mr. John Ed O'Connell, Consultant Maxillofacial Surgeon, St James' Hospital, James St, Dublin 8

Contact Phone Number: (01) 6127391

PART 1 – THE STUDY

Introduction

You are being invited to take part in a research study. It is a local study that will involve patients from Dublin Dental Hospital. Before you decide whether you wish to be involved, it is important to understand why the research is being done and what it will involve. Please take time to read the following information and ask us if there is anything that is not clear to you or if you need more information.

Why is this study being done?

Dry socket, formally known as alveolar osteitis, is a painful complication of a tooth extraction. It tends to happen when the blood clot in the extraction socket is lost or disrupted, leaving the bone unprotected and exposed. Our aim in this study is to investigate whether there is any treatment benefit to adding a platelet-rich clot from your blood (PRF) into your dry socket compared to treating it with a commonly used sedative dressing (Alveogyl).
PRF and other platelet-rich clots made from a blood sample are used widely in both dentistry and medicine to help with healing. Studies have shown that these blood clots are rich in growth factors important for healing and produce faster and better results than natural healing alone.

What will happen to me if I agree to take part?

If you kindly agree to participate in the study, your treatment will be carried out in line with normal hospital protocol in the Oral Surgery department at Dublin Dental University Hospital by Dr Maeve Cooney and her experienced oral surgery colleagues. This will involve taking a blood sample from a vein in your forearm on the day you present to us with a dry socket. We will obtain two 9ml tubes of blood (approximately 1.5 tablespoons in total). This blood sample will be used to create a platelet-rich jelly clot which may be added to the extraction socket after it is cleaned out with salt water under local anaesthetic (numbing). The decision to add this **jelly clot** **or** the **medicated dressing** will be made using computer software, and you will not be aware of the outcome.

What will I be required to do?

You will be asked to complete a short questionnaire on the day of the procedure. This questionnaire should take no more than five minutes to complete. You will be given a questionnaire to fill in at home three days after the procedure and you will receive a telephone call where you will be asked a series of questions and given any advice you may need. You will then be required to attend the Oral Surgery department for in person review seven days after your procedure. During these review visits, we will carry out a short examination of your mouth and take some healing measurements.

You will be asked to complete the same short questionnaire as before. The review appointment will last approximately ten minutes.

Are there any benefits to me or others if I take part in the study?

By carrying out this study, we hope to get a better understanding about whether there is any additional benefit in receiving a blood-derived product compared to traditional techniques in the treatment of dry socket. It will help guide our treatment choices in the future for other patients who experience this painful condition following tooth extraction.

What are the possible disadvantages and risks of taking part?

There will be a small pin-point bruise on your arm for around a day or two after taking the blood sample. There is also a very low risk for developing infection or inflammation at the blood sample site on your arm as with all blood tests; the utmost care will be taken to avoid such complications. There are no extra risks involved with using platelet rich fibrin in your dry socket as it produced from your own blood. Alveogyl, the sedative dressing, is the most used treatment for dry socket in dental practices and carries no additional risks. We will not retain any of your blood products after the procedure has been completed. All blood tubes and biological samples will be disposed of in sharps containers in line with normal hospital protocol.

What other treatments are available to me?

If you do not wish to take part in this study, you will continue under the care of your treating dentist and your dry socket will be treated following normal hospital protocol.

PART 2 – DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Information will be gathered in an anonymised format relating to your age, sex, medical history, medications, smoking status, the history of your extraction and subsequent development of dry socket. With your permission, we may seek the additional assistance of your pharmacist or general medical practitioner if you require additional support with your knowledge of your past medical history or medications. This data will be used to inform the wider community of dentists treating patients with dry socket.

What will happen my personal data? How will my data be kept safe?

All hard copy information will be stored securely in a locked cabinet in a private office and will remain onsite in the dental hospital. Participant data will be stored on a password protected DDUH computer with access granted only to the principal investigator and supervisors. It will be handled with the strictest confidence for the 24-month study period. You will be allocated an individual study number. No one will be able to identify you in photos or on the questionnaire and you will not be identifiable in any reports or publications we write in future. A data protection impact assessment was carried out to ensure the level of risk is low. The principal investigator, Maeve Cooney, will only have access to your data.

Who will access and use my personal data as part of this study? Will my personal data be kept confidential?

