CORTICOTOMY-FACILITATED ORTHODONTICS

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Clinical Dentistry

by

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3. SIGNED STATEMENT

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Berna Kim

4. SUMMARY

The duration of orthodontic treatment is an important determinant of patient satisfaction, and the demand for shorter-duration treatment options appears to be increasing. Prolonged orthodontic treatment can become an obstacle to certain social interactions – especially in adults. From a biological point of view, disadvantages of prolonged treatment time include white spot lesions and root resorption. Therefore there has recently been a renewed interest in investigating options to reduce orthodontic treatment time.

Corticotomy-facilitated orthodontic tooth movement (OTM) has been reported to reduce treatment time by two thirds, and involves surgical intervention to the cortical bone. The insult to the bone induces the regional acceleratory phenomenon whereby OTM is increased via up-regulation of bone remodelling and transient osteopenia. Contrary to popular belief, the method dates back to 1959 and results are well documented with one author in 1991 publishing the outcome of 395 treated cases. Nevertheless, despite its long standing history in the study of orthodontics, the method has still not been widely adopted by orthodontists.

The reasons behind this lack of adoption were examined in the first study "Accelerating orthodontic tooth movement with the aid of periodontal surgery – what the practitioners are thinking". Two separate questionnaires were developed for specialist periodontists and orthodontists. For the periodontists, a survey questionnaire was handed out by the primary investigator at the Australian and New Zealand Academy of Periodontists' 16th scientific conference, which was held in Hobart, Australia, from 6-9th of March 2013. For the orthodontists, a survey questionnaire was handed out by the principal investigator at the Australian Society of Orthodontists' Foundation Meeting which was held in Canberra Australia from 15-17th of March 2013.

The results showed that a majority of orthodontists and periodontists believe more research is required on the topic of corticotomy-facilitated orthodontic tooth movement before they would be willing to recommend it to patients. More than half of the orthodontists would never recommend corticotomy-facilitated orthodontics to their patients, while the minority who would recommend the procedure would limit it to adult patients, ankylosed teeth, impacted canines and patients susceptible to root resorption. Over 90% of periodontists believe that there are side effects associated with the corticotomy procedure. Finally, the proportion of practitioners who have undertaken at least one case per annum was quite low,

with few orthodontists (11.5%) and periodontists (18.2%) reporting experience with the procedure.

Despite the perceived lack of research on the topic by the professional community, numerous studies have already attempted to validate the biological mechanism behind corticotomy-facilitated OTM. For example utilising radiographic, tomographic, molecular biology techniques along with histology, studies have investigated the possible mechanism behind corticotomy-facilitated OTM using the rat. Incapable of demonstrating the dynamic remodelling of the bone in the region pertaining to the corticotomy, the methods described above only quantify the static effects of the corticotomy surgery. Furthermore, these studies use a mesially-directed force to the upper first molar; this may be applicable to the closing of an extraction space, but the direction of this force does not represent the clinical scenario of expansion-based, non-extraction treatment plans.

For these reasons, the second study in this thesis titled "Dynamic response of the alveolar bone to corticotomy-facilitated orthodontic tooth movement" aimed to augment the research evidence on the mechanism by which corticotomy accelerates OTM. Using double fluorescent bone labelling to quantify the mineral apposition rate, the changes that take place in bone over a period of time – rather than at a specific time-point – add another dimension to the understanding of corticotomy-facilitated OTM.

To conduct this analysis, thirty-six male Sprague Dawley rats were obtained from Laboratory Animal Services (University of Adelaide), and for comparison a control group without any intervention was included. A bone label, calcein was administered three days prior to appliance insertion and a second label, alizarin red, was administered five days after appliance placement. The rats were randomly assigned to one of six groups:

Group	Appliance	Surgery
1	No	No
2	No	Flap
3	No	Corticotomy
4	Yes	No
5	Yes	Flap
6	Yes	Corticotomy

For the groups undergoing orthodontic tooth movement, buccally directed force (100g) was delivered to the maxillary right first molar. The activated appliance remained *in situ* for seven days. The animals were sacrificed at the end of the observation period, and the maxilla was dissected and embedded in polymethylmethacrylate. Coronal sections of 5μm thickness were then chosen to study the effects of corticotomy along the length of the root of the first molar tooth in the buccal aspect. Histomorphometric analysis of the mineral apposition rate (MAR) was performed by selecting five random slides.

There was a statistically significant difference in mean average values between the six groups ($p < 0.0001$). From the six groups tested, the OTM+corticotomy group had the highest MAR. This was followed by OTM only, OTM+flap, corticotomy only, flap only and control. The MAR for the OTM+corticotomy group was approximately 1.19 times higher than for the OTM-only group and 2.37 times higher than the control group. When the groups were compared to each other, there was no significant difference in the MAR of OTM and OTM+flap.

Based on these results it is concluded that when no OTM is involved, there is a trend towards increasing MAR accompanying both the raising of a mucoperiosteal flap and a corticotomy procedure. In contrast when OTM is involved, raising a flap does not significantly increase the MAR beyond the levels of OTM; therefore, it is concluded that injury to the cortical bone is essential to increase MAR, and thus the rate of OTM. OTM itself increases MAR and it is postulated that this is a result of micro-damage to the alveolar bone in the vicinity of the tooth undergoing OTM.

5. LITERATURE REVIEW

Introduction

With an increasing number of adults seeking orthodontic treatment, methods to reduce overall treatment time are being investigated. Currently, accelerating orthodontic tooth movement (OTM) can be divided into two main categories: non-surgical and surgical. Under the non-surgical category there are pharmacological methods and vibrational methods. Human studies on pharmacological methods to increase OTM are limited and there are uncertainties regarding the dosage, frequency of administration and systemic side effects. Despite introduction into the market, the efficacy of vibrational methods has yet to be tested by randomised clinical trials.

Employing surgical methods to enhance tooth movement is not new. Corticotomy has been described as early as 1959 to accelerate tooth movement but it did not gain acceptance amongst the orthodontic community due to its invasive nature. As with any surgical procedure, significant risks are present. However, in selected cases, it is possible to employ surgical methods such as corticotomy to biologically expedite tooth movement. It is not the intention of this literature review to persuade the clinician into employing the technique of corticotomy-facilitated orthodontic tooth movement but to review the biological basis of OTM, examine the various methods available to accelerate tooth movement and explore the possibility of using corticotomy in selected cases.

Orthodontic Tooth Movement

Early Pioneers

Knowledge on Orthodontic Tooth Movement (OTM) was developed on the founding histological studies of Sandstedt and Oppenheim[1]. Sandstedt's experiment consisted of moving the six maxillary incisors of a dog lingually by 3mm using light forces. Histological observations showed bone deposition on the alveolar wall on the tension side of the tooth. Conversely on the pressure side, alveolar bone was resorbed by multinucleate osteoclasts in Howship's lacunae. With the application of heavy force, localised cell free areas were observed and these areas were referred to as hyalinisation due to its glasslike appearance[1].

Oppenheim, using the monkey model, employed labial tipping movement and, surprisingly, found different results to that of Sandstedt. He observed that the original bone was completely replaced by new bone with an entirely new architecture. Oppenheim's work supported Angle's non-extraction philosophy and the widespread belief amongst the orthodontic community at that time on "growing bone". Meikle reports that Sandstedt's early death in conjunction with the lack of English translation of his work gave Oppenheim the advantage of propelling his theory on OTM[1].

Investigations on OTM gained momentum in the 1950s and Reitan of Norway used human premolars that were destined for extractions. Reitan observed through histological sections that during the initial stages of tipping movement, hyalinized areas were frequently created subsequent to a continuous force of 30 g. He also observed that hyalinisation was associated with tipping because bodily movement caused the force to be distributed more evenly along the length of the root[1].

Twenty years later, Kvam and Rygh demonstrated that during the removal of the hyalinised layer, root resorption takes place. Scanning electron microscopy studies of premolar root surfaces demonstrated that when the hyalinised area was intact, root resorption was absent[2]. More recently, Brudvick and Rygh showed, on a cellular level, that tartrate-resistant acid phosphatase (TRAP) positive macrophages and multinucleate giant cells are involved in the removal of hyalinised tissue. During the removal of the hyalinised layer, the TRAP positive cells also tend to remove cementum resulting in root resorption[3]. Collectively, these initial histological findings led to the development of OTM theories.

Theories of OTM

Pressure-Tension Theory

Classic histological studies carried out by Sandstedt, Oppenheim and Schwarz led to the development of the pressure-tension theory[4]. When a force is applied to a tooth, a "pressure" side and a "tension" side is created. Vascular constriction in the pressure side leads to decreased cellular activity and decreased fibre production. Conversely on the tension side, stretching of the PDL fibres results in increased cellular activity and increased fibre production[4]. Schwarz emphasised the need to carefully control the magnitude of orthodontic force as pressure greater than that of the capillary bed blood pressure (20-25 g/cm^2 of root surface) would result in tissue necrosis.

The cellular response to force application is in part a result of an inflammatory response. Force application may result in either frontal resorption whereby osteoclasts are responsible for the direct resorption of bone or undermining resorption whereby macrophages and osteoclasts from undamaged areas invade the necrotic tissue as well as bone. Following the inflammatory response, there is loss of bone mass at locations of pressure along the PDL and apposition at areas of tension. The sequence of events starting from the application of force to the regulation of cellular activity and the response of the bone formed the central theme of the pressure-tension hypothesis[4].

The Bone Bending Theory

Baumrind recognised a conceptual flaw within the pressure-tension theory of OTM. According to Pascal's law, the PDL is a continuous hydrostatic system and, therefore, any force delivered to it would be transmitted equally to all regions. Furthermore, Baumrind pointed out that the only part of the periodontium whereby differential pressures as suggested by the Pressure-Tension theory could arise was in the hard tissues – namely the bone and the tooth[4].

When a force is applied, it results in the bending of the bone which responds in the most elastic manner whereby bone turnover is initiated via the activation of cellular processes. The re-organisation of bone is not only limited to the lamina dura of the alveolus but extends to the surface of trabeculae. The force delivered to the tooth results in the development of stress lines and the biological response takes place in cells that are positioned perpendicular to the

stress lines. The overall result from the cellular events is change in the shape and internal organisation of the bone[5].

The bone bending theory can explain several clinical observations including the relative slowness of en-masse retraction of teeth, the rapid movement of teeth towards an extraction site and the increased velocity of OTM in children who have less calcified bones compared to adults[5].

Bioelectric Signalling in OTM

Bassett and Becker in 1962 proposed that in response to the application of mechanical forces, electrical potentials are generated in the stressed tissues. The resultant effects included the charging of macromolecules which would subsequently interact with cell membranes or the mobilisation of ions across cell membranes[6]. Subsequently, in 1973 Zengo measured the electric potential in the alveolar bone of a dog which in which the tooth was under mechanical loading[7].

The experiment demonstrated that the concave side of the alveolar bone was electronegative and favoured osteoblastic activity whereas the convex side favoured osteoclastic activity (Figure 1).

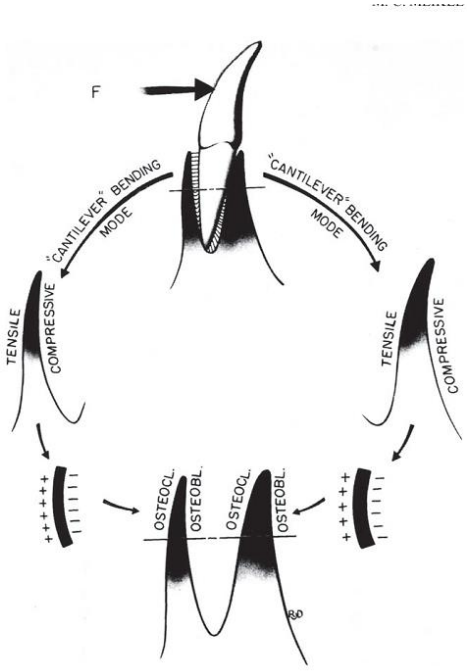

Figure 1: Hypothetical model of the role of bioelectric potentials [7]

During the 1960s and 1970s, the biological signalling concept enjoyed support amongst the orthodontic and orthopaedic profession. However, Meikle points out that from a biological point of view, it is questionable whether electrical phenomena can sufficiently discriminate and regulate metabolic activity of cell types that lie in close proximity such as osteoblasts and osteoclasts[1].

The Present and the Future

The three theories presented above aspire to demonstrate in a simplified way the possible mechanisms behind OTM. The theories are not mutually exclusive and will continue to aid the understanding of OTM. Today, the research trend is directed at the molecular level of OTM and at elucidating the relationship between genes and transcription factors that control bone and PDL remodelling. Advances in the future may be able to enhance OTM on an individual basis at the genetic level.

Phases of Tooth Movement

Burstone first suggested the division of OTM into three distinct phases: initial strain, lag phase and progressive tooth movement[8]. Typically lasting 1-2 days, initial strain can be characterised by PDL displacement, bone strain and extrusion due to the inclined plane of the alveolar bone. Tooth displacement occurs instantaneously due to displacement of the tooth within its socket. The lag phase takes place during the removal of the hyalinised layer which histologically presents as a cell free zone. Removal of this cell free, necrotic zone is required to progress to the next phase of tooth movement. Osteoclasts are recruited from the neighbouring marrow spaces or surface of the alveolar bone to remove the hyalinised layer and tooth movement is at a standstill until this layer is removed and a new PDL is established. Progressive OTM takes place as the bone is remodelled ahead of the advancing tooth.

More recently, the four phase model of OTM has been published by Van Leeuwen *et al*(Figure 2)[9]. Phase 1 is identical in nature to the initial strain and is characterised by the displacement of the tooth within the PDL space. In a dog model, this phase lasts 1-2 days. Phase 2 which lasts 20-30 days involves areas of hyalinization and the cessation of OTM. Burstone's progressive tooth movement is divided into phase 3 and phase 4. Phase 3 involves the removal of necrotic tissue followed by accelerated tooth movement and phase 4 consists of tooth movement of constant velocity which takes place after 40 days.

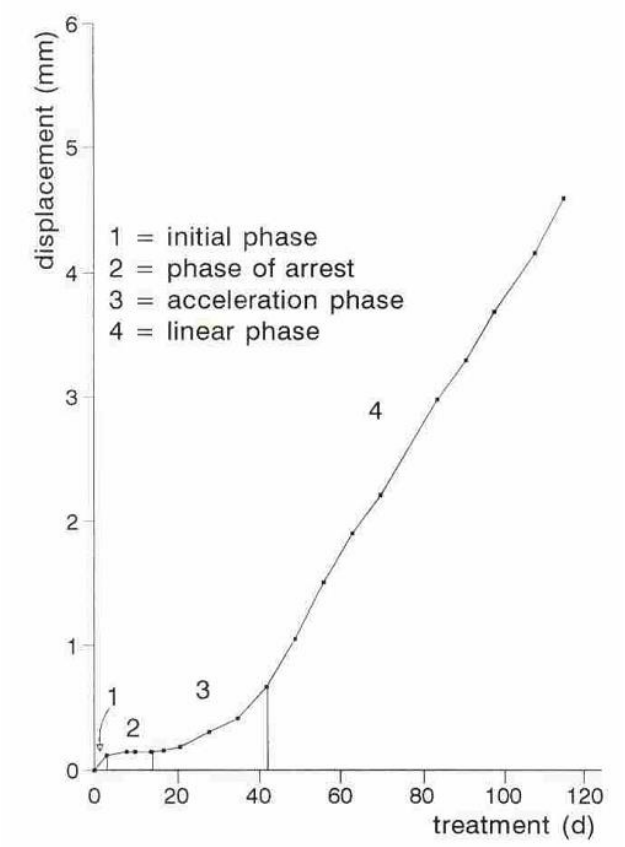

Figure 2: Four phases of OTM [9]

Hyalinisation

It is evident from studies of OTM that hyalinisation and its removal is the rate limiting step in OTM. The time required for the removal of necrotic tissue in the dog model is approximately 20-30 days during which, multi-nucleated giant cells without a ruffled border and mono-nucleated macrophage-like cells are recruited to the area via chemotaxis[3]. It was previously thought that light forces may prevent hyalinisation, but this has been disputed in the literature. Von Bohl *et al* demonstrated focal hyalinisations are not necessarily dependent on the applied force but on local stresses or strains that may result due to irregularities in the periodontal tissues or bone[10]. This may previously have been overlooked due to the orientation of the serial sections that are employed in histological studies. By using serial coronal sections from mesial to the distal side, it was shown that light forces do not prevent hyalinisation of the PDL[10].

If light forces do not prevent hyalinisation it was uncertain how the lag phase could be reduced or bypassed. Baloul *et al* found that corticotomy assisted OTM showed a continuous movement without any evidence of a lag phase[11]. Previous authors have suggested that the

rapid alveolar bone remodelling associated with the corticotomy procedure results in less hyalinisation of the PDL[12]. The acceleration seen in corticotomy-facilitated orthodontics is currently believed to be due to the early elimination of the hyalinization; however, further studies employing histological methods are required to verify this current belief.

Variation of tooth movement between individuals

The rate of tooth movement can vary significantly between different individuals. For an equivalent amount of stress, tooth movement three times faster can be observed[13]. Even in animal studies, variability in OTM can be observed amongst littermates[14]. At the macroscopic level, the difference can be attributed to individual variation in bone density, metabolism of the bone and the periodontal ligament (PDL). Morphological and biomechanical differences in the teeth and PDL may also play a role[10]. Recent advances in genetic studies will provide a more comprehensive picture behind the variation in OTM between individuals which will then potentially allow the clinician to tailor treatment for individual patients depending on their needs.

Iwasaki *et al* (Figure 3) show that OTM is the phenotype which is determined by the effects of the environment and genotype[15].

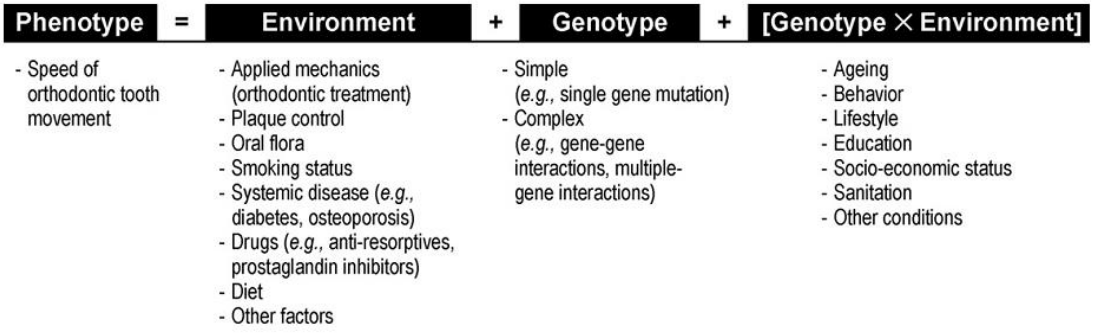

Figure 3: Model of factors affecting phenotype [15]

If the effects of the environment as well as the genotype are unfavourable for efficient OTM, the clinician can then explore methods to increase OTM. Some patients may benefit from adjuncts that increase OTM due to their inherent cell biology which favours slow bone remodelling. Other patients may be more genetically susceptible to enhanced bone remodelling, and despite measures to enhance OTM, may not benefit in a significant way from such measures.