When the study comes to an end, the data will be analysed by the Research Team (Dr Maeve Cooney, Dr Anna Beattie and Mr John Ed O'Connell) with the help of an experienced Medical Statistician, Dr Erica Donnelly-Smith. Anonymised, aggregated data will be published to inform the wider community of dentists treating patients with dry socket. You will not be identifiable by any data collected.

What will happen with the information collected in the study?

When the study comes to an end, the data will be analysed by the Research Team (Dr Maeve Cooney, Dr Anna Beattie and Mr John Ed O'Connell) with the help of an experienced Medical Statistician, Dr Erica Donnelly-Smith. You will not be identifiable. Once all data has been analysed and disseminated in a dental journal, it will be destroyed by the Research Team in approximately September 2024.

What is the lawful basis to use my personal data?

Processing of your personal data will be lawful if you give your explicit consent for the Research Team to process your personal data for the purposes of this research according to Article 6 and Article 9 of GDPR.

What happens if I change my mind about taking part in the study? What are my rights?

Your participation in the study is entirely voluntary. You are free to decline to enter or withdraw from the study at any point without having to give a reason. You have right to have any inaccurate information about you corrected or deleted and the right to lodge a complaint with the Data Protection Commissioner, if applicable. If you choose not to enter the study, or withdraw from the study, this will in no way affect your future medical care. If you decide to take part, you will be given this information sheet to keep.

Has this study been approved by a research ethics committee?

The study has been reviewed and approved by the Joint Hospital Research Ethics Committee (JREC) St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee.

Where can I get further information?

If you have any queries, you can contact Dr Maeve Cooney, Dublin Dental University Hospital at the following email address: maeve.cooney@dental.tcd.ie or use the contact number as above.

Thank you for your co-operation.

Yours sincerely,

Dr Maeve Cooney

Appendix 3: Patient Consent Form

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

DUBLIN DENTAL HOSPITAL

CONSENT FORM

Participant Study No: _____

Title of Research: A clinical investigation of the efficacy of Platelet Rich Fibrin (PRF) compared to Alveogyl in the treatment of alveolar osteitis

Principal Investigator: Dr Maeve Cooney Postgraduate Student in Oral Surgery, Dublin Dental Hospital, Lincoln Place, Dublin 2

Contact Phone Number: (01) 6127391

You are being asked to participate in a research study. The oral surgery team at Dublin Dental University Hospital are investigating a method to help improve pain and healing of alveolar osteitis ("dry socket") following tooth removal. In order to decide whether you wish to be part of this research study, you should understand enough about its risks and benefits to make an informed judgement. This consent form gives detailed information about the research study, which will be discussed with you and explained in the patient information leaflet. Once you understand the study, you will be asked to sign this form if you wish to participate.

To be completed by the **PARTICIPANT**:

General		
I confirm that I had read and understood the Information Leaflet for the above study and the Information within the Leaflet has been fully explained to me.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I understand that the study is entirely voluntary and, if I decide that I do not want to take part, I can stop taking part in this study at any time without giving a reason. I understand that not taking part will not affect my future medical care.	YES ☐	NO ☐
I understand that medical notes and records may be looked at by my Dr Maeve Cooney and her Research Team at Dublin Dental Hospital where it is relevant to do research. I agree that these individuals can access my medical records. I understand that all information will be kept private and confidential and that my name will not be disclosed.	YES ☐	NO ☐
I also agree to allow non-medical researchers to access my medical records and understand that my data will be kept confidential and that my name will not be disclosed.	YES ☐	NO ☐
I understand that I will not be paid for taking part in the study	YES ☐	NO ☐
I know how to contact the research team if I need to	YES ☐	NO ☐
I agree to be contacted by researchers by (email/phone) as part of this study	YES ☐	NO ☐
I agree to allow Dr Maeve Cooney to take unidentifiable photographs for use in this study.	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study as set out in the information leaflet which I have been provided with.	YES ☐	NO ☐

I understand that there are no direct benefits to me from participating in this study. I understand that results from analysis of my personal information will not be given to me.	YES ☐	NO ☐
Data Protection		
I agree to allow personal information about me to be shared with third parties including, national and international hospitals, and academic research institutions for the purposes of completing the research as laid out in this information leaflet	YES ☐	NO ☐
I give my explicit consent to have my data processed as part of this research study	YES ☐	NO ☐
Biological Samples		
I agree to provide samples of my blood for use in this study as described in this information leaflet. The risk of taking samples has been explained to me.	YES ☐	NO ☐
I understand that my biological samples will be disposed of in a lawful and respectful way.	YES ☐	NO ☐
I understand that I can stop taking part in this study and request withdrawal of my samples and request that my biological samples are destroyed at any time without negative impact on my medical care.	YES ☐	NO ☐
I understand that the results from the analysis of my samples will not be given to me/will be given to me.	YES ☐	NO ☐
I understand that I will not be paid for the use of my samples.	YES ☐	NO ☐