The speed of OTM is determined by bone remodelling which at the cellular level requires co-ordination between osetoblasts, osteoclasts, precursor cells from the PDL and fluid transport and mechano-transduction by osteocytes. These cellular mechanisms are influenced by genetics and currently, a large number of bone active substances with heritable polymorphisms have been identified as in Table 1[15]. Further research into each of the bone active substances will slowly expose the extent that genetics may play in OTM and clinical applications may involve tests to quantify an individual's expected rate of tooth movement.

Table 1: Candidate bone active substances with heritable polymorphisms[15]

Bone-active substance	*Abbreviation*	*Bone-related Activity*
Androgen receptor	AR	Osteoblast differentiation
Aromatase		Bone maintenance
Bone morphogenetic protein-2	BMP-2	Osteoblast differentiation
Calcitonin	CT	Bone formation
Calcitonin receptor	CTR	Bone formation
Collagen type I (α1)	COLIA1	Bone matrix protein
Estrogen receptor-α	ER-α	Decreased fracture risk
Estrogen receptor-β	ER-β	Bone density
Growth hormone	GH	Bone formation
Insulin-like growth factor-1	IGF-1	Bone formation
Interleukin-1β	IL-1β	Bone resorption
Interleukin-1 receptor antagonist	IL-1RA	IL-1β antagonist
Interleukin-6	IL-6	Bone resorption
klotho protein	*klotho*	Bone density
Lipoprotein-related receptor-5	LRP5	Bone density
Matrix metalloproteinase-9	MMP-9	Bone density/remodeling
Osteoprotegrin	OPG	Prevention of bone resorption
Parathyroid hormone receptor	PTHR	Bone formation
Transforming growth factor-β1	TGF-β1	Bone resorption
Vitamin D receptor	VDR	Bone density

Accelerating OTM

Orthodontists are frequently asked by patients as to when the treatment will be completed. Companies exploit this by investing heavily in technology to reduce treatment time – whether real or perceived. It is the goal of many clinicians to provide a stable outcome to all patients via optimal tissue response, minimal iatrogenic damage in the shortest possible time[16]. Optimising treatment is a fundamentally important factor for patient care as increased time in fixed appliances has been associated with increased susceptibility to white spot lesions and root resorption [17,18]. At present, methods to accelerate OTM are largely divided into non-surgical and surgical means.

Non-Surgical

Gene Transfer

During orthodontic tooth movement, osteoclasts on the compression side resorb the alveolar bone and two cytokines, receptor activator of nuclear factor kappa β ligand (RANKL) and macrophage colony stimulating factor (M-CSF) regulate the process of osteoclastogenesis. RANKL is a membrane bound-protein which is expressed by osteoblasts and stromal cells which then acts on the receptor RANK which is present on the osteoclast lineage of cells. Signalling by RANKL is inhibited by osteoprotegerin (OPG) which acts as a competitor ligand for RANK and the relative proportion of RANKL and OPG regulates the activity of bone resorption[19].

Kanazaki *et al* found that local gene transfer of OPG to periodontal tissues induced OPG expression and inhibited RANKL mediated osteoclastogenesis in the rat model[20]. Conversely, it was hypothesised that local RANKL gene transfer to the periodontal tissue would increase the RANKL concentration in the periodontal tissue and up-regulate osteoclastogenesis and subsequently, accelerate the process of OTM[21].

Twenty five 6 week-old male Wistar rats were used in the study and were divided into three groups. Ten were used as controls, 11 were subjected to an orthodontic force and the remaining four were used to transfect a mock vector. A standardised spring made out of Nickel Titanium (NiTi) wire was placed in the animal's mouth between the upper right and left first molars resulting in the palatal movement of both molars. The extent of tooth movement was determined by plaster casts which were digitally scanned[21].

The gene was transferred to the periodontal tissues of the upper first molar by injecting around the first molar using the inactivated hemagglutinating-virus of Japan (HVJ) envelope vector containing the RANKL. There were no apparent systemic effects as the rats did not lose weight nor did the bone mineral density of the tibia change after the injection with RANKL. The RANKL gene transfer group's rate of movement was 30-70% higher compared to the controls, however, the increase in rate decreased over the experimental period of 21 days[21].

Kanazaki *et al* concluded that local RANKL gene transfer may be a useful tool for decreasing the time required for orthodontic treatment as well as for moving ankylosed teeth. Unlike injections of Vitamin D3, prostaglandins, osteocalcin or PTH whereby rapid absorption into

the blood almost requires daily injection, gene transfer maintains a local concentration and protein expression is maintained. Although the authors could not discern any systemic side effects on the rats the application to human subjects at this stage would be unlikely. The duration of observation after the gene transfer should be increased and the experiment repeated on larger animals before human trials. If local RANKL gene transfer to periodontal tissue can accelerate OTM without systemic side effects, it will no doubt have a place in clinical orthodontics in the future especially when anchorage issues become a problem or where an ankylosed tooth requires movement as part of a treatment plan.

Prostaglandins (PGs)

Prior to studies on gene transfer mechanisms, the focus of various studies during the 1980s was the changes which take place at a cellular level during orthodontic tooth movement. Namely, there was considerable interest in the role of prostaglandins, a group of lipid compounds derived enzymatically from fatty acids, in bone resorption[22]. Goodson *et al* demonstrated that repeated injection of PGE_1 into rat calvaria resulted in increased loss of bone matrix, fibrous replacement and increased vascularity[23]. Such findings prompted the investigation of prostaglandins with respect to alveolar bone remodelling during orthodontic tooth movement.

Yamasaki *et al* used the rat model to determine the role of PGs in periodontal tissues[22]. The injection of PGE_1 or PGE_2 increased the number of osetoclasts observed histologically and the increase was dose dependent[22]. Conversely, when indomethacin, an inhibitor of PG synthetase was injected into the rats, osteoclast recruitment was suppressed.

Two years later, Yamasaki et al published a similar study using monkeys[24]. PGE_2 was injected locally into the submucosal area of the distal side of the upper right canine. The injection protocol was carried out at zero, one, five, nine, twelve and fifteen days after orthodontic tooth movement commenced. The total amount of tooth movement on the control side was 1.2mm at completion of the experiment whereas the PGE_2 treated experimental side demonstrated 2.5mm and nearly double the rate of tooth movement. When the tooth movements were graphically recorded, the control side experienced a plateau during tooth movement, indicative of hyalinisation and undermining resorption, whereas the experimental side treated with PGE_2 showed continuous tooth movement.

Yamasaki *et al* reported that the local administration of PGs accelerated the rate of tooth movement in monkeys without significant side effects to the gingiva on a macroscopic level.

As a result, Yamasaki et al undertook clinical application of PGE_1 in orthodontic patients[25]. Nine patients scheduled to have upper first premolar extractions for treatment reasons volunteered for the study. The right first premolar received injections of PGE_1 in the submucosal area on the buccal side and on the left side lidocaine was given as a control. The rate of tooth movement on the experimental side in all patients was double or more. No significant side effects were reported by the patients with the exception of discomfort on both sides which were consistent with orthodontic tooth movement in the first 2 to 24 hours after initial force application.

In order to clarify the mechanism of the role of PGE_1 in orthodontic tooth movement, Lee used Wistar rats to investigate the differences in systemic and local administration of PGE1 on a histological level[26]. The number of Howship's lacunae and osteoclasts were significantly increased on the compression side in the PGE_1 administration groups when compared to their respective controls and the differences in the number of Howship's lacunae and osteoclasts were significantly higher in the groups that received PGE_1 by systemic administration compared with local administration.

The mechanism behind the increased osteoclastic activity as a result of PG can be explained by the increase in the level of cyclic AMP. Davidovitch *et al* reported that in the cat model, orthodontic treatment results in the up-regulation of cyclic AMP levels in the alveolar bone[27]. Cyclic AMP is a second messenger involved in the action of hormones and drugs and during orthodontic treatment it is involved in the modulation and activation of osteoclastic activity and subsequent bone resorption[28]. Orthodontic tooth movement results in the production of PGs which activate osteoclastic activity thus increasing the concentration of PGs exogenously and normal osteoclastic activity is upregulated to accelerate OTM.

Although PGs have been shown to increase the rate of tooth movement, clinical applications are currently limited for numerous reasons. PGs, in particular PGE_1 at high concentrations, induce pain and at low concentrations sensitise pain receptors to chemical and mechanical stimulations[26]. The rats used in Lee's study showed agitation about 3 minutes after repeated local administration of PGE_1. Lee states that the agitation was a result of the pain caused by inflammation which was subsequently enhanced by the injection of the PGE_1[26].

In response to the pain at the injection site, some authors have advocated the use of PGE_1 by dissolving it in dental lidocaine. However, this results in local vasoconstriction at the site of administration which consequently suppresses local inflammation which is required for bone

resorption[26]. Systemic administration was found to be more effective in accelerating tooth movement compared to local administration but also had drawbacks such as rapid inactivation of the PGE_1 in the lung and other side effects such as phlebitis[26]. This led to the testing of an alternative molecule called misoprostol, an analog of PGE_1, on rats. Results were promising with statistically significant acceleration of OTM and the authors concluded that, based on their initial findings, a clinical trial with oral misoprostol to facilitate orthodontic treatment is strongly recommended[29].

Despite promising results on animal models and even on human samples, the use of PG or its analogs at present are limited. Although Yamasaki's results were based on humans, the sample was limited and to justify its routine use on patients would require a prospective randomised clinical trial (RCT) to demonstrate its effectiveness. Misoprostol, a PGE_1 analog may confer the benefits of accelerating OTM with less side effects but once again its use in humans is limited without further research.

Vitamin D

Vitamin D is a steroid hormone and has a fundamental role in calcium homeostasis. It activates DNA and RNA expression within the target cell and results in the formation of proteins and enzymes involved in bone resorption[30]. The active form of Vitamin D, 1,25-dihydroxycholecalciferol (1,25D) is a potent stimulator of osteoclasts and, although it has a relatively short half-life in plasma approximating 2 to 3 hours, its cellular activation may last for several days[31]. For this reason, it has been investigated as a potential accelerator of orthodontic tooth movement due to its role in the formation of osteoclasts from precursor monocytes[32].

Collins investigated the effects of local administration of 1,25 D on the rate of orthodontic tooth movement in cats[33]. The experimental cats, which received a local injection of 1,25D demonstrated tooth movement 60% greater when compared to the controls. The histologic evaluation showed that on the pressure side, contrary to the classic presence of multinucleated cells residing in the resorption lacunae, the alveolar bone of the experimental teeth showed an entire resorption front covered with a large number of osteoclasts and their precursors. The increase in bone resorption was not only evident in the frontal surface but also within the deep surface of the alveolus; thus the depth of the demineralizing process was greater[33].

As the rate limiting step in orthodontic tooth movement is the adequate recruitment of osteoclast precursor cells, by providing 1,25D which acts directly on the nucleus of circulating monocytes via their specific receptors, accelerated recruitment of osteoclasts takes place[33]. Despite the acceleration in tooth movement, the optimum dosage, frequency of injection and potential local and systemic side effects are unknown in human subjects. Similar to PGs, although promising results are shown in experimental animals, human studies have not been undertaken for various reasons for Vitamin D to have clinical applications in modern orthodontics.

Osteocalcin

Bone resorption involves a cascade of events from the recruitment of osteoclast precursor cells, their differentiation and activation which is influenced by hormonal as well as local factors. In addition to hormonal and local factors such as parathyroid hormone (PTH), 1-25 dihydroxy Vitamin D3, interleukin-1 (IL-1), interleukin-6 (IL-6) and prostaglandins, bone matrix proteins may also have a significant role in the process of bone resorption[34].

Bone Gla Protein (BGP), better known as osteocalcin, is a bone matrix protein which shows chemotactic activity for multinucleated cells with osteoclastic features[35]. Previous studies have shown that bone matrix which is deficient in osteocalcin is inefficient in recruiting osteoclasts. Glowacki *et al* demonstrated that synthetic crystalline apatite with 0.1 % osteocalcin resulted in increased activation of multi-nucleated, TRAP-positive cells. These cells also displayed features consistent with that of osteoclasts such as ruffled borders and clear zones. In comparison, pure synthetic crystalline apatite, synthetic crystalline apatite with bovine serum albumin and synthetic crystalline apatite with rat bone collagen lacked ruffled borders and were TRAP negative[35].

Following on from the study of Glowacki *et al*, Kobayashi *et al* evaluated the effects of the local administration of osteocalcin on OTM using the rat model. An elastic band was inserted between the maxillary first and second molars and the resultant mesial movement of the first molar in conjunction with administration of osteocalcin was then examined. Upper molars in rats have naturally occurring distal drift, thus when an elastic band is inserted between the two molars, there is a dramatic change in the bone physiology as the resorption and apposition sides reverse[34].

The effects of OTM were evaluated by measuring the amount of tooth movement on a plaster model generated from an impression and via histological means. Tooth movement in the

osteocalcin injected group was significantly more than the control group. Histological evaluation involved the quantification of TRAP positive multinuclear cells. Compared with controls, there were more osteoclasts on the surface of the alveolar bone on the pressure side of the tooth socket and along the marrow surface and, overall, fewer osteoclasts were noted in the control rats[34].

Kobayashi *et al* elucidated that the effects of osteocalcin did not result from the secondary effects of inflammation or immunological reactions from the injection as there were no differences with respect to infiltration of inflammatory cells in control and experimental groups. The authors also highlighted that osteocalcin confers advantages over PGE1 and Vitamin D3 as it has no effect on intact bone surfaces whereas PGE1 has demonstrated increased bone resorption at the injection site and Vitamin D3 has shown enlarged osteoclasts on the bone surface[23,36,37].

Similar obstacles faced by PG and Vitamin D also apply to osteocalcin and its clinical application. First of all, would the statistically significant increase in tooth movement demonstrated in animal studies be clinically significant in a human patient? What dosage would be required for optimal increase in the rate of OTM? How often would the intervention be required? Are there any biological side effects both immediate and long term? Until these questions can be answered through further research, clinical application will be doubtful.

Vibration

Bone biologists have long recognised that bone architecture can be altered by mechanical stress. Many studies have attempted to find the parameters of mechanical forces necessary for an anabolic response and although the exact mechanism behind mechanical stimulus and bone apposition is not fully elucidated, animal models have shown promising results even with short daily doses of mechanical stimuli. For example, vibration signals stimulated a large increase of cortical bone in turkeys and, similarly, a daily 20 minute session of high frequency mechanical stimulation of sheep over a period of a year resulted in a 35% increase in bone mass density[38]. Human clinical trials have also shown the potential for low magnitude, high frequency mechanical signals in the form of vibration to improve the bone mineral density in young women[39].

The mechanism behind the osteogenic potential of vibration may be related the enhanced fluid flow through the extracellular spaces in the canaliculi and lacunae of bone. The increase in fluid flow results in shear stress on the cell membrane due to cellular deformation that

results from the shear stress. Potential mechanisms for converting the shear stress into cellular responses have been postulated and they include: membrane mechanoreceptors[40], focal adhesion proteins[41], cytoskeletal signaling[42] and extracellular fibre bowing[43].

The osteogenic effects of vibration on bone propelled research into alveolar bone remodelling during tooth movement. Nishimura *et al* investigated the rate of tooth movement in the rat model by intermittent stimulation of the periodontal tissue by resonance vibration[44]. The maxillary first molars of 6 week old Wistar rats were used for the experiment and a spring was used to apply buccal tooth movement. The duration of the experiment was 21 days and vibrational stimulation was applied using a resonance vibration delivery system on days 0, 7 and 14. The animals were then sacrificed and the maxilla was dissected and embedded in paraffin for immunohistochemical analysis of RANKL expression and histological evaluation[44].

Results showed that there was a statistically significant increase in the amount of tooth movement in the experimental group when compared to the control group. The increase may be explained by enhanced RANKL expression which was observed at fibroblasts and osteoclasts in the periodontal ligament of the experimental group on day 3. Furthermore, the experimental group showed significantly increased numbers of osteoclasts on day 8 and did not demonstrate adverse effects such as root resorption[44].

Unlike pharmacological interventions which have not been incorporated into clinical practice, a hand held vibrating device has been introduced to promote OTM. Despite the fact there are no randomised clinical trials to demonstrate its efficacy, its non-invasive nature has led to the development of Acceledent (Ortho Accel Technologies®, Houston, Texas) which is being marketed to both practitioners and prospective patients.

Surgical

Surgical intervention is another mode by which OTM can be accelerated. Several authors have described techniques by which surgical intervention on the bone activates the remodelling process and up-regulates OTM. Unlike pharmacological interventions whereby systemic side effects and dosage still remain unanswered, side effects associated with surgical interventions are well established. The following section will cover distraction and corticision but will mainly focus on the procedure of corticotomy.

Dental Distraction

Liou and Huang in 1998 first described the concept of "dental distraction" whereby they hypothesised that the periodontal ligament can be distracted like the mid-palatal suture in rapid palatal expansion. Fifteen consecutive patients requiring first premolar extraction either in the maxilla or mandible and required the retraction of the canine were included[45]. The ages of the patients ranged from 10 to 19 years old. Twenty six canine distractions (15 upper and 11 lower) were carried out with custom made, tooth borne, intra oral devices[45].

The intra oral procedure involved the placement of the fixed appliance prior to premolar extraction. The first molar and second premolar provided anchorage for the distraction of the canine. Following the extraction of the first premolar, the inter-septal bone distal to the canine was vertically undermined (Figure 4). The direction of the cuts extended obliquely towards the base of the interseptal bone as to decrease the resistance during movement of the canine. The custom made distractor was subsequently placed and was activated 0.5mm to 1mm per day commencing right after the extraction until the canine was distracted into the desired position. The patient was monitored every week during the distraction process[45].

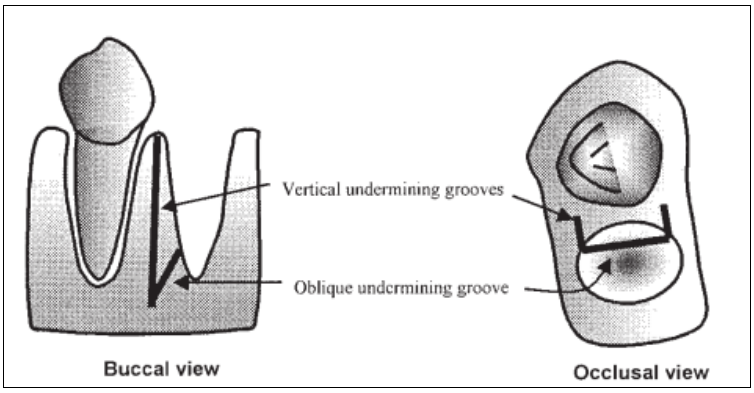

Figure 4: Liou's dental distraction - no cuts are performed on buccal and lingual plates [45].

By using dental distraction, the authors found that on average, the canine was moved 6-7mm in three weeks. The authors commented that the periodontal ligament could have been torn during the distraction process; however, it healed uneventfully a month after the distraction and there was evidence that the bone created became radiographically mature in 3 months. The authors advocated this method may be especially useful in patients where all of the extraction space is required for the unravelling of anterior crowding as there is minimal loss

of anchorage as the molar tooth is still in the lag phase as the canine is distracted through the extraction space[45].

Liou and Huang's technique of dental distraction was clinically validated by Sayin *et al* and their findings were published in 2004[46]. Their sample consisted of 43 canine teeth in 18 patients. The distractors were activated three times a day. The surgical procedure replicated that of Liou and Huang with the exception of the fixed appliance being placed after the distraction. The reasoning behind this protocol was that levelling could possibly trigger a lag period.

Sayin *et al* reported that the maxillary canines were distalised an average of 5.76 mm with 11.47° of distal tipping while the maxillary first molars moved mesially 0.56 mm and extruded 0.64 mm. In the mandible, the mean distal movement of the mandibular canines was 3.5 mm with 7.16°of distal tipping. Anchorage loss was not observed in the mandibular first molars. The authors concluded that the major advantages in dental distraction included the reduction of overall treatment time, which was on average three to four months, and eliminating the need for additional anchorage[46].

More recently, Allgayer *et al* published a case report entailing a 2-year follow up of a patient treated using the dental distraction technique[47]. Their pre-treatment, post-treatment, and 2-year follow-up records demonstrate that dental distraction is a viable treatment alternative. One major advantage of this procedure is that there are no additional surgical implications as the procedure is carried out at the same time as the extractions. In certain types of malocclusion requiring rapid movement of the canines with minimal or no anchorage loss, dental distraction is a technique which could be considered as an adjunct to conventional treatment. However, Liou and Huang highlighted that the long-term effects on root resorption, pulp vitality and possible ankylosis of the canine has not been properly investigated[45].

Corticotomy

Historical Background

Despite the recent resurgence in the topic, surgically facilitated orthodontic tooth movement is not a new concept in orthodontics. The term "surgically facilitated orthodontic tooth movement" encompasses a range of clinical techniques that exploit wound healing and the literature shows that the use of surgically facilitated OTM predates the twentieth century[48]. Predominantly, osteotomies were employed to facilitate OTM, whereby a surgical cut was

placed through the entire thickness of both buccal and lingual cortical plates in addition to the medullary bone thus creating segments of bone that could be mobilised. As large osteotomies were associated with complications such as necrosis of bone, loss of pulpal vitality and bony dehiscence at the surgical site, the procedure did not gain much support amongst the profession[49].

It was not until 1959 when Kole published his landmark paper titled "Surgical Operations on the Alveolar Ridge to Correct Occlusal Abnormalities", describing a procedure similar in nature to an osteotomy but less traumatic to the supporting structures of the dentition[50]. The objective of this new procedure, called "corticotomy", was to provide correction of malpositioned teeth which would normally require surgery or extended orthodontic treatment.

The surgical procedure as described by Kole was limited to the cortical bone only as this allowed the underlying medullary bone to maintain the blood supply to the dentition. A full thickness flap was raised buccally and lingually from the gingival margin to beyond the apex of the teeth. Interdental vertical cuts were made with a round bur and extended from the alveolar crest to 1cm below the apex of the teeth. These cuts were relatively shallow and barely penetrated the medullary bone. The vertical cuts were then joined to horizontal cuts which extended below the apex of the dentition and communicated bucco-lingually [50]. The proposed advantages of this new method in comparison to traditional osteotomies included preventing injury to the periodontium, minimising pocket formation and maintaining vitality to a single tooth or to a group of teeth.

Kole showed case reports highlighting the clinical application of corticomy assisted OTM on different types of malocclusions and on average the treatment duration was 6-12 weeks and the rate of tooth movement was estimated to be 0.5mm per day initially which later decreased to 0.25mm. At the time, the reduction in treatment time was attributed to the weakening of the cortical bone, which was believed to increase the resistance to OTM. Therefore, by weakening the structural integrity of the rigid cortical bone, the teeth could be used as an embedded handle which could be moved through the medullary bone. Kole believed that overall the corticotomy procedure allowed the movement of blocks of bone with the teeth rather than moving individual teeth through bone[50].

Unfortunately, contributions made by Kole and his seminal work detailing the procedure and its clinical advantages did not win enthusiasm throughout the dental community and the technique remained undeveloped. Davidovitch and Murphy believe this was due to the

"naivete of the early surgeons" and their concerns regarding bone necrosis and periodontal pocket formation[48]. It was not until 32 years after the initial publication of Kole's work that Suya revived academic interest in the topic by showcasing three hundred and ninety five of his treated cases[51].

The corticotomy procedure as described by Kole was modified by Suya and involved excluding the buccal and lingual sub-apical cuts. Furthermore, Suya proposed the vertical cuts should be initiated 2-3mm below the crest of the alveolar bone in order to maintain the vascular supply to the medullary bone. Suya's technique was only dependent on the vertical cuts but, nonetheless, dramatically reduced treatment time. It was reported that 69% of the time, comprehensive orthodontic treatment was completed within 127 days[51]. Suya specifically used the term "corticotomy-facilitated orthodontics" to describe his technique.

Suya's work promoted research from other groups in the nineties but a major resurgence did not take place until 2001 when the Wilcko brothers, one being a periodontist and the other an orthodontist, published two case reports outlining their method of corticotomy-facilitated orthodontics with the addition of periodontal regenerative surgery. Instead of Suya's "corticotomy-facilitated orthodontics", they named their procedure "accelerated osteogenic orthodontics" [52].

Accelerated Osteogenic Orthodontics/Wilckodontics

The terms accelerated osteogenic orthodontics (AOO) and periodontally accelerated osteogenic orthodontics (PAOO), are registered trademarks of Wilckodontics. PAOO is used when AOO patients present with periodontal defects such as fenestrations/dehiscences. The procedure was first published in the literature in 2001 in which two case reports were used to demonstrate the modified technique[52].

The technique followed that of Suya and involved the raising of a full thickness soft tissue flap followed by selective decortication both buccally and lingually. Vertical cuts stopping just short of the alveolar crest were made between the roots of the teeth and these vertical cuts were connected beyond the apices of the teeth with a scalloped horizontal cut as shown in Figure 5. Round perforations in the cortical bone were then made to enhance bleeding in the area and grafting material, which can be 100% demineralised freeze dried bone allograft (DFDBA), a mixture of DFDBA and bovine bone or a mixture of DFDBA and mineralised free dried bone allograft[53]. The authors suggested that bony fenestrations and dehiscences

could be treated with DFDBA in conjunction with clindamycin phosphate solution as it has demonstrated osteo-inductive properties[54].

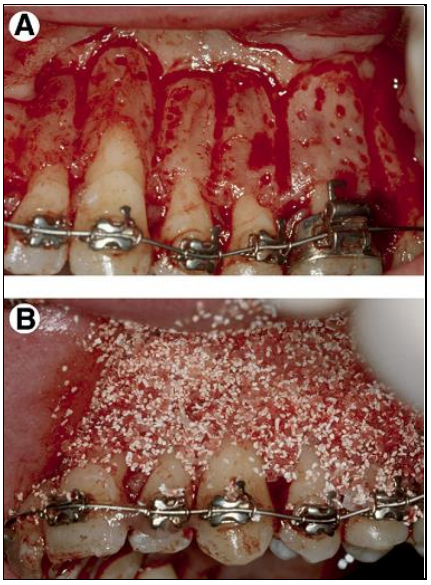

Figure 5: PAOO technique as described by Wilcko et al [53]

The first patient in the case report was a 24 year old male who presented with severe crowding, a constricted maxilla and a posterior crossbite on a Class I skeletal base. The authors believed that conventional treatment with the objective of correcting the posterior crossbite would have required orthognathic surgery with a total treatment duration of approximately 24 months. Following informed consent, the treatment plan involved orthodontic expansion of the arches to resolve the crowding as well as the constricted maxilla. The treatment duration was 6 months and 2 weeks, with 12 orthodontic adjustment appointments[52].

Similarly, the second patient described in the case report was of a 17-year old female with Class I crowding. Non extraction treatment was prescribed with expansion of the arches with periodontal grafting using PerioGlas. The patient required 11 orthodontic adjustments and the total treatment time was 6 months and 2 weeks[52].

Approximately 8.5 months after the removal of fixed appliances, the authors raised a full thickness flap on the first patient to assess the effects of the orthodontic expansion on bone. They reported that there was a substantial increase in the thickness of the buccal bone and good alveolar bone height. Some particles of bovine graft were not incorporated into the new layer of bone and were simply wiped off with a piece of gauze[52]. The authors did not

elaborate on whether this re-entry is necessary and the consequences of not removing the particles that did not incorporate into the existing bone.

In theory, the capacity to expand beyond the anatomical limits by using bone grating methods appeared feasible. Wilcko *et al* indicated that the ability to increase alveolar bone volume was apparent from a comparison of pre-treatment and post-treatment cone beam computed tomography (CBCT) images. For example, bone grafting in an area of dentoalveolar deficiency resulted in 2.4mm increase in alveolar bone width at B point and 3.5mm lingually and this is believed to increase post-treatment stability. So far, Wilcko *et al* have shown a CBCT scan after 2.5 years on one patient and the bone graft seems to be stable (Figure 6)[53].

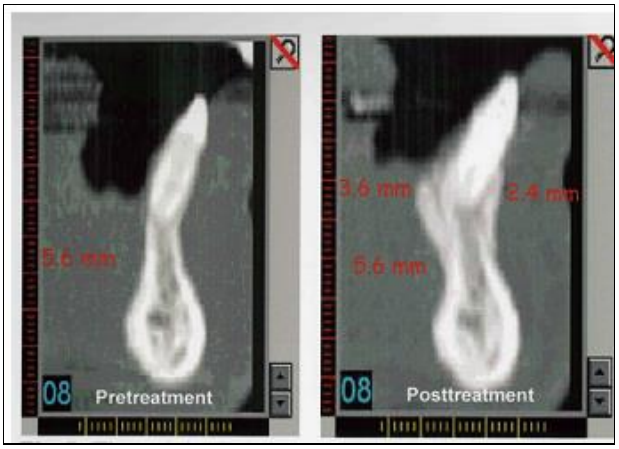

Figure 6: CBCT post grafting demonstrating 2.4mm of additional labial bone and 3.6mm of lingual bone at B point [53].

Despite promising case reports, long term results are required to demonstrate stability of the grafting material. Becker *et al* in their pilot study using 7 human subjects requiring implants after extraction of periodontally compromised teeth, demonstrated that commercially available DFDBA does not induce bone formation within a 3-13 month period and that the material is not osteo-inductive. They cautioned that the retention of bone chips may be detrimental to normal bone formation, taking years to be replaced and may even weaken the bone at the graft site. Conversely, sockets grafted with autologous bone chips healed uneventfully with vital bone[55].

Indications

Wilcko *et al* stated several advantages and indications to their technique:

- Increase in the limits of tooth movement and a decreased need for extractions
- Increased rate of tooth movement and, therefore, decreased treatment time

- Correction of pre-existing bony dehiscences and fenestrations
- Alveolar reshaping for the subtle enhancement of a patient's profile when indicated
- Simultaneous rapid recovery of shallow un-erupted teeth [53]

Such advantages provided an alternative solution for a population of patients who would have otherwise not pursued orthodontic treatment due to the duration of proposed therapy. However, it is unlikely for orthodontists and periodontists to embrace a relatively invasive procedure without long term follow up of treated patients. Although there may be a group of patients who might benefit and indeed be enthusiastic with the prospect of a shorter treatment time the proportion of the orthodontic and periodontic profession is willing to carry out this procedure is unknown. For the corticotomy procedure to be successful and evolve into a mainstream treatment option, it requires the multi-disciplinary expertise of at least two specialist groups.

Contra-indications and Side Effects

Patients who are taking medication that slow bone turnover such as bisphosphonates are not good candidates for the AOO procedure. Long term use of NSAIDS leads to decreased osteoclastic activity and, therefore, is also contraindicated. In terms of side effects, Anholm showed minor attachment loss in his patient treated with corticotomy-facilitated orthodontics[56]. However, Murphy believes this could have been attributed to a dehydrated flap[57].

The Wilcko brothers have trademarked their technique and now run courses for orthodontists on the surgical technique. They report there are minimal side effects associated with the procedure including:

- decreased root resorption
- no loss of vitality
- no loss of alveolar bone
- no periodontal pocket formation

The Wilckos explain that the regional acceleratory phenomenon, or "RAP", is the biological basis for the increased rate of tooth movement in the AAO technique. The decortication of alveolar bone results in an increase in regional bone turnover and remodelling which ultimately results in a transient osteopenia facilitating a greater rate of tooth movement[58].

Regional Acceleratory Phenomenon – RAP

Introduction

The term regional acceleratory phenomeonon, or RAP, was first described by Harold Frost, an orthopaedic surgeon and a renowned bone researcher. Frost had noticed during an autopsy of a patient that the resected sixth rib, which had undergone thoracotomy seven years earlier, demonstrated a higher bone turnover compared to the adjacent rib. He consistently noticed in his human subjects that injury to bone results in accelerated turnover and described this "complex reaction of mammalian tissues to diverse noxious stimuli" as regional acceleratory phenomenon[59].

RAP involves an anatomical region, encompassing skeletal and soft tissue components[59]. The reason behind RAP seems to be protective in which acceleration of vital processes reduces the time required for healing. More specifically, the speed of wound healing is increased above normal levels. The accelerated healing may involve one or more of:

- growth of skin, bone, cartilage and hair
- turnover of bone, cartilage, synovial fluid, connective/fibrous tissue
- chondral and bone modelling
- skin epithelialisation
- cicatrisation
- cellular metabolism [59]

With respect to bone, turnover increases and the affected region increases in temperature as is often the case in acute and chronic osteomyelitis or actively healing fractures. Imaging studies (X-ray and Photon absorption studies) show decreased regional bone density due to an increased remodelling space. As RAP describes the sequence of events that occur in tissues adjacent to the site of injury, orthodontic force application alone is believed to be sufficient to trigger a mild RAP phenomenon[59,60]. Combining an orthodontic force along with surgical insult would increase the effect of the RAP but to what extent, how long would it last and how far would the effect extend?

Duration of RAP

Frost states that in healthy humans, following a single stimulus such as a fracture, clinical evidence of RAP typically lasts approximately four months in bone and less in soft tissues. The severity of the stimulus also affects the duration with the RAP lasting longer following a more severe injury. As there is a finite time in which the RAP can be exploited, there has been some skepticism in exploiting the RAP phenomenon during orthodontic treatment. In response to this, transmucosal perforation after the initial corticotomy in order to perpetuate the RAP phenomenon has been proposed to increase the duration of RAP during OTM[57].

Specific to tooth movement, Sebaoun *et al* found that in rats, 3 weeks post corticotomy surgery represented the peak in both catabolic and anabolic activity[60]. This was demonstrated by osteoclast count and apposition width of fluorescent bone labels which were three-fold higher when compared to control groups. Baloul *et al* similarly demonstrated that enhanced OTM takes place during the initial tooth displacement phase in the rat model due to decreased bone volume - suggesting the early involvement of RAP. By twenty one days there was a decrease in activity of bone remodelling[11].

Bone Modelling and Remodelling

A good knowledge of the features of bone modelling is crucial in understanding the RAP phenomenon. Roberts defines bone modelling as a "mechanically mediated adaptive process for changing a bone's size, shape or position"[61]. Such changes occur along vascularized periosteal surfaces via uncoupled anabolic and catabolic events and this is what enables the tooth to move following the application of force. This is in contrast to remodelling, which is defined as continuous turnover of the alveolar process, encompassing bone maturation, skeletal maintenance and mineral metabolism. Essentially, both features contribute to OTM as well as the RAP phenomenon[61].

Bone remodelling is an essential component of the healing process and involves the removal and replacement of discrete, measureable packets of bone. In both cortical and trabecular bone, remodelling involves a coupled process of bone resorption and formation[62]. Inflammation up-regulates the recruitment of circulating osteoclast precursors and initiates vascular invasion. Cells derived from different sources co-ordinate these sequences of events and are referred to as the basic multicellular unit (BMU).

BMUs are responsible for the constant remodelling of bone by resorbing damaged bone to form a resorption cavity which is filled by new bone. In the literature, this process is often referred to as A→R→ F (activation, resorption, formation)[63]. Following activation by inflammatory mediators, resorption takes place by the removal of the non-mineralised layer by matrix metalloproteinases (MMPs) which are secreted by osteoblasts. This process exposes the mineral layer to osteoclasts for subsequent resorption[64]. Finally, formation of bone takes place by osteoblasts in the manner of a cutting/filling of a cone as demonstrated in Figure 7[65].

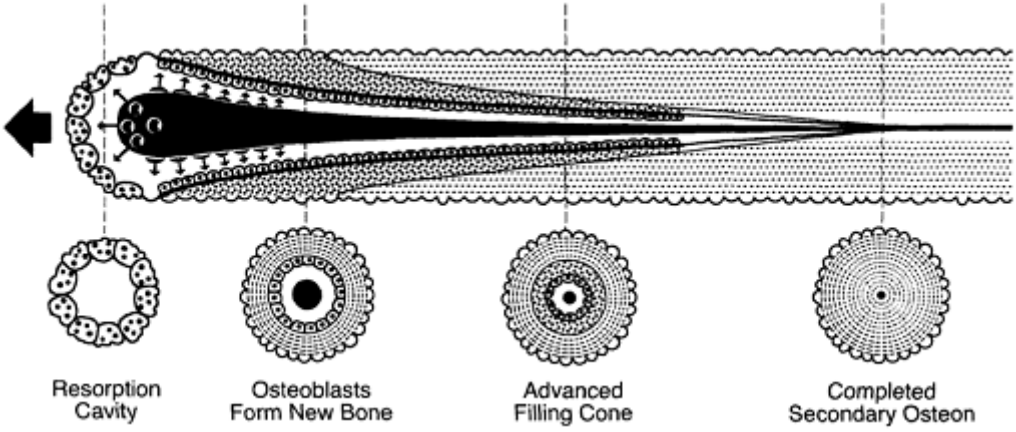

Figure 7: Evolving secondary osteon in the longitudinal dimension [65]

The mechanism behind the co-ordination of osteoblastic and osteoclastic cell activity is via the RANK/RANKL/OPG system. In bone, RANKL is expressed by cells of the osteoblast lineage and exerts its activity by binding to its receptor RANK which is present on osteoclastic precursor cells. The binding of the ligand to the receptor results in rapid differentiation and proliferation of hematopoietic osteoclast precursors to mature osteoclasts[66]. The regulation of osteoclast upregulation by RANK/RANKL is carried out by OPG – a decoy receptor produced by osteoblastic cells whose role is to compete with RANK for RANKL binding. The biologic effects of OPG can be summarised as the inhibition of terminal stages of osteoclast differentiation, suppression of activation of matrix osteoclasts and induction of apoptosis[65].

Under normal physiological conditions, bone resorption and formation occur concurrently by the RANK/RANKL/OPG system. However, during RAP, bone formation cannot keep pace with bone resorption and the net result is bone loss. By exploiting the transient osteopenia,

orthodontic tooth movement can be accelerated and this is the biological basis of corticotomy-facilitated OTM.