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES ☐	NO ☐
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES ☐	NO ☐

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

Appendix 4: Study Within a Trial (SWAT)—Rationale of Selection of Control Intervention Material

The purpose of this part of the research was to gain an understanding of the knowledge of general dental practitioners and oral surgery specialists specific to AO. It also provided the opportunity to gain information on how various clinicians choose to manage patients with AO and whether they have facilities to use autologous blood products in their practice. This information was gathered through an anonymised questionnaire on SurveyMonkey.

Ethical approval was obtained for the questionnaire from the School of Dental Science Research Ethics Committee, Trinity College Dublin (Appendix 7).

Due to a lack of previously validated questionnaires published in the field, an original 4-item questionnaire was designed by the principal investigator composed of both closed and open-ended format questions (see Appendix 8). The closed format questions consisted of yes/no questions and tick box answers, leaving a box if the respondent had a different answer. The questionnaire was piloted on two clinicians; a specialist trainee in oral surgery and a general dentist with no involvement in the study which allowed for any corrections to be made before the questionnaire was circulated via SurveyMonkey. All questionnaires were distributed via email or Whatsapp groups and recipients included all staff in the Oral & Maxillofacial Department of Dublin Dental Hospital including trainees and Non-Consultant Hospital Doctors (NCHDs), postgraduate students, the members of

the Irish Committee of Oral Surgeons, Classes of 2016, 2017 and 1999. Each participant gave implied consent by volunteering to complete the survey. A total of 107 questionnaires were returned anonymously via SurveyMonkey.

Results from Questionnaire:

Respondents

A total number of 154 dentists were sent a link for the questionnaire (see Appendix 8), with 107 (69%) returning the questionnaires. Within the questionnaire itself, there was a 76% completion rate and the estimated time for completion was one minute. All 107 (100%) respondents reported they had managed a dry socket in their dental career.

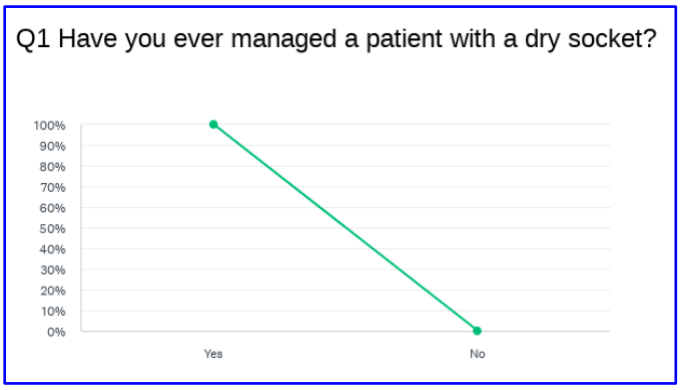


Figure 24: Assessment of whether respondents have managed a patient presenting with alveolar osteitis

Knowledge of timeline for presentation of alveolar osteitis

Of the 107 respondents, 86/107 (80.3%) felt that a patient would present for treatment two to five days following extraction, while 11/107 (10.2%) dentists felt

that it may be one to two days following extraction. Less dentists 10/107 (9.3%) felt that the presentation of AO would be five days or more following extraction.

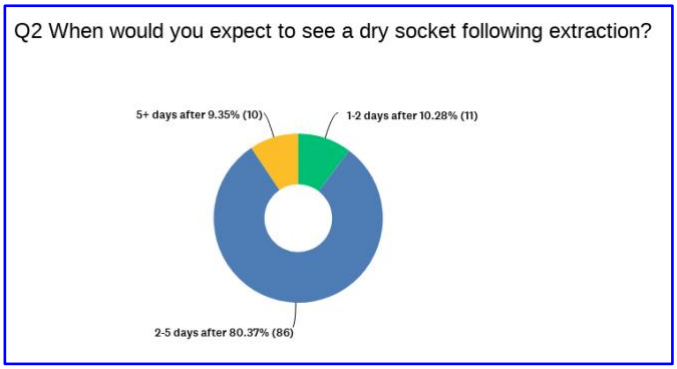


Figure 25: Awareness of the timeline for presentation of patients with alveolar osteitis following extraction

Treatment Strategies used to manage alveolar osteitis

103/107 respondents completed this question and of note, no clinician manages their patients with dry socket using blood derived products. The majority of clinicians (91/103, 88.3%) manage with irrigation and placement of Alveogyl into the affected socket while a smaller percentage of clinicians use another medicinal product such as eugenol-based alternatives to dress the affected socket (6/103, 5.8%). Only one clinician chose to manage dry socket with irrigation only (1/103, 0.97%). Some clinicians manage their patients without any means of intervention giving analgesia and reassurance only (5/103, 4.85%).