Corticotomy-facilitated OTM - Case Reports

At present, literature on corticotomy-facilitated OTM abounds with case reports. Although at the low end of hierarchy of evidence, case reports demonstrate the possible application of a technique and should not to be simply dismissed. A summary of possible applications of corticotmy facilitated OTM in clinical practice is presented in this section.

Intrusion

The intrusion of an over-erupted molar tooth due to the loss of an antagonist is frequently requested by restorative dentists. Grinding the over-erupted tooth may be an option but if the extrusion is extensive, elective endodontic treatment may be required. In such circumstances, pre-prosthetic orthodontic treatment may provide a more conservative option. Traditionally, the use of conventional orthodontic mechanics to intrude the over-erupted tooth may lead to undesirable extrusion of the neighbouring teeth. Furthermore, in adult patients, the treatment time may be prolonged due to the lack of growth, decreased blood supply and smaller marrow spaces when compared to growing patients[67].

The use of corticotomy as an adjunct in the intrusion of an over-erupted molar has been highlighted by different authors. Hwang *et al* demonstrated that molars could be intruded efficiently and with few side effects using corticotomy and magnets[68]. The procedure was performed on a 21 year old female patient who was referred by her general dentist for pre-prosthetic orthodontic treatment due to an over-erupted tooth 16 due to the extraction of the antagonist tooth. The procedure was performed under local anaesthesia as well as intravenous sedation.

Mucogingival flaps were elevated on the buccal and palatal aspect and a fissure bur was used with saline irrigation to place the vertical cuts which started 2mm below the alveolar crest and extended 2 mm beyond the apex(Figure 8). The cuts were limited to the cortical bone, barely reaching the medullary bone. A horizontal cut connected the 2 corresponding vertical cuts and this procedure was repeated on the lingual aspect. The authors highlighted that the resection was 3-4mm wide in order to facilitate the intrusion. The soft tissue flaps were sutured in their original position and a periodontal dressing was placed.

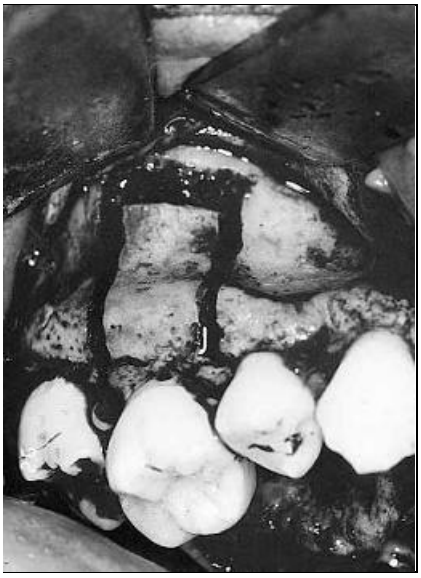

Figure 8: Hwang's Corticotomy for Intrusion [68]

The tooth that required the intrusion (the upper right first molar) was fitted with a band with magnets soldered on the buccal and lingual aspects. A removable appliance was then worn in the lower arch with magnets attached to cantilever springs which would sustain contact with magnets on the opposite arch without continual adjustment by the clinician. The removable appliance was inserted one week after the corticotomy procedure and force application with the removable appliance was initiated. The patient was instructed to wear the removable appliance full time except during meals and oral hygiene. It was reported that one month after the application of the magnetic force, the maxillary first molar was intruded(Figure 9)[68].

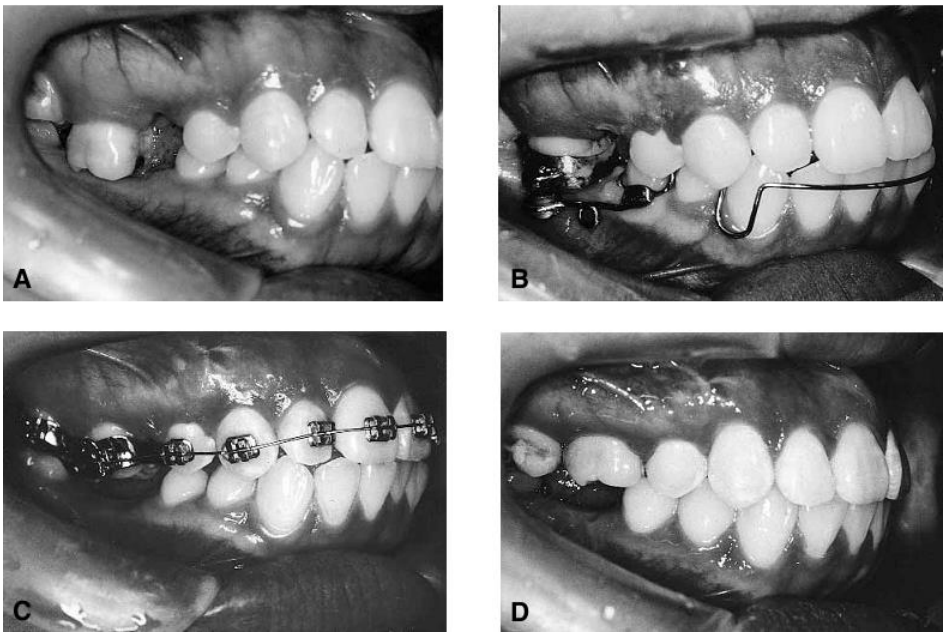

Figure 9: Intrusion of tooth 16 by corticotomy and magnetic appliance [68]

Instead of a magnetic device, Moon and co-workers employed skeletal anchorage in the form of mini-plates and mini-screws to intrude the upper first and second molars. The case report described the over-eruption of 26 and 27 in a twenty six year old female patient who required pre-prosthetic orthodontic treatment. The surgical procedure for the corticotomy was similar to that described by previous authors. At the time of the corticotomy, an L-shaped miniplate was fixed in the buccal vestibule using two bone screws (Figure 10). Two weeks later, a separate procedure was undertaken in which two miniscrews were implanted in the mid-palatal area. An impression of the palate was taken in order to fabricate a customised hook which allowed an ideal vector for the intrusion the 26 and 27. This hook was attached to the miniscrews using a metal primer, bonding agent and resin after sandblasting. Force application was initiated immediately[69].

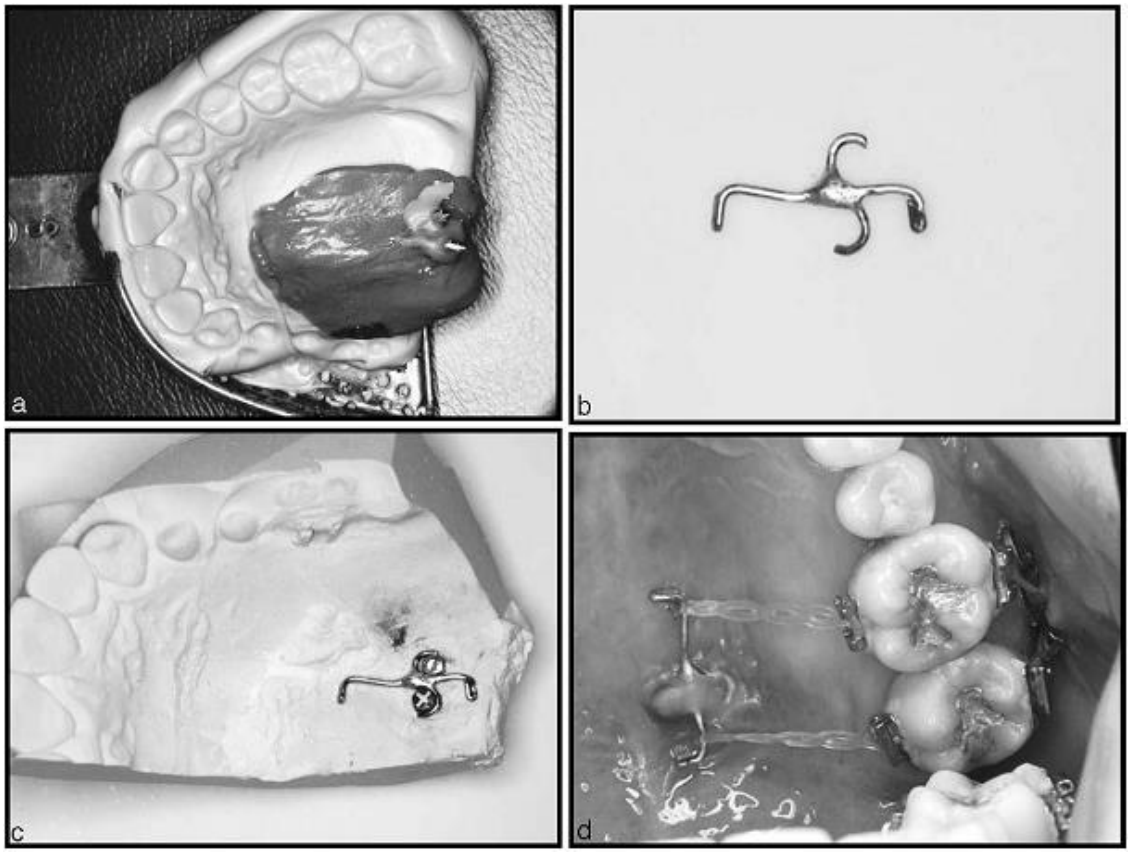

Figure 10:Custom made hook and TAD used in conjunction with corticotomy to intrude 26 and 27 [69]

The authors reported that after a month of force application, a satisfactory amount of intrusion had taken place with the mesial marginal ridge of the first molar level with the distal marginal ridge of the second premolar. However, intrusion was continued for another month

in order to establish the curve of Spee. Cephalometric superimposition after treatment showed that the 26 had intruded approximately 3.5mm and the post-treatment radiograph (OPG) demonstrated that the teeth were intruded without root resorption[69]. The authors did not comment on whether there was any movement of the anchorage units – especially the mini-screws in the palate. A study designed to show the movement of miniscrews under the effects of corticotomy would discern the compatibility of the two procedures. A map to guide the extent of the RAP with reference to the local structures would enable the clinician to employ a miniscrew but do so without risk of significant loss in anchorage.

Impacted Canines

Case reports in the literature have demonstrated the use of corticotomy-facilitated orthodontics in the treatment of impacted canines. Authors have reported a reduction in treatment time due to the RAP phenomenon[70-72]. On average, treatment involving an impacted canine is 26.31 months and thus decreasing time where impacted canines are present would confer advantages for patients and clinicians[73].

Fischer used a split mouth design to evaluate the effectiveness of corticotomy in the treatment of palatally impacted canines[74]. It was a preliminary study with a small sample consisting of six patients with bilateral palatally impacted canines. The sample consisted of four girls and two boys, all of Caucasian descent with an age range of 11.1 to 12.9 years and all patients underwent non-extraction orthodontic treatment. By random selection, one canine had an additional procedure of corticotomy which consisted of a series of circular holes made along the mesial and distal aspect of the tooth (Figure 11). This procedure was carried out by the oral surgeon and the orthodontist had no knowledge of which canine had undergone the corticotomy procedure[74].

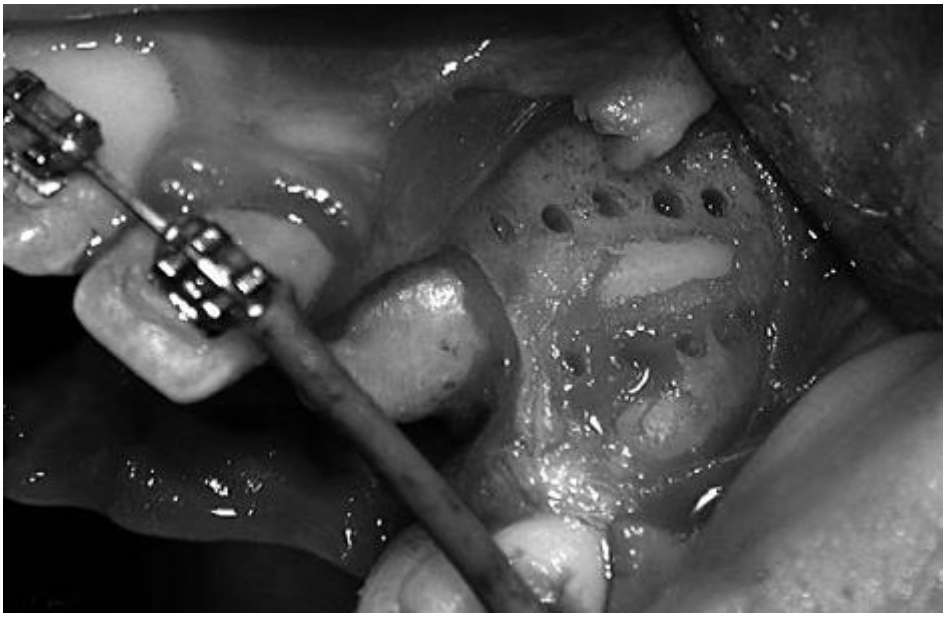

Figure 11: Corticotomy cuts [74]

Orthodontic force application was applied using 60g of force and patients were seen at 4 to 6 week intervals which reduced to two weeks when the author subjectively decided that the canine was close to its proper position. Patients were seen until both canines were brought into the arch and at that point, the two canines were compared in terms of the duration. Fischer reported that in all six patients, treatment time was reduced for the corticotomy group and this reduction was quantified in the range between 28% to 33%. Additionally, the velocity of each canine was calculated and all corticotomy-facilitated canines had significantly greater tooth movement velocity when compared with the contralateral side[74].

Despite the small sample, the results are encouraging and thought provoking as during the exposure of a canine, adding the corticotomy component does not increase the discomfort for the patient in any way. In addition, Fischer noted that periodontal probing and the alveolar bone level (as examined on peri-apical X-rays) did not differ between the two groups. As Fischer points out in his paper, further studies with larger sample sizes would be indicated to increase the power of the statistical results[74].

Ankylosed Teeth

Ankylosis is defined as the fusion of a proportion of the root surface with the surrounding alveolar process due to localised periodontal ligament damage. Local trauma to the permanent maxillary incisors often results in ankylosis and is detected clinically by the

typical metallic sound, limited mobility, radiographic loss of periodontal ligament space and dental infra-occlusion. Although helpful, only a third of patients exhibit a metallic sound and only a third of patients demonstrate radiographic loss of the periodontal ligament space, the definitive diagnosis is derived from tooth immobility under an applied orthodontic force. An ankylosed tooth in growing patients poses a problem as it fails to erupt along with the remaining vertical growth of the alveolar process[75-77].

Hwang and colleagues used an isolated corticotomy procedure on an ankylosed central incisor and demonstrated how corticotomy-facilitated orthodontic treatment can be employed on an ankylosed tooth to bring the affected tooth to the level of the occlusal plane[78]. Initially, an orthodontic force was applied to the suspected tooth for 3 months at which time the tooth's immobility confirmed the diagnosis of ankylosis. The treatment plan was also complicated by the fact that the patient had an open bite on a Class II skeletal pattern with a hyperdivergent growth tendency.

The authors highlighted that several surgical treatment protocols apart from corticotomy were considered in treatment planning and they included:

- Single tooth osteotomy
- Surgical luxation
- Distraction osteogenesis

Single tooth osteotomy in the maxilla could have been feasible for the rapid movement of the tooth due to favourable vascularity. However, if the amount of movement of the bony block is large, the stretching of the soft tissues may result in dehiscence. Surgical luxation involves breaking the fusion between the cementum and bone but carries with it the risks of root fracture and loss of vitality of the tooth. For the above reasons, the authors chose corticotomy as their preferred method to bring the ankylosed tooth into alignment (Figure 12).

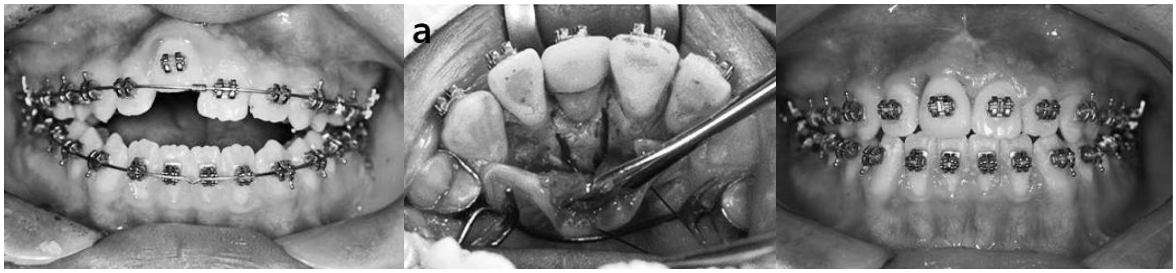

Figure 12: Ankylosed 11, corticotomy surgery and final result [78]

Corticotomy-facilitated Orthodontics - Animal Studies

Expert opinion and case reports have dominated the subject of corticotomy-facilitated orthodontics rather than scientific evidence. Wilcko *et al* speculated that the increase in OTM may be due to a demineralisation-remineralisation process, namely the RAP phenomenon. Previously, the increase in OTM was thought to be due to the bony block movement in which the teeth acted as handles. This apparent lack of scientific validation has led to several research groups seeking to elucidate the biological mechanisms underlying corticotomy-facilitated OTM.

Sebaoun *et al* investigated the alveolar response to corticotomy as a function of time and proximity to the surgical site of injury using histology[60]. Their study design consisted of 18 rats divided into three groups of six based on 3,7 or 11 week time points. Transverse sections capturing the first, second and third molar roots were utilised at three levels of the root (coronal, mid and apical) and these were stained with haematoxylin and eosin (H&E). Tartrate-resistant acid phosphatase (TRAP) staining was employed to identify and quantify the number of osteoclasts using a standardized grid at the first molar. Catabolic activity, as measured by the number of TRAP positive cells, was found to be significantly increased in the surgery group compared with the controls[60].

The anabolic response to corticotomy was evaluated using fluorescent bone labels which measured the bone apposition rate adjacent to each first molar root. At the three week time point, the percentage of new bone apposition in the first molar area was significantly greater in the corticotomy group compared with the control group. The authors concluded that the peak in both catabolic activity and anabolic activity was observed at 3 weeks and it was three-fold higher in the experimental group. Furthermore, the changes in bone metabolism

pertained to the vicinity of the injury and by week 11, the effects dissipated suggesting that the role of RAP is transient.

Sebaoun's study was instrumental in elucidating the mechanisms by which corticotomy enhances OTM. However, as the study excluded tooth movement for the purpose of clarifying the dynamics of the periodontium change as a consequence of corticotomy, clinical extrapolation is limited. Baloul *et al* in 2011 used radiographic, tomographic and molecular methods to further investigate the biological mechanisms behind corticotomy enhanced OTM[11].

Baloul's study used 114 Sprague-Dawley rats which were divided into three treatment groups; selective alveolar decortication (SADC), tooth movement alone (TM) and combined therapy of SADC and TM. The tooth movement was performed on the first molar using a 25g Sentalloy spring which provided a mesial movement for the maxillary first molar. The surgery consisted of raising a buccal and palatal flap with and creating decortication marks with a small ¼ round bur.

The study design consisted of using half of the animals for MicroCT and Faxitron analyses and the remaining half for molecular biology studies consisting of RNA isolation and real time PCR. The animals were sacrificed along a time line of 3, 7, 14, 21, 28 and 42 days of active OTM(Figure 13).

Table I. Study design*

Time (Days)	*Subgroup*	*Faxitron, Micro-CT*	*Molecular markers (RNA)*
0	Baseline controls	3	3
3	SADc	3	3
	TM	3	3
	SADc + TM	3	3
7	SADc	3	3
	TM	3	3
	SADc + TM	3	3
14	SADc	3	3
	TM	3	3
	SADc + TM	3	3
21	SADc	3	3
	TM	3	3
	SADc + TM	3	3
28	SADc	3	3
	TM	3	3
	SADc + TM	3	3
42	SADc	3	3
	TM	3	3
	SADc + TM	3	3
		57	57
Total		114	

Figure 13: Study Design and animal numbers in each group [11]

The magnitude and rate of OTM was assessed by Faxitron analysis. At seven days, the amount of tooth movement was higher in the SADC+TM group compared with the TM group. However, between 28 and 42 days, there was a similar amount of tooth displacement between the SADC+TM group suggesting that the effects of RAP which was responsible for the initial acceleration, dissipated by 28 days.

Structural changes in the alveolar bone were assessed using Micro-CT imaging. Three measurements were made, including:

- Total Volume (TV): The volume of tissue enclosed by the region of interest
- Bone Volume (BV): The volume of the voxels that were above the threshold (8192) and, therefore, considered to be bone
- Bone volume fraction (BV/TV): The ratio of bone volume to total volume which describes the proportion of volume that is bone

An analysis of the BV demonstrated that the SADC+TM group showed the most significant decrease in 7 days and the lowest at 14 which suggested that the remodelling phase in this

group took place earlier. In contrast, the TM group also demonstrated a significant decrease in bone volume but this took place a week after the SADC+TM group at 21 days.

Correspondingly, initial tooth movement took place by 14 days in the TM group and there was decreased movement over the next 7 days whereas SADC+TM group showed continuity of the tooth movement over the 14 days suggesting that the lag phase of traditional tooth movement did not take place. Therefore, it can be extrapolated that SADC bypasses the lag phase and initiates OTM earlier. In spite of early decrease in BV and bypassing the lag phase of OTM bone homeostasis remained the same and bone density, mass and volume were all restored to baseline levels.

Molecular analyses further confirmed the observation found with MicroCT analyses. The expression of macrophage-colony stimulating factor (M-CSF) stimulated osteoclast proliferation and differentiation was increased in the SADC+TM group at 3 days and 14 days, demonstrating an early increase in osteoclast proliferation and differentiation compared with the TM only group.

Similarly, RANKL and OPG were also measured as they regulate osteoclast differentiation and survival. RANKL expression increased in the TM group at 14 days and declined from that point onwards whereas the SADC+TM group exhibited a steady increase during 14-21 days suggesting a sustained expression.

The tooth movement in Baloul's study consisted of mesial movement of the maxillary first molar. Clinically, this would represent the movement of teeth for closure of space. Although corticotomy could be employed in extraction cases, the surgical nature of the extraction may provide a RAP effect without the additional procedure and other methods as periodontal distraction described by Liou *et al* may be more applicable in such situations. Case reports by Wilcko *et al* are predominantly non-extraction in which the arches are expanded.

Current knowledge indicates that there are no studies which have evaluated the biological mechanisms when the tooth is moved buccally using double flurochrome bone labelling. Using a dynamic method of quantification which is time dependent will enable the elucidation of the mechanism behind corticotomy-facilitated orthodontics in another dimension previously unchartered.

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6. STATEMENT OF PURPOSE

Despite long standing history in the dental literature, corticotomy has not been readily utilised. The first article will examine the thoughts and attitudes of orthodontists and periodontists in Australia and New-Zealand to corticotomy-facilitated orthodontic tooth movement (OTM). Comparisons will be made of the two specialities with regards their knowledge on the procedure, their opinions regarding the use of corticotomy-facilitated OTM in practice and reasons for or against the utilisation.

The focus of the second article is on the biological basis of corticotomy-facilitated OTM. Double fluorescent bone labelling, which enables a dynamic method of quantifying bone remodelling will be employed to investigate the effects of corticotomy surgery on the buccal alveolar bone. In particular, whether the raising of the mucoperiosteal flap alone can upregulate the regional acceleratory phenomenon to the same level as corticotomy will be investigated as some contend that if bone remodelling could be up-regulated without insult to the bone, it would be a preferred method for accelerating tooth movement.

7. RATIONALE OF THE CURRENT STUDY

Article 1: Accelerating orthodontic tooth movement with the aid of periodontal surgery – what the practitioners are thinking.

Research Questions

There is growing interest amongst the orthodontic community in methods to reduce overall treatment time. Currently, there are two main methods to accelerate OTM; these are classified as non-surgical and surgical. This study will focus on a surgical method known as corticotomy-facilitated OTM, which utilises injury to the bone or soft tissues to promote a regional acceleratory phenomenon that up-regulates the healing process.

Research demonstrating the biological basis for corticotomy-facilitated OTM is increasing. However a significant barrier that restricts application to this procedure is the interdisciplinary nature, requiring the combined expertise of both orthodontists and periodontists. To this end, a number of questions were put forward to practitioners to better understand the general awareness of the specialist communities to corticotomy-facilitated OTM, and possible barriers to increased consideration of the procedure. Questions included:

- Have you heard about corticotomy-facilitated orthodontic tooth movement or periodontally accelerated osteogenic orthodontics or Wilckodontics^{TM}?
- Where did you first hear about the procedure?
- For what reasons would you decide against undertaking the corticotomy procedure?
- What would make you feel more open to undertaking this procedure?
- Have you undertaken the treatment and if so how many cases in *total (per year)* have you undertaken?

The questionnaire highlights the similarities and differences in the awareness, knowledge, experience and desire for corticotomy-facilitated orthodontics between the two specialist groups in Australia and New Zealand. This in turn may lead to recommendations that may facilitate provision of this procedure in clinical practice to a select group of patients.

Aims/Objectives of the project

The aims of this study were to evaluate the similarities and differences in the knowledge, awareness, experience and desire to consider application of corticotomy-facilitated orthodontics between orthodontists and periodontists. By determining the differences in the attitudes, recommendations can be made regarding communication between the two specialist groups, continuing education and whether this procedure should be offered as a treatment option in a select group of patients.

Hypotheses

The null hypotheses to be investigated are as follows:

- There is no difference between orthodontists and periodontists with regard to their knowledge or awareness of corticotomy-facilitated orthodontics.
- Both groups of specialists currently do not recommend the procedure to their patients.
- Both groups of specialists do not believe more research is required before recommending the procedure to their patients.
- Both groups of specialists do not believe there are side effects associated with the procedure.

Article 2: Dynamic response of the alveolar bone to corticotomy-facilitated orthodontic tooth movement.

Research Questions

The current evidence behind corticotomy-facilitated OTM is predominantly composed of case reports. Although they have low hierarchy of evidence, case reports have a place in identifying unexpected outcomes and can often be the first step in prompting more research into a topic. After reviewing the literature, it was apparent that scientific articles that evaluate the biological basis of corticotomy-facilitated OTM are currently limited.

Of the studies that investigated corticotomy-facilitated OTM, all the surveyed literature only focused on quantifying the static effects of the corticotomy surgery. Furthermore, these studies use a mesially-directed force to the upper first molar, which may be applicable to the closing of an extraction space, does not represent the clinical scenario of expansion-based, non-extraction treatment plans.

For these reasons, the second study addressed the following research questions:

- What changes take place in the buccal alveolar bone when the tooth is moved buccally instead of in a mesial direction in the rat model?
- Could a mucoperiosteal flap be raised in order to increase the bone turnover without injuring the cortical bone?
- How does OTM change the dynamics of the bone response?

Aims/Objectives of the project

The aims of this study were to investigate the dynamic response of the buccal alveolar bone in response to raising a flap and applying the corticotomy procedure with and without OTM using fluorescent bone labels.

Hypotheses

The null hypotheses to be investigated are as follows:

- There is no difference in the mineral apposition rate (MAR) between the groups when subjected to a flap or corticotomy alone.
- There is no difference in the MAR between the groups when subjected to **OTM** in conjunction with a flap or corticotomy procedure.

Significance/contribution to the discipline

Patients frequently ask orthodontists when their treatment will be completed. Duration of treatment may be especially important for adult patients who see fixed appliances as a barrier to social interactions. Furthermore, increased time in fixed appliances has been associated with detrimental side effects such as white spot lesions and root resorption. Therefore, methods to reduce the duration are becoming increasingly attractive as an adjunct in a select group of adult patients.

Despite the topic prevailing in the orthodontic literature since 1959, the profession has been seemingly reluctant to adopt corticotomy-facilitated OTM, with the specific reasons for this reluctance currently not known. In addition, an interdisciplinary treatment approach is essential for the procedure to be offered and at present, the proportion of orthodontists and periodontists who know about the procedure or who are willing to recommend the procedure is unknown. It is inevitable that with the information that is now readily available on the

internet, prospective patients may request the corticotomy procedure in the future. Consequently, education and communication between the two specialist groups is prudent so that recommendations are based on sound, evidence-based dentistry. The questionnaire will highlight any discrepancies in the opinions and attitudes of the two groups, and recommendations will be offered in light of the results.

Case reports describing corticotomy-facilitated orthodontics show that the procedure is three to four times quicker than conventional orthodontic treatment. In the hierarchy of evidence, case reports rate just above ideas and opinions; therefore, it is imperative that the biological mechanism is better understood prior to recommending this procedure to adult patients on a routine basis.

Current understanding of the acceleration in OTM is believed to be due to the coupling of demineralisation/remineralisation in the early stages of tooth movement but this knowledge is limited for two primary reasons. Firstly, the tooth movement that has been investigated is usually the mesial movement of the upper first molar of the rat. The case reports demonstrating accelerated OTM are primarily based on non-extraction therapy with expansion of the dental arches to accommodate the teeth. Therefore, the current animal experiments do not convey what is being done clinically as reported in the case reports. Secondly, previous studies on this topic have predominantly employed static methods, and a dynamic method that quantifies bone remodelling at two different time points has not yet been utilised. Simulating tooth movement in the direction of that involved in clinical case reports in conjunction with using a dynamic quantification of bone turnover will provide a new dimension in the understanding of corticotomy-facilitated OTM.

8. ARTICLE 1

Accelerating orthodontic tooth movement with the aid of periodontal surgery – what the practitioners are thinking

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Introduction: There has been a revival of interest in accelerating orthodontic tooth movement (OTM) by inducing injury to the cortical bone. Coined the term corticotomy, the procedure offers advantage to adult patients whose bone metabolism can result in extended treatment time. While the procedure may at first seem radical and invasive, it has been refined for over 100 years often reducing the length of treatment often by as much as a third. For the procedure to be successful, careful interdisciplinary management by orthodontists and periodontists is required. However, little is known about knowledge of or attitudes toward the procedure in either Australia or New-Zealand, or how often it is used.

Methods: A questionnaire was formulated and tested in a pilot on post graduate orthodontic and periodontic students at The University of Adelaide. As a consequence of the responses, the wording was clarified and sequence of questions modified to produce the final form. Two questionnaires were developed for specialist orthodontists and periodontists to reflect the different emphases and were distributed at two separate conferences.

Results and Conclusions: The proportion of practitioners who had undertaken at least a case per annum involving corticotomy was low with few orthodontists (11.5%) and periodontists (18.18%) reporting experience with the procedure. The majority of orthodontists and periodontists surveyed believed that more research is required on the topic of corticotomy-facilitated OTM, and would not recommend the procedure to patients without subjecting the technique to greater scrutiny. More than half of the sampled orthodontists indicated that they would never recommend corticotomy-facilitated orthodontics to their patients. The minority who were willing to recommend the procedure would limit it to adult patients, ankylosed teeth, impacted canines and patients susceptible to root resorption. Over 90% of sampled periodontists believe that there are side effects associated with the corticotomy procedure.

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Introduction

There is growing interest in accelerating the biological mechanisms behind orthodontic tooth movement (OTM) so that treatment time may be reduced, particularly for adult patients whose orthodontic appliances may become a barrier for social interactions. Upregulating bone turnover through selective surgery to enhance OTM is not a new idea and involve a spectrum from osteotomy whereby the surgical cut is made through both the cortical and medullary bone being the most invasive to corticision whereby a scalpel is used interproximally to injure the cortical bone without raising a flap[1].

As an osteomy induce considerable bone trauma, surgeons have investigated less invasive interventions. In 1959, Köle published a landmark paper titled 'Surgical operations on the alveolar ridge to correct occlusal abnormalities', describing a procedure similar to an osteotomy but less traumatic to the supporting structures of the dentition[2]. The objective of this new procedure, coined 'corticotomy', was to provide rapid movement of teeth by weakening the cortical bone.

Despite studies detailing the less invasive procedure, the dental community did not warm to its use. Davidovitch and Murphy believe this was due to the 'naiveté of the early surgeons' who feared bone necrosis and periodontal pocket formation[3]. It was 32 years after the initial publication of Kole's work that Suya finally revived academic interest in the topic by showcasing 395 cases in which he had used corticotomy-facilitated orthodontics[4].

More recently, the Wilcko brothers – a periodontist and an orthodontist – published two case reports outlining their method of corticotomy-facilitated orthodontics with the addition of periodontal regenerative surgery[5]. Their patented technique, referred to as Accelerated Osteogenic Orthodontics (AOO) or Periodontally Accelerated Osteogenic Orthodontics (PAOO) involves raising a full thickness soft tissue flap followed by selective decortication buccally and lingually. Vertical cuts are also made between the roots of the teeth just short of the alveolar crest and are connected beyond the apices of the teeth with a scalloped horizontal cut. Round perforations in the cortical bone are then made to enhance bleeding in the area, and grafting material is employed where there are bony fenestrations and dehiscence[6].

Similar to orthognathic surgery, a well co-ordinated interdisciplinary approach between orthodontists and periodontists is necessary for the procedure of corticotomy-facilitated

orthodontics to be successful. Yet, even with growing evidence in the literature which demonstrates the increased rate of tooth movement during the initial tooth displacement phase and its potential usage in selected cases such as impacted canines and ankylosis, enthusiasm for the procedure remains muted, and it is unclear why orthodontists and periodontists aren't more interested.

Corticotomy, along with other methods that are capable of accelerating orthodontic tooth movement, appear to become an inevitable aspect of care for adult patients. However, it is currently unclear who and how many orthodontists and periodontists are aware of and would support its practice. The current study sought to determine the proportion of orthodontists and periodontists practising corticotomy as an adjunct to other techniques that promote tooth movement. Reasons preventing the adoption of corticotomy were evaluated and the results are offered as a stepping stone for discussion, communication and education among orthodontists and periodontists. Particular interest was paid to the level of interdisciplinary cooperation between periodontists and orthodontists since significant teamwork is required between these two groups of specialists in order to use this procedure successfully, and lack of collaboration is clearly a barrier to its uptake.

Methods

The questionnaire was formulated from a pilot study conducted on post-graduate orthodontic and periodontic students at The University of Adelaide. The pilot study allowed the refinement of questions and the sequence in which they were asked to minimise ambiguity and optimise clarity. Expert opinion on questionnaire design was sought from the Australian Research Centre for Population Oral Health (ARCPOH).

Two separate questionnaires were developed, one for specialist periodontists and another for orthodontists (and the postgraduates in training of the respective specialties) and distributed on two separate occasions. The questionnaire was anonymous but respondents were asked for their year of graduation or prospective year of graduation as a specialist, the University where specialist qualification was or is to be attained, whether they were actively involved in teaching or research, and finally their city and state of main practice. Participation was voluntary and no financial incentives were provided.

The periodontal questionnaire was distributed by the primary investigator at the Australian and New-Zealand Academy of Periodontists' 16th scientific conference from 6-9th of March

2013. Similarly the orthodontic questionnaire was distributed by the principal investigator at the Australian Society of Orthodontist's Foundation Meeting which was from 15-17th of March 2013. The questionnaires were distributed at the beginning of a session and collected at the end of the session.

Questions common to both groups included:

- *Have you heard about corticotomy-facilitated OTM or periodontally accelerated osteogenic orthodontics or Wilckodontics ™?*
- *Where did you first hear about the procedure?*
- *For what reasons would you decide against undertaking the corticotomy procedure?*
- *What would make you feel more open to undertaking this procedure?*
- *Have you undertaken the treatment and if so how many cases in total have you undertaken?*

Questions specific to orthodontists included:

- *Would you recommend this procedure to any of your patients?*
- *If you were to recommend the procedure to patients, to what type of cases would you limit the corticotomy procedure?*
- *How important do you believe the reduction in treatment time is for patients?*
- *Are you using any other method to reduce the treatment time for your patients and if so please state the methods.*

Questions specific to periodontists included:

- *If an orthodontist colleague referred you a patient for the procedure described above, how comfortable would you feel about carrying out the procedure? (please mark on the scale below)*
- *As a periodontist, do you believe that there are side effects to this procedure?*

The principal investigator coded the questionnaires and the data were transferred manually into a spreadsheet. The correctness of the data was verified by a second person. Statistical analysis was performed using Microsoft Excel.

Results

Out of the 257 registered orthodontists who registered at the Australian Society of Orthodontists' Foundation Meeting, 114 responded (44.4%). Of the 138 periodontists surveyed at the Australian and New-Zealand Academy of Periodontists' conference, 77 (55.8%) responded. The response rate was calculated on the number of practitioners registered at the conference and not specific to those present at the session. Results have been

organised according to (1) questions common to both groups; (2) questions specific to orthodontists; and (3) questions specific to periodontists.

Questions common to both groups:

As shown in Figure 1, a greater proportion of orthodontists (95.6%) had heard of the corticotomy procedure when compared with periodontists (67.5%) and this difference was statistically significant ($p < 0.0001$). If post-graduate students were excluded from the count, more periodontists (67.9%) were aware of the corticotomy procedure compared to orthodontists (41.9%). Amongst those who had heard about the procedure, there was no difference between orthodontists and periodontists in the distribution of where they had heard about the procedure. Approximately of half of orthodontists (49.1%) had first heard of corticotomy at a conference, followed by journal articles (24.1%) (Figure 2). Similarly, a large majority of periodontists (44.2%) first heard of corticotomy at a conference followed by colleagues (32.7%). No orthodontists or periodontists had first heard of the corticotomy procedure through a patient.

A large proportion of orthodontists (73.5%) deemed the corticotomy procedure as being too invasive, whereas periodontists (76.6%) would not recommend the procedure on the basis that they didn't know enough (Figure 3). The majority of orthodontists (61.1%) and periodontists (70.1%) believed further research on corticotomy-facilitated OTM was the most important reason for them to feel more comfortable in making a recommendation to patients (Figure 4). Only a small proportion of orthodontists (11.5%) and periodontists (18.2%) had experience with the corticotomy procedure on a per annum basis (Figure 5). The practitioners that had experience with corticotomy came from ACT, NSW, QLD, SA and VIC. These results demonstrated that corticotomy was being utilised by a small minority of practitioners due to perceived invasiveness of the procedure and limited knowledge.