There was an open question within this choice of treatment question and an additional 16 respondents wrote in the free text box with further information. The majority of answers combined reassurance and analgesia with irrigation and placement of Alveogyl. One clinician advised they would curettage the socket to

promote a new clot, one advised they would use clove oil and one clinician chose to give a prescription of Metronidazole 400mg 8 hourly for 5 days.

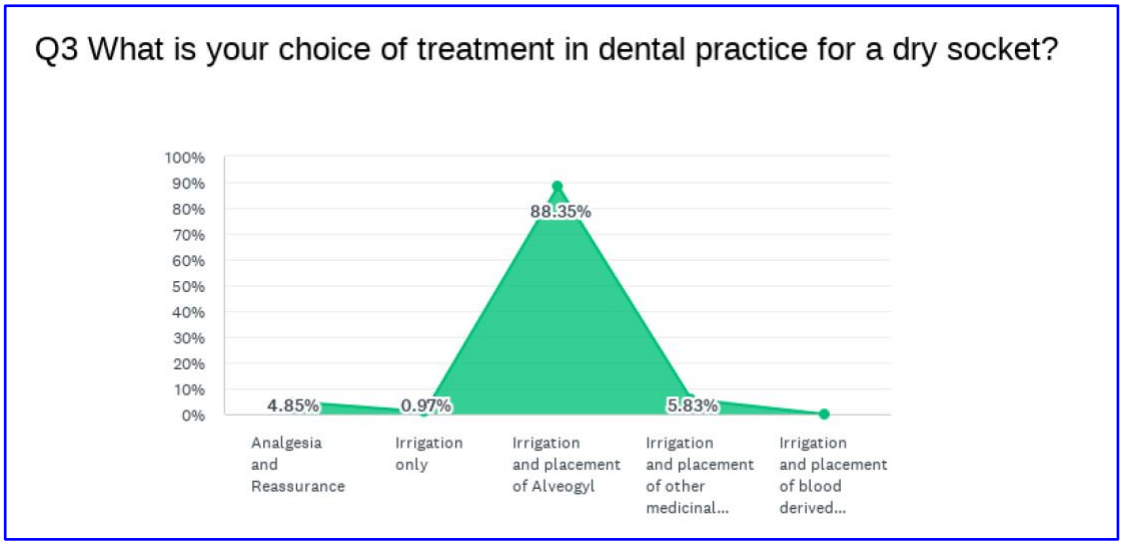
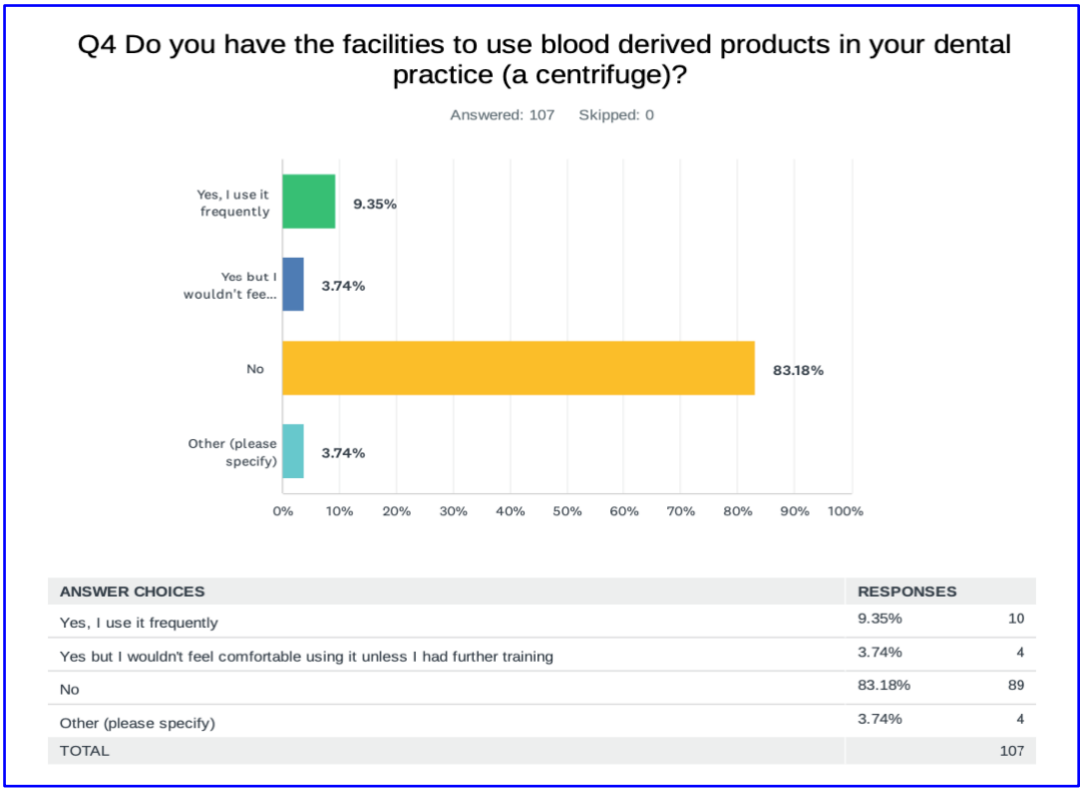