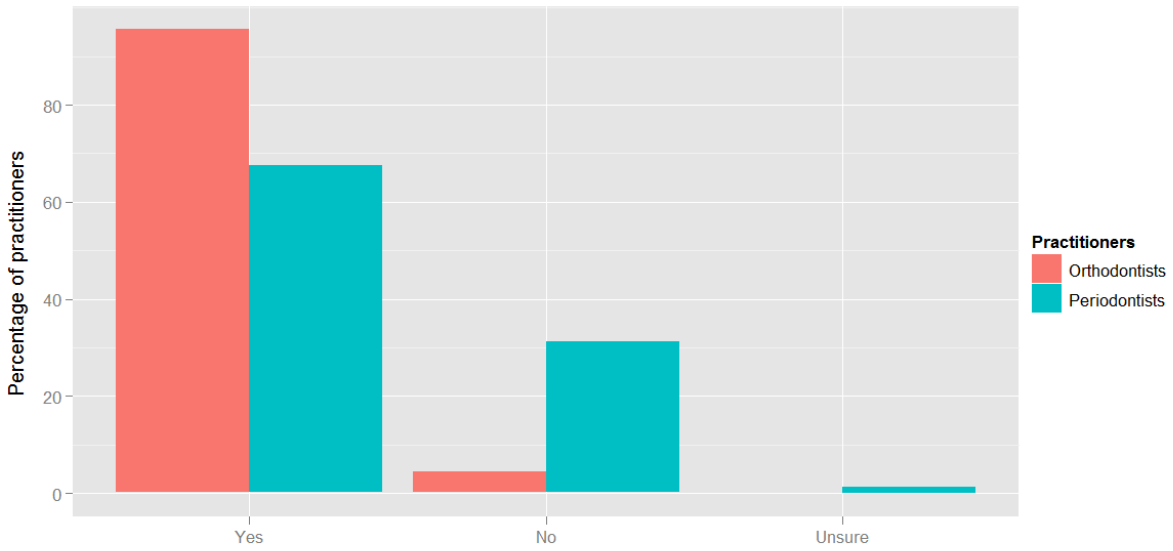

Figure 1: Have you heard about this procedure?

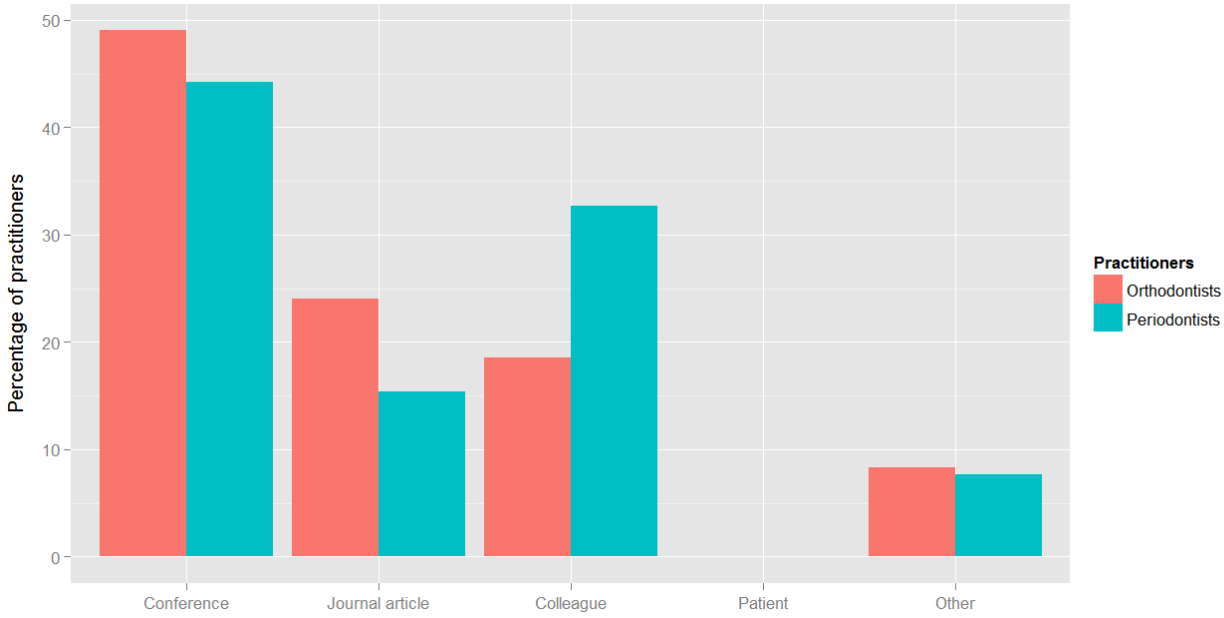

Figure 2: Where did you first hear about the procedure?

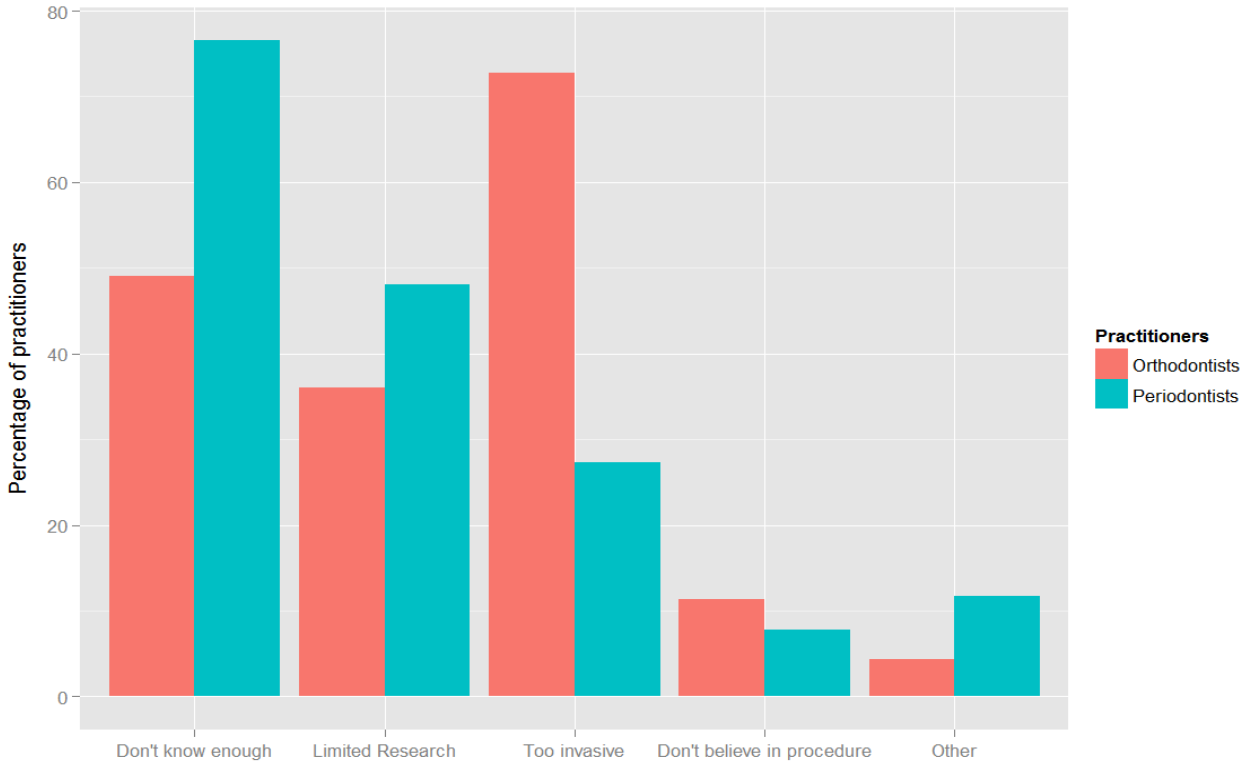

Figure 3: For what reasons would you decide against recommending the corticotomy procedure?

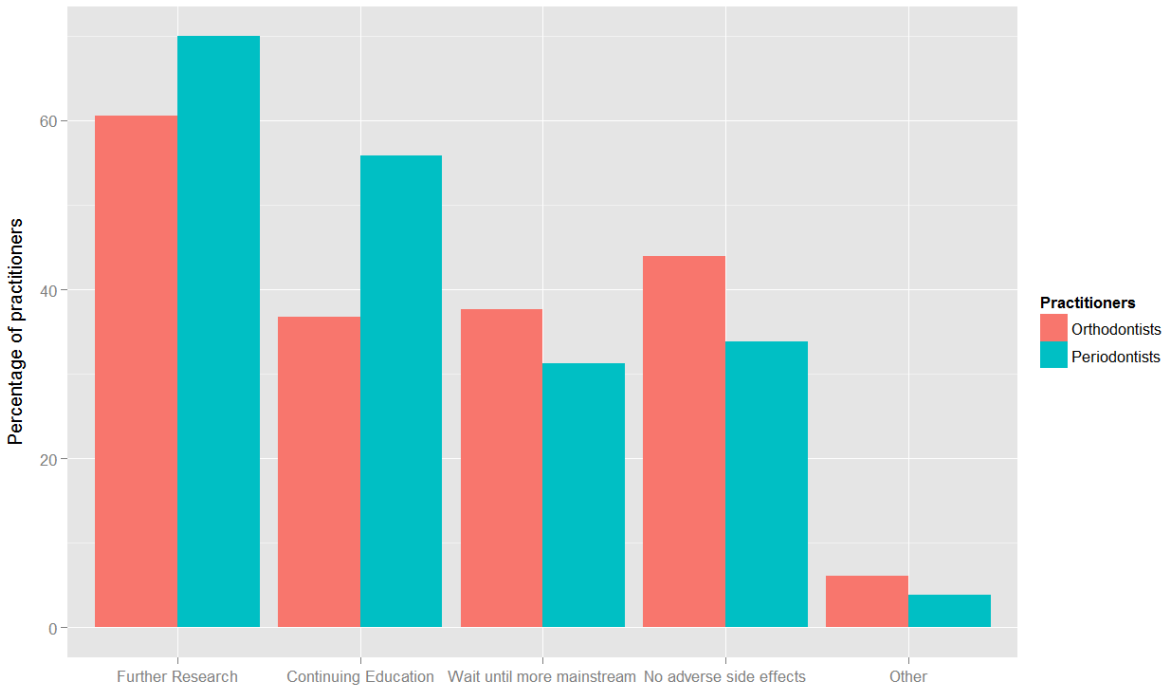

Figure 4: What would make you feel more likely to recommend this procedure to your patients?

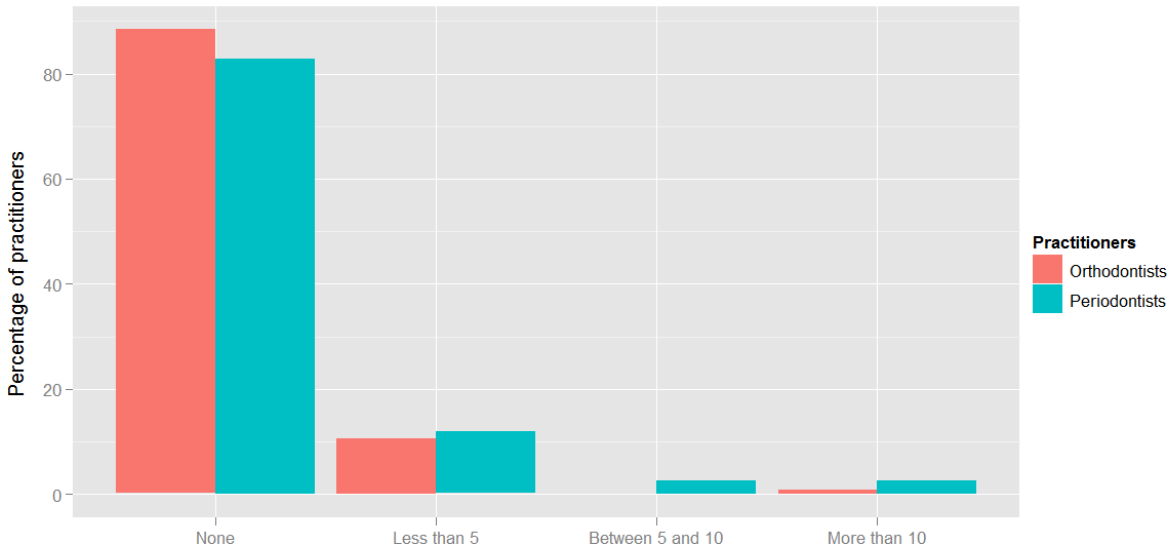

Figure 5: How many cases have you undertaken (per year)?

Questions Unique to Orthodontists:

Over half of orthodontists (57%) said they would never recommend the corticotomy procedure to their patients (Figure 6). Of those who were prepared to recommend the procedure, the largest proportion of orthodontists would limit the procedure exclusively to adult patients (48%), followed by ankylosed tooth (26%), impacted canine (11%), patients susceptible to root resorption (7%) and other (8%) (Figure 7). Only 18% of orthodontists believed a reduction in treatment time was not very important for patients with the remainder stating it was at least important if not very or extremely important (Figure 8). Methods to reduce treatment time were being utilised by 69% of orthodontists and included: Acceledent, Suresmile, Damon, Insignia, indirect bonding and temporary anchorage devices (TADS)(Figure 9). Twelve orthodontists specifically reported their use of the Acceledent device.

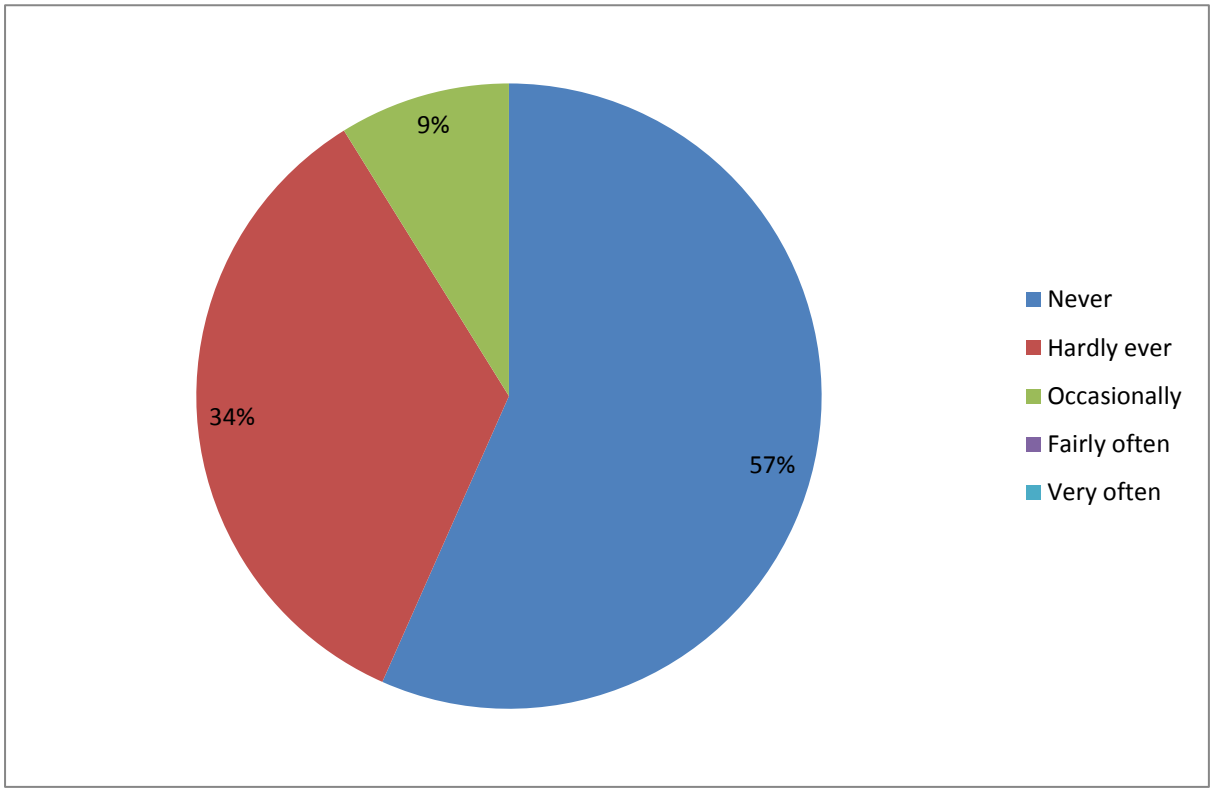

Figure 6: Would you recommend this procedure to your patients?

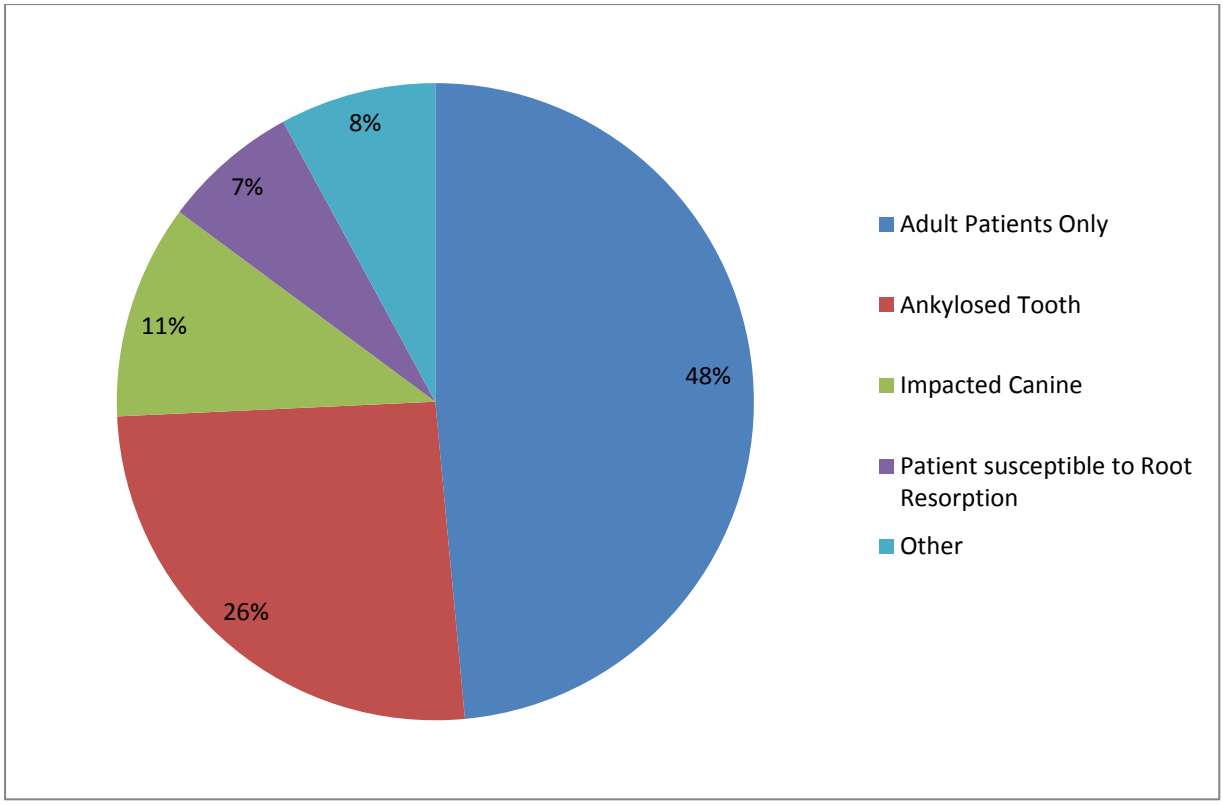

Figure 7: What type of cases would you limit the corticotomy procedure to?