Figure 26: Strategies employed by respondents for the treatment of alveolar osteitis

Access to Autologous Blood Products in Practice

Clinicians were asked if they had facilities to use blood derived products in dental practice (i.e. a centrifuge). Of the 107 respondents, 89 responded with "No" (83.1%) while 4 responded " Yes but I wouldn't feel comfortable using it unless I had further training" (3.7%). 10 clinicians (9.3%) have access to a centrifuge and use it frequently.

In the free text section, there were an additional four comments recorded and two included that they work in hospital-based practice with access to a centrifuge as a result (n=2), one comment admitted using it but never for treatment of dry socket (n=1) and one comment alluded to seeing few dry sockets as their oral surgeon uses blood products prophylactically (n=1).



ANSWER CHOICES	RESPONSES	
Yes, I use it frequently	9.35%	10
Yes but I wouldn't feel comfortable using it unless I had further training	3.74%	4
No	83.18%	89
Other (please specify)	3.74%	4
TOTAL		107

Figure 27: The access and use of facilities to make autologous blood products in general practice settings

Discussion:

Our questionnaire found that an inordinate majority of clinicians manage AO with use of irrigation and placement of Alveogyl into the affected socket (91/103, 88.3%). We felt it important from an ethical standpoint that our control material was one that would likely provide an analgesic effect which is why we chose Alveogyl compared to a placebo alternative such as saline. Despite the paucity of literature supporting the efficacy of any intervention in the treatment of AO, there were two studies (Supe et al., 2018; Lenka et al., 2019) included in the recent Cochrane review (Daly et al., 2022) that showed Alvogyl (old formulation) is more effective than ZOE at reducing pain at day seven post intervention. It is unclear

however if the findings of these studies are transferable following the reformulation of Alvogyl as two of the material's active ingredients have been removed.

There has only been one RCT with 88 patients that has investigated the efficacy of Alveogyl (new formulation) against ZOE. They found that initial pain relief at baseline as well as at 10 days was improved with ZOE. This is contrary to the summary of findings in the Cochrane review (Day et al., 2022) but the robustness of the methodology in this study is questionable and pain reduction was the sole outcome recorded (Chaurasia, Upadhyaya, and Dixit 2017). Our study appears to be the second randomised controlled trial examining the efficacy of Alveogyl (new formulation), where patients prescribed post-operative antibiotics were excluded. Though inferior to the pain reduction with H-PRF, our study found a positive trend in pain reduction over the seven days following intervention with Alveogyl. Worst pain scores reduced consistently in the Alveogyl group from a mean of 86.81 at baseline, to 64.11 at day 3 and 23.67 at day 7. This shows the efficacy of Alveogyl as a treatment option. Healing outcomes were also positive for Alveogyl albeit inferior to H-PRF. Most sockets in the Alveogyl group were graded with "good" healing (n=11, 61.1%), with only one socket falling into the poor/ very poor healing categories at day 7.

Appendix 5: Patient Pain Diary

Patient Diary of Symptoms

Today's Date:

Answer the following questions in terms of how you felt in the past 24 hours.