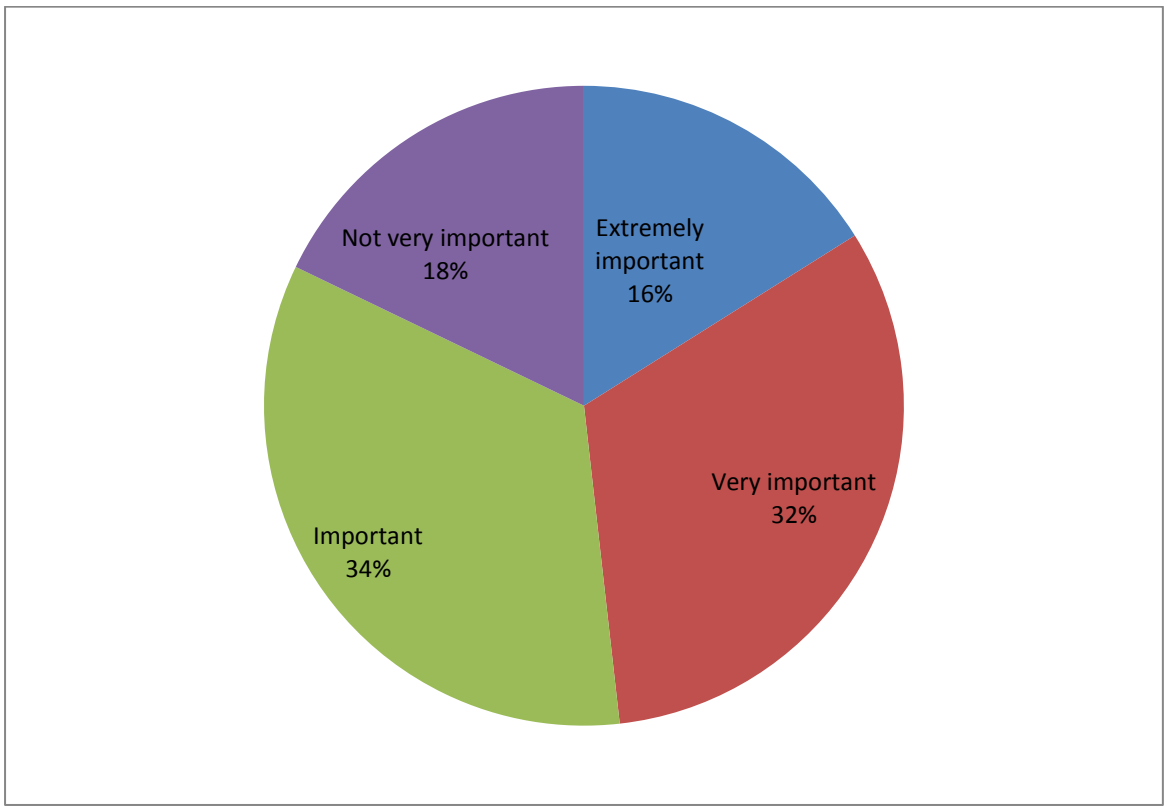

Figure 8: How important do you believe that the reduction in treatment time is for patients?

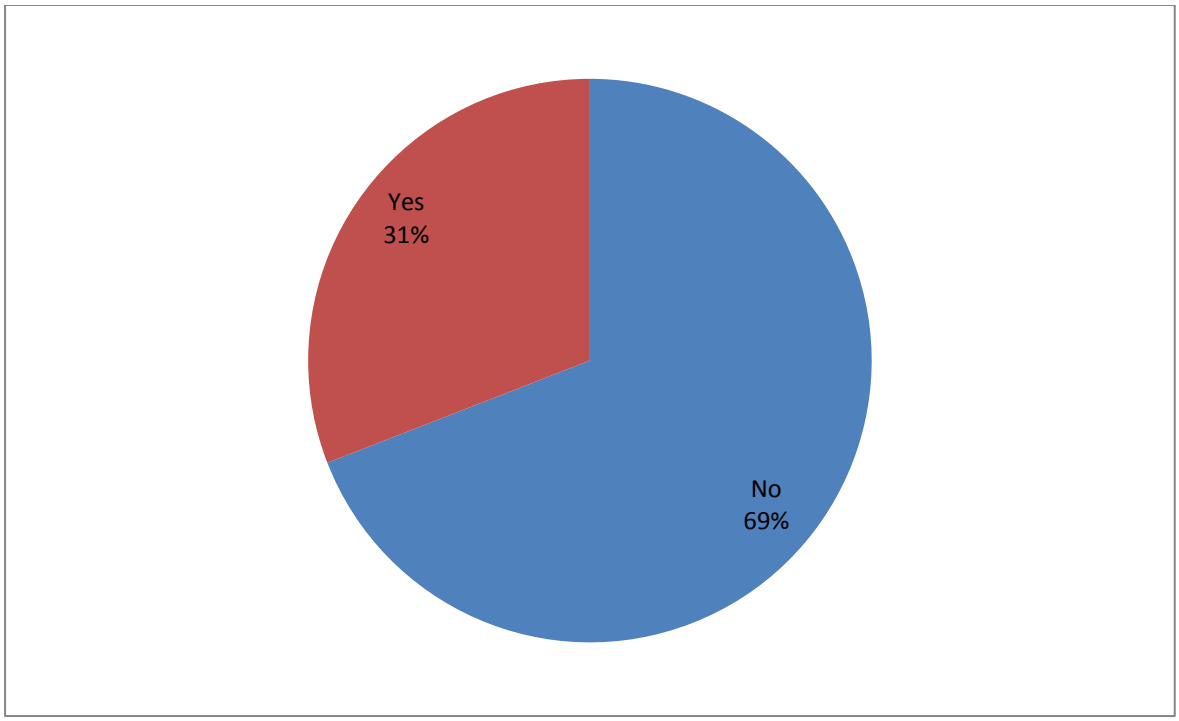

Figure 9: Are you using other methods to reduce treatment time?

Questions Unique to Periodontists:

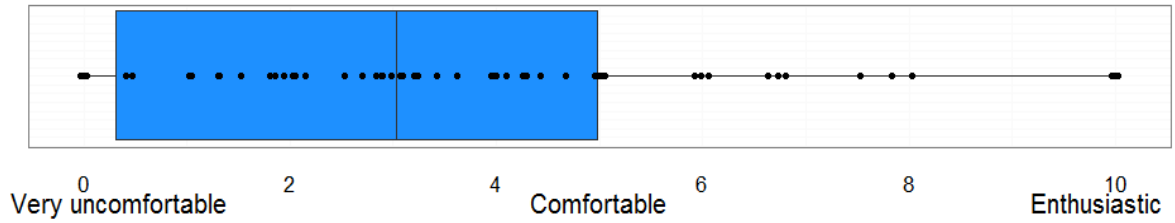

Figure 10: Distributions of how comfortable periodontists are in conducting the procedure. The box plot shows the median, first and third quartiles, while the black dots represent the jittered raw data.

The mean value describing the level of comfort in carrying out the corticotomy procedure upon receiving a referral from an orthodontist colleague was 3.11 on a scale of zero to ten with zero being ‘very uncomfortable’ and ten being ‘enthusiastic’. The standard deviation was 2.69 and 75% of periodontists were either comfortable or less than comfortable with performing the corticotomy procedure.

Discussion

The need for further research

It is clear from the results of the survey that the orthodontists and periodontists were more likely to recommend a corticotomy procedure once further research had been conducted (61.1% orthodontists, 70.1% periodontists). Currently, periodontists would feel less than comfortable undertaking the corticotomy procedure if a referral were made by an orthodontist colleague. Orthodontists for their part seemed just as uncomfortable with the procedure with 59.26% stating that they would never recommend corticotomy-facilitated orthodontics to their patients. The remaining orthodontists would limit the corticotomy procedure to adult patients, ankylosed teeth, impacted canines, patients susceptible to root resorption and 'other', in that order. The proportion of practitioners who were undertaking at least one case per annum was low, with only 11.5% of orthodontists and 18.2% of periodontists reporting their experience.

The majority of the literature on this topic consists of case reports written by clinicians. However, the number of scientific articles has been increasing and, in fact, the Milo Hellman award provided for an original investigation that gives new and significant material or value to the art and science of orthodontics in the United States and Canada in 2010 was awarded to a study that assessed the mechanism and morphological changes in the alveolar bone in response to corticotomy-facilitated OTM[7]. The awarded study used the rat model in conjunction with MicroCT, Faxitron analyses and molecular biology studies to conclude that the early rapid movement observed in the corticotomy and tooth movement group was due to increased bone modelling as a result of the surgical intervention. More specifically, the increase in OTM is due to a coupled mechanism of bone resorption and formation during the earlier stages of treatment.

Other research groups are concurrently working on deciphering the biological basis of corticotomy-facilitated OTM using animal models because the mechanism behind the acceleration in tooth movement needs to be fully elucidated. Currently, the Orthodontic Department at The University of Adelaide is conducting a series of investigations using MicroCT and histomorphometric analyses using fluorescent labels to investigate the biological basis of corticotomy-facilitated OTM using the rat model. The research group anticipates that their findings, along with other studies, will clarify the physiological basis of corticotomy-facilitated OTM.

As opposed to RCTs, which are often expensive, time consuming and difficult to design, a long term evaluation of the effects on patients who have undergone the procedure may be more practical. A clear majority of the surveyed periodontists (91.2%) in the current study believe that corticotomy-facilitated orthodontics is associated with side effects and emphasised their concerns regarding recession, devitalisation through root damage and bone loss.

Follow-up regarding the long term effects of the bone grafting material which can be employed in the presence of fenestrations and dehiscences[6] is also required. The constituents of the grafting material include:

- 100% demineralised freeze dried bone allograft (DFDBA)
- a mixture of DFDBA and bovine bone
- a mixture of DFDBA and mineralised free dried bone allograft

So far, Wilcko *et al* have shown a CBCT scan after 2.5 years on one patient in which the bone graft seemed to be stable. The same authors, however, found particles of bovine graft that had not been incorporated 8.5 months after removal of fixed appliances on another patient[5].

Improved interdisciplinary communication

The surveys conducted were able to identify a number of differences of opinion between orthodontists and periodontists on corticotomy-facilitated orthodontics. The awareness of the procedure differed between the two groups as a higher proportion of orthodontists stated that they were aware of corticotomy-facilitated orthodontics compared to periodontists. This result is not surprising as the procedure benefits the orthodontic patient and a referral is made by the orthodontist to the periodontist for the surgical aspect of treatment. A conflict identified in this study is that if a referral was made from an orthodontic colleague, periodontists on average would feel less than comfortable in performing the surgical procedure. Interestingly, as a group, periodontists did not state invasiveness as the prime reason for not undertaking the corticotomy procedure if a referral was made from an orthodontist. Their limited knowledge of the procedure came to be the foremost reason followed by limited research on the topic.

Such issues revealed by the survey emphasise the need for future research and education to be carried out in an interdisciplinary fashion. While periodontist responders stated that their

main reason for not undertaking the procedure was due to limited knowledge, the orthodontists perceived the procedure to be invasive and felt this negated any recommendation. There were two very different opinions on why the practitioners felt uncomfortable about performing or recommending the procedure.

If corticotomy-facilitated orthodontics is to be offered as a useful option to selected patients, orthodontists and periodontists need to hold similar attitudes towards the procedure. This can be achieved through improved communication encompassing joint research, joint continuing education, discussion/debate at conferences and study groups. The momentum has already been gained with the Wilcko brothers presenting their Periodontally Accelerated Osteogenic Orthodontics 'PAOO' or Wilckodontics for both specialists. The possibility of collaboration to be achieved in the coming years will determine how this procedure is applied for the benefit of patients.

Are we ready to recommend corticotomy-facilitated orthodontics to patients?

The majority of orthodontists (82.1%) and periodontists (81.8%) responding in the current study had never undertaken a case involving corticotomy, suggesting that most practitioners are not yet ready to recommend corticotomy-facilitated orthodontics to patients. Despite the lack of enthusiasm for the procedure, 82.0% of orthodontists believed that a reduction in treatment time was important for patients. It was also interesting to note that almost a third of orthodontists surveyed used some method of reducing the duration of treatment, with the most common method being the Acceledent device. Other methods included Suresmile, Damon, Insignia, indirect bonding and temporary anchorage devices (TADS). Common sense prevailed in some answers and 'good treatment goals' and 'efficient mechanics' were also stated as methods to reduce treatment time by orthodontists.

Due to its non-invasive nature, Acceledent and other appliance driven methods of reducing treatment time may be more appealing to clinicians than corticotomy-facilitated orthodontics with accompanying inherent surgical risks. However, orthognathic surgery, distraction osteogenesis, and exposure of unerupted teeth all carry surgical risks and these should be discussed in detail with the patient prior to embarking on treatment. If the duration of treatment is a critical factor for a patient, perhaps corticotomy could be discussed as an adjunctive treatment along with other methods. Some practitioners have already taken this initiative, albeit only a small proportion of the profession judging from the percentages of professionals with at least a yearly experience of the technique found in the current study.

Less invasive options for consideration

Researchers are investigating less invasive methods of optimising the regional acceleratory phenomenon, thereby accelerating OTM. Aside from corticotomy, which is unlikely to be adopted by clinicians due to its invasiveness, as well as lack of clinical research, alternatives such as corticision and piezopuncture may be considered to confer similar benefits.

Corticision is an alternative method of injuring the cortical bone without raising a muco-periosteal flap[8]. As implied by the name, a reinforced scalpel is used in conjunction with a mallet to incise the interproximal cortices trans-mucosally. In cat studies, the mean apposition area of new bone when orthodontic force was used with corticision showed a 3.5-fold increase when compared to the use of orthodontic force alone[9].

Dibart published a case report outlining the use of a piezotome in order to evoke the RAP effect as he saw the use of a mallet in corticision 'somewhat aggressive'[10]. Furthermore, unlike corticision, bone grafting material could be added in selected areas without raising a full thickness flap by manipulating vertical incisions in gingiva.

A recent report of 'piezopuncture' whereby a piezotome is used to make cortical punctures penetrating the gingiva around the moving tooth has shown promising results in accelerating OTM in the dog model[8]. In contrast to conventional osteotomies, it has numerous advantages, including the selective cutting of mineralised tissues without damaging surrounding soft tissues and nerves, which is a concern for most practitioners. Providing RAP and, therefore, the rapid movement of teeth along with decreased potential for side effects, piezopuncture and its derivatives may be able to provide a reduction in treatment time by exploiting the underlying biological mechanism of the bone.

The request for shorter treatment time will inevitably become a recurring request by adult patients. Companies are already marketing hand held devices such as the Propel system which harness the RAP effect by making punctures of pre-determined depth into the cortical bone[11]. Instead of letting companies drive the market, orthodontists and periodontists need to cooperate in finding efficient ways of accelerating OTM with minimal side effects that are supported by research.

Limitations of the current study

Not all Australian or New-Zealand orthodontists and periodontists had the opportunity to participate as the questionnaire was distributed at a conference. There may be a bias present to those present at a conference, however, the results were polarised in most questions. Analysis of the demographics of the current sample compared to the Australian Society of Orthodontists in terms of average age, number of practitioners in each state and the number of student members would have enhanced the interpretation of results. The response rate of orthodontists and periodontists in this study is comparable to other recent questionnaire based studies[12].

Conclusions

Previously, there was cynicism about corticotomy amongst the profession due to the level of invasiveness and the lack of scientific evidence. Despite an increase in the quality of research, the results of this study demonstrate that uptake remains limited. The perception that modern surgical methods should be minimally invasive may have left corticotomy in the 'too hard' basket in the armamentarium of practitioners, although it may be a valid option in certain situations. However, this may change in the near future as several proprietary groups have started marketing devices based on the science of corticotomy and RAP[11].

- A majority of surveyed orthodontists and periodontists believe more research is required on the topic of corticotomy-facilitated OTM before recommending it to patients.
- More than half of the surveyed orthodontists would not recommend corticotomy-facilitated orthodontics to their patients.
- The minority who would recommend the procedure would limit it to adult patients, ankylosed teeth, impacted canines and patients susceptible to root resorption.
- Over 90% of surveyed periodontists believed that there were side effects associated with the corticotomy procedure.
- The proportion of surveyed practitioners who had undertaken at least one case requiring a corticotomy per annum was exceptionally low with few orthodontists (11.5%) and periodontists (18.18%) reporting that experience.

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9. ARTICLE 2

Dynamic response of the alveolar bone to corticotomy-facilitated orthodontic tooth movement

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Introduction: Due to case reports that demonstrate a dramatic reduction in time, interest in the topic of corticotomy-facilitated orthodontics has resurged. Despite most of these case reports showing a buccal movement of the teeth via the expansion of the arches, animal studies continue to use a mesially directed movement for their investigate purposes. Furthermore, there are proponents to suggest that the raising of a mucoperiosteal flap should be sufficient to produce an up-regulation of bone remodelling. The purpose of this study was to determine, using a dynamic method, whether injury to the cortical bone is essential in upregulating bone remodelling using a buccally directed orthodontic force.

Methods: Thirty six male Sprague Dawley rats aged between 6-8 weeks were randomly included in three control groups (no surgery; flap surgery; corticotomy) and three tooth movement groups (tooth movement only; tooth movement and flap; tooth movement and corticotomy). Each group consisted of six rats and a fixed appliance exerted a buccally tipping force of 100g over 7 days. Double bone labelling consisting of calcein and alizarin red was used to for histomorphometric analysis of the buccal alveolar bone turnover. Coronal sections of 5μm thickness were chosen to study the effects of corticotomy on the buccal bony plate along the length of the root of the first maxillary molar tooth with histomorphometric analysis using a fluorescent microscope. From each rat, five random slides were selected to quantify the mineral apposition rate at our defined region of interest.

Results: From the six groups tested, the tooth movement and corticotomy group had the highest mineral apposition rate (MAR) followed by tooth movement only, tooth movement and flap, corticotomy only, flap only and control. There was a statistically significant difference between the tooth movement and flap group and tooth movement and corticotomy group ($p<0.05$) but not between tooth movement only and tooth movement and flap group.

Conclusion: When no orthodontic tooth movement (OTM) is involved, there is a trend of increasing MAR with the raising of a mucoperiosteal flap and corticotomy procedure but when OTM is involved, raising a flap does not significantly increase the MAR beyond the levels of OTM. Therefore, we conclude that injury to the cortical bone is essential in increasing the MAR and thus the OTM when a buccally directed force is applied to a tooth.