1. From 1 (none) to 5 (a lot), how much did having your dry socket affect your ability to do each of the following in the past 24 hours?
   (Circle one number for each statement that applies to you)

Function	None	A Little	Some	Quite a bit	A lot
Chew the foods you want	1	2	3	4	5
Open your mouth wide	1	2	3	4	5
Talk and carry-on conversation	1	2	3	4	5
Sleep	1	2	3	4	5
Go to work or school	1	2	3	4	5
Perform your regular daily routine	1	2	3	4	5
Carry on your regular social life	1	2	3	4	5

2. **At its worst…**
   How would you rate your pain during the last 24 hours? Place an X on the line below to indicate the severity of the pain at its worst

No Pain _____ Worst Imaginable Pain

3. **On average…**
   How intense was your pain during the last 24 hours? Place an X on the line to indicate the average intensity of pain

No Pain _____ Worst Imaginable Pain

4. How much did your pain interfere with your routine activities in the past 24 hours? Place an X on the line to indicate the amount of interference.

No interference _____ Unable to carry out my normal activities

5. If you took any pain medication to relieve pain, write in the type of medication, the strength and the number of tablets you took today

Name of Medication	Strength (e.g. mgs)	Number of tablets in the last 24 hours

Appendix 6: Healing Assessment

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Title of Research: A clinical investigation of the efficacy of Platelet Rich Fibrin compared to Alveogyl in the treatment of alveolar osteitis

HEALING ASSESSMENT BY 2ND BLINDED OPERATOR

STEP 1: Give the patient their **3rd copy of the diary of symptoms** and ask them to fill it out. At this stage they should be familiar with this from Day 0 and Day 3 copies.

STEP 2: **Take a photograph** of the socket and upload to Salud before carrying out assessment measurements. Irrigate if necessary to enable a clear visual examination of the socket healing e.g., if there is food impaction

STEP 3: Circle which finding(s) you feel is most appropriate under each subheading, then select the most accurate representation of the socket's healing.

Healing Index	Tissue Colour	Bleeding on palpation	Suppuration	Exposed Bone	Your selection (x)
1. Very poor (two or more signs are present)	≥ 50% of red gingiva	Yes	Yes	Yes	
2. Poor	≥ 50% of red gingiva	Yes	No	Yes	
3. Good	25 - 50% of red gingiva	No	No	No	
4. Very good	< 25% of red gingiva	No	No	No	
5. Excellent	all pink tissues	No	No	No	

ADDITIONAL COMMENTS (if applicable)

_____

_____

Patient Study No: _____ **Your name:** _____

Date: _____

Appendix 7: Ethical Approval for Questionnaire

DUBLIN DENTAL UNIVERSITY HOSPITAL
OSPIDÉAL DÉADACH OLLSCOILE ÁTHA CLIATH

Research Ethics Committee
School of Dental Science &
Dublin Dental University Hospital
Lincoln Place
Dublin 2
Ireland

25th June 2024

RE: "The Age Old Dry Socket Debate- A Survey for GDPs"

REC Reference: DSREC2024-03

Dear Dr Cooney,

Thank you for your recent application to the Dental School Research Ethics Committee (DSREC). Your application has been granted ethical approval. Please quote the above reference in all future correspondence.

Yours sincerely,

Prof. Gary Moran
Associate Professor in Microbiology
Chair DSREC
School of Dental Science and
Dublin Dental University Hospital,

Appendix 8: Questionnaire distributed to Dental Practitioners

The Age Old Dry Socket Debate

1. **Have you ever managed a patient with a dry socket?**

- ◯ Yes
- ◯ No

2. **When would you expect to see a dry socket following extraction?**

- ◯ 1-2 days after
- ◯ 2-5 days after
- ◯ 5+ days after

3. **What is your choice of treatment in dental practice for a dry socket?**

- ◯ Analgesia and Reassurance
- ◯ Irrigation only
- ◯ Irrigation and placement of Alveogyl
- ◯ Irrigation and placement of other medicinal product (e.g. eugenol-based alternatives)
- ◯ Irrigation and placement of blood derived product (e.g. PGRF, L-PRF etc)

Other (please specify)

4. **Do you have the facilities to use blood derived products in your dental practice (a centrifuge)?**

- ◯ Yes, I use it frequently
- ◯ Yes but I wouldn't feel comfortable using it unless I had further training
- ◯ No
- ◯ Other (please specify)