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Introduction

One of the factors that may determine patient satisfaction after orthodontic treatment is the duration of treatment[1]. With increasing numbers of adult patients seeking orthodontic treatment, modalities to increase orthodontic tooth movement (OTM) are becoming more pertinent[2]. Increased time in fixed appliances is also associated with risk factors such as white spot lesions and increased susceptibility to root resorption, therefore in a select group of patients, accelerating orthodontic tooth movement may confer certain benefits[3].

Currently, methods of accelerating OTM can be broadly classified into non-surgical and surgical. Non-surgical modalities are primarily pharmacological in nature and include the use of prostaglandins (PGs), vitamin D, osteocalcin and gene transfer methods[4-11]. Vibrational methods have been developed for patient use but randomised clinical trials to test its efficacy are not yet available[12]. Animal studies of the above methods have all shown promising results but their clinical application is currently limited. Until questions on dosage, frequency of intervention required, biological side effects (both immediate and long term) can be answered, it is doubtful whether pharmacological interventions will have a place in clinical practice.

Despite the recent resurgence in the topic, surgically-facilitated OTM is not a new concept and predates the twentieth century[13]. Predominantly, osteotomies have been employed to facilitate OTM but due to complications such as necrosis of bone, loss of pulpal vitality and bony dehiscence at the surgical site, the procedure has not gained support amongst the profession[14].

In 1959, Köle described a procedure called “corticotomy” because the surgery pertains to the cortical bone thus allowing the underlying medullary bone to maintain the blood supply to the dentition. The reduction in treatment time is attributed to the weakening of the cortical bone at which point the teeth can be used as a handle which is moved through the medullary bone. Köle believes that the corticotomy procedure allows the movement of blocks of bone with the teeth rather than moving individual teeth through bone[15].

Thirty-two years after the initial publication of Köle’s work Suya revived academic interest in the topic by showcasing three hundred and ninety five of his treated cases[16]. Suya’s work fostered research from other groups but a major resurgence has not taken place since 2001

when the Wilcko brothers published two case reports outlining their method of corticotomy-facilitated orthodontics with the addition of periodontal regenerative surgery. Instead of Suya's "corticotomy-facilitated orthodontics", they named their procedure "accelerated osteogenic orthodontics" as the original technique has been modified[17].

Case reports by the Wilcko brothers demonstrated a dramatic reduction in treatment time and the biological basis for this is hypothesised to be a result of the regional acceleratory phenomenon or "RAP". First described by Frost, RAP induces increased wound healing above normal levels and involves an anatomical region, encompassing both skeletal and soft tissue components[18]. The decortication of alveolar bone results in an increase in regional bone turnover and remodelling which ultimately results in a transient osteopenia facilitating a greater rate of OTM[19].

Whether RAP is responsible for the acceleration in rate of OTM has been investigated by several authors using the rat model. Sebaoun *et al* have investigated the alveolar response to corticotomy as a function of time and proximity to the surgical site of injury using histology[20]. Anabolic response to corticotomy was evaluated using fluorescent bone labels, which measured the bone apposition rate adjacent to each first molar root. At the three week time point, the percentage of new bone apposition in the first molar area was significantly greater in the corticotomy group compared with the control group. The authors concluded that the peak in catabolic and anabolic activity was observed at 3 weeks and it was three-fold higher in the experimental group. Furthermore, the changes in bone metabolism pertain to the vicinity of the injury site and by week 11, the effects dissipate to a steady state, suggesting the role of RAP. The study of Sebaoun *et al* has been instrumental in elucidating some of the mechanisms by which corticotomy enhances bone remodelling. For the purpose of clarifying the dynamics of the periodontium, the study excluded OTM therefore clinical extrapolation is somewhat limited.

Baloul *et al* in 2011 used radiographic, tomographic and molecular methods to further investigate the biological mechanisms behind selective alveolar decortication, which was essentially the same procedure as corticotomy[21]. The early rapid movement observed in the selective alveolar decortication and OTM group was due to increased bone modelling as a result of the surgical intervention. More specifically, the increase in OTM was found to be

due to a coupled mechanism of bone resorption and formation during the earlier stages of OTM which resulted in the bypassing of the lag phase of classic OTM. This study used several methods including Micro-CT, Faxitron analyses and molecular biology techniques to validate the mechanism behind corticotomy-facilitated OTM; however, histomorphometric analyses to elucidate the dynamics of the bone remodelling were not included.

The OTM in the Sebaoun and Baloul studies consisted of mesial movement of the maxillary first molar. Clinically, this would most likely represent the movement of teeth for closure of extraction space and, although corticotomy could be employed in extraction cases, the surgical nature of the extraction might already provide some degree of RAP. Case reports by Wilcko *et al* are predominantly non-extraction in which the arches are expanded and to our knowledge, there are no studies currently available which evaluate the biological mechanisms pertaining to the dynamics of the buccal alveolar bone when the tooth is moved buccally[17]. Furthermore, Binderman has proposed that simply raising a flap without a corticotomy procedure stimulates a RAP response[22].

The aim of this study was to evaluate the dynamic response of the buccal alveolar bone with and without OTM to the raising of a mucoperiosteal flap and to a corticotomy procedure. Histomorphometric analysis was used to measure the mineral apposition rate, defined as the rate at which osteoid matrix is mineralised. The null hypothesis was that there is no difference in the mineral apposition rate of the buccal alveolar bone following a mucoperiosteal flap procedure and a corticotomy procedure with and without OTM, compared with controls.

Materials and Methods

Ethics Approval

Ethics approval was obtained from the University of Adelaide Animal Ethics Committee (Project No: M-2009-172 and M-2009-172B).

Experimental Animals

Thirty-six, male, Sprague Dawley rats, aged between six and eight weeks with an average body weight of 262gms (range of 169-367gms) were obtained from Laboratory Animal Services (The University of Adelaide). The animals were housed at The University of Adelaide's animal house where all live animal procedures were performed. They were fed rat chow and chocolate spread and water ad libitum.

Experiment Protocol

All treatment procedures were performed on the right maxillary first molar and the treatment was undertaken according to the timeline indicated in Figure 1. Although a split mouth design has been advocated by authors in the orthodontic literature due to high inter-animal variation it was not relied upon due to reported systemic effects of the RAP phenomenon[23]. Experimental duration of seven days was chosen as bone turnover in adult rats has been estimated to be approximately six days[24]. For comparison, a control group without any intervention was included.

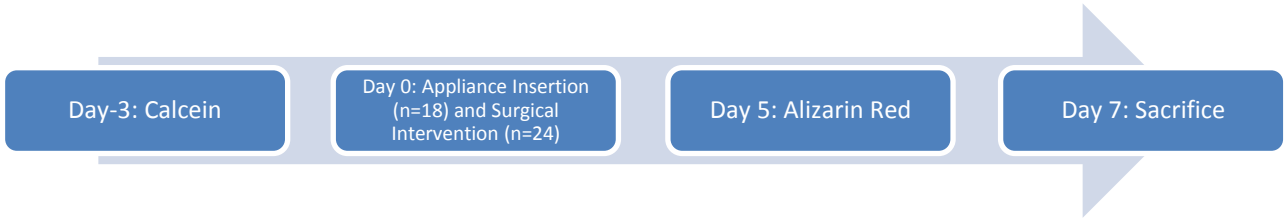

Figure 1: Bone Label Timeline

The first bone label (calcein at 5mg/mL) was administered three days prior to appliance insertion by intra-peritoneal injection under isoflurane vapour and oxygen inhalation

anaesthesia. The second label (Alizarin red at 30 mg/mL) was administered at day five under the same anaesthetic protocol.

Study Design

The 36 rats were received in random order and assigned to one of six groups (N=6):

Group	Appliance	Surgery
1	No	No
2	No	Flap
3	No	Corticotomy
4	Yes	No
5	Yes	Flap
6	Yes	Corticotomy

Anaesthesia

The rats were sedated within a gas chamber using isofluroane and oxygen for several minutes prior to procedures. The isofluorane concentration was set between 2.5% and 3.0% depending upon the weight of the rat.

Deep anaesthesia was provided through intraperitoneal injection of Hypnorm®(fentanyl citrate, 0.315mg/mL and fluanisone 10mg/mL;Janssen-Cilag Ltd, High Wycombe, UK), Hypnovel® (midazolam hydrochloride, 5mg/mL;Roche, Berne, Switzerland) and sterile water in a 1:1:2 ratio. Each rat was also administered Temgesic® (buprenorphine 0.3mg/mL; Reckitt Benckiser Healthcare Ltd, Dansom Lane, Hull, UK) 0.05mg/mL at 1mL/Kg bodyweight by intraperitoneal injection, as required.

Appliance Construction

The appliance was custom made for each animal on a stone model which was obtained from a polyvinylsiloxane impression (Honigum, Gunz Dental, Australia) of the animal's oral cavity taken at day -3(Figure 2). The purpose of the appliance was to deliver a buccally-directed force to the maxillary first molar. This was achieved by designing an appliance with three components:

- Anchorage Unit
- Connector
- Spring

The anchorage unit was provided by the cementation using multi-cure glass ionomer (3M Unitek, Monrovia, USA) of a band around the incisors. The major connector was a length of half round wire 1.5mm in diameter (Dentaurum, Australia) which connected the spring and the anchorage unit. The spring component consisted of a 100g NiTi push coil spring (GAC Australia, Australia) which was compressed within the plunger. The spring/plunger complex was attached to the maxillary right first molar with a stainless steel ligature (3M Unitek, Monrovia, USA). The ligature attaching the plunger to the maxillary right molar was passed between the contact point of the first and second molars and twisted tightly. Subsequently, composite resin (Neobond, Dentsply GAC International, Bohemia, NY, USA) was used to bond the remaining pigtail and plunger to the tooth for retention and comfort (Figure 3). This was light cured with a halogen curing light.

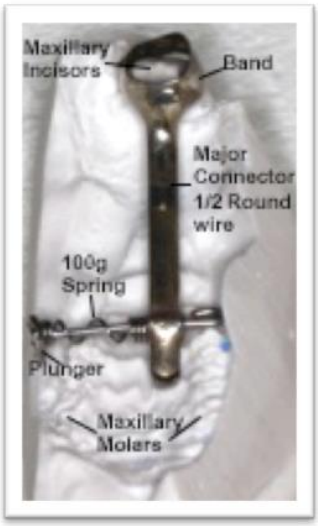

Figure 2: Appliance Design

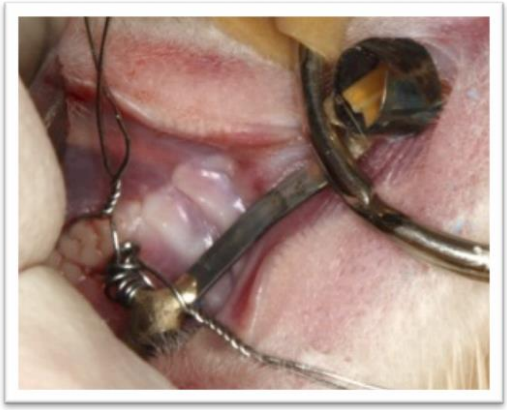

Figure 3: Appliance being placed in the oral cavity

Surgical Protocol

The surgical interventions were carried out by a single operator MJ[25]. In the flap only and corticotomy group, a full thickness soft tissue flap was raised on the buccal aspect of the upper right first molar. An intrasulcular incision was extended from the maxillary first molar in a mesial direction towards the edentulous area. Posteriorly, a vertical incision extended between first and second maxillary molars beyond the mucogingival junction.

In the corticotomy groups, a slow speed hand piece and a 0.5mm round, stainless steel bur was used to create a trench the thickness and depth of the bur. This extended from the apices of the first molar horizontally and mesially to the edentulous area, creating an L-shape (Figure 4). A tissue glue, GLUture (60% 2-octyl and 40% N-butyl cyanoacrylate, Abbott Laboratories, North Chicago, USA) was used to apposition the flaps and promote healing by primary intention.

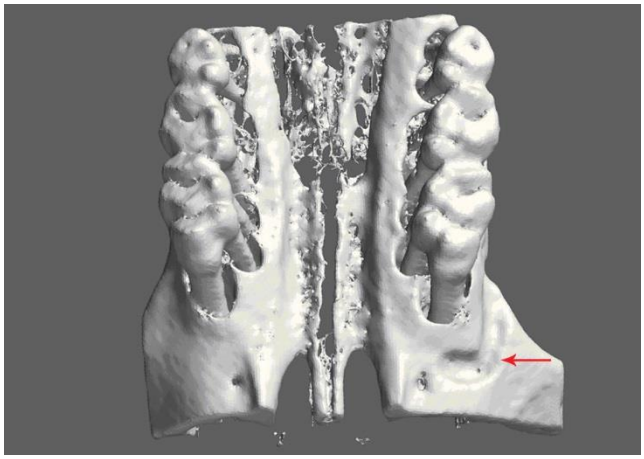

Figure 4: Corticotomy Cut

Orthodontic Tooth Movement

For the groups undergoing OTM (Groups 4, 5 and 6) the appliance was inserted at day 0, applying a buccally directed force to the maxillary right first molar. The activated appliance remained in situ for 7 days until the animals were sacrificed.

Specimen Collection

At the end of the observation period, the animals were sacrificed by Lethabarb lethal injection (60 mg/mL with 1mL/kg of barbiturate derivative, Virbac, Australia). The maxilla was dissected, stripped of soft tissues and placed in 70% ethanol. Tissue dehydration was carried out in 25mL polypropylene tubes with a graded ethanol series prior to defatting with acetone and infiltration with methylmethacrylate. A vacuum chamber was used as part of the processing protocol (IMVS SA Pathology Bone and Joint Research Laboratory (Appendix 1). Polymerisation of the methylmethacrylate took place in a 37°C oven for 2 days or until polymerisation was achieved.

Histological Slides

Coronal sections of 5µm thickness were chosen to study the effects of corticotomy along the length of the root of the first molar tooth in the buccal aspect. Sections were obtained from a microtome (Leica Polycut 2600 automated mircrotome) and cuts were initiated from 2mm mesially from the crown of the 1st molar tooth and extended to 1mm distal to the crown of the first molar so that the regional effects around the first molar tooth could be captured histologically. Each section was transferred onto a gelatine-coated slide, spread using spreading solution (30mL ethylene glycol monoethyl ether in 70mL of 70% alcohol) and placed into a warm oven at (37°C). The slides were cover-slipped with DePex mounting medium (Sigma Aldrich) and sequentially numbered for analysis.

Histomorphometric Analysis

Histomorphometric analysis was performed on a fluorescent microscope Leica DM6000B at 20x objective magnification. The region of interest was the buccal alveolar bone and this was

defined as bone in the buccal direction from the furcation. A random number generator was used to select 5 slides from each rat. From each digitised slide, the mineral apposition rate (MAR), defined as the rate at which the non-mineralised osteoid is mineralised and also an indicator of osteoblastic activity[26] (expressed in units of microns per day), was calculated using the following equation:

$$MAR(\mu m/day) = \sum_x \frac{(e)(\pi/4)}{nt}$$

where Σ_x is the sum of all the measurements between double labels, *e* is the micrometer calibration factor (mm), $\pi/4$ is the obliquity correction factor, *n* is the total number of measurements, and *t* is the time interval expressed (days)[27]. The longest set of parallel lines of calcein and alizarin red from the region of interest was used for quantification to minimise error, and the MAR was subsequently calculated by the software Leica QWin (Figure 5). Similar method of calculating the MAR has been used by other authors in the literature[28,29]. One operator (BK) carried out the quantification under blinded conditions.

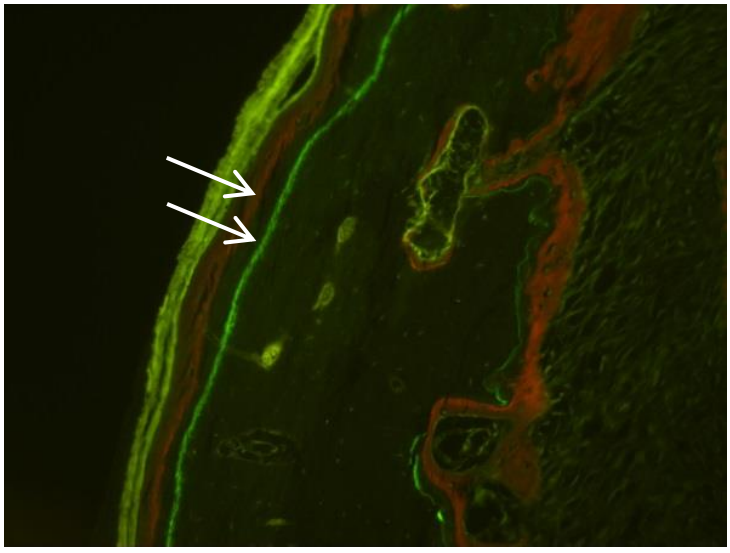

Figure 5: Histomorphometric slide showing the double labelling of calcein (green) and alizarin red (orange).

Intra-examiner reliability

The bias and random error were calculated from repeat measurements of six random slides. The bias was calculated as the mean differences of pairs of measurements and the random error was calculated as the standard deviation of the differences of pairs of measurements[30]. The bias was 6.75% and random error was 8.95% which was deemed to be acceptable.

Statistical Analysis

Statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA). MAR was compared between the six groups using a linear mixed effects model. In the model, the rat was included as a random effect to adjust for the dependence in the data due to repeated measurements within each rat. The differences between the groups were analysed using Post Hoc tests.

Results

From the six groups tested, group 6 (OTM+corticotomy) had the highest MAR followed by group 4 (OTM only), group 5 (OTM+flap), group 3 (corticotomy only), group 2 (flap only) and group 1 (control)(Table 1). The MAR for group 6 (OTM+corticotomy) was approximately 1.19 times higher than for group 4 (OTM only) and 2.37 times higher than group 1 (control). Raw data is included in Appendix 3.

Table 1: Rat groups and their adjusted means of mineral apposition rate

Adjusted Means of MAR					
Effect	Group	Estimate	Standard Error	Lower 95% confidence limit	Upper 95% confidence limit
Group	1	1.3889	0.1588	1.0746	1.7032
Group	2	1.7489	0.1612	1.4298	2.0680
Group	3	2.2441	0.1833	1.8813	2.6069
Group	4	2.7703	0.1547	2.4639	3.0766
Group	5	2.6677	0.1668	2.3375	2.9978
Group	6	3.2911	0.1618	2.9707	3.6114

In the three groups in which there was no OTM, there was an increase in the MAR when raising the mucoperiosteal flap (not statistically significant; *p* value = 0.1141), and a further increase with the corticotomy procedure (statistically significant; *p* value = 0.0446) (Figure 6). The combined effects of raising the mucoperiosteal flap and the corticotomy procedure showed a highly significant increase in the MAR relative to the control group (*p* = 0.0006).

In the three groups in which there was OTM, there was no significant difference when raising the mucoperiosteal flap relative to the OTM-only group. In contrast, the corticotomy procedure produced a significant increase in the MAR relative to both the OTM-only and the OTM+flap group (*p* value = 0.0217 and 0.0083, respectively).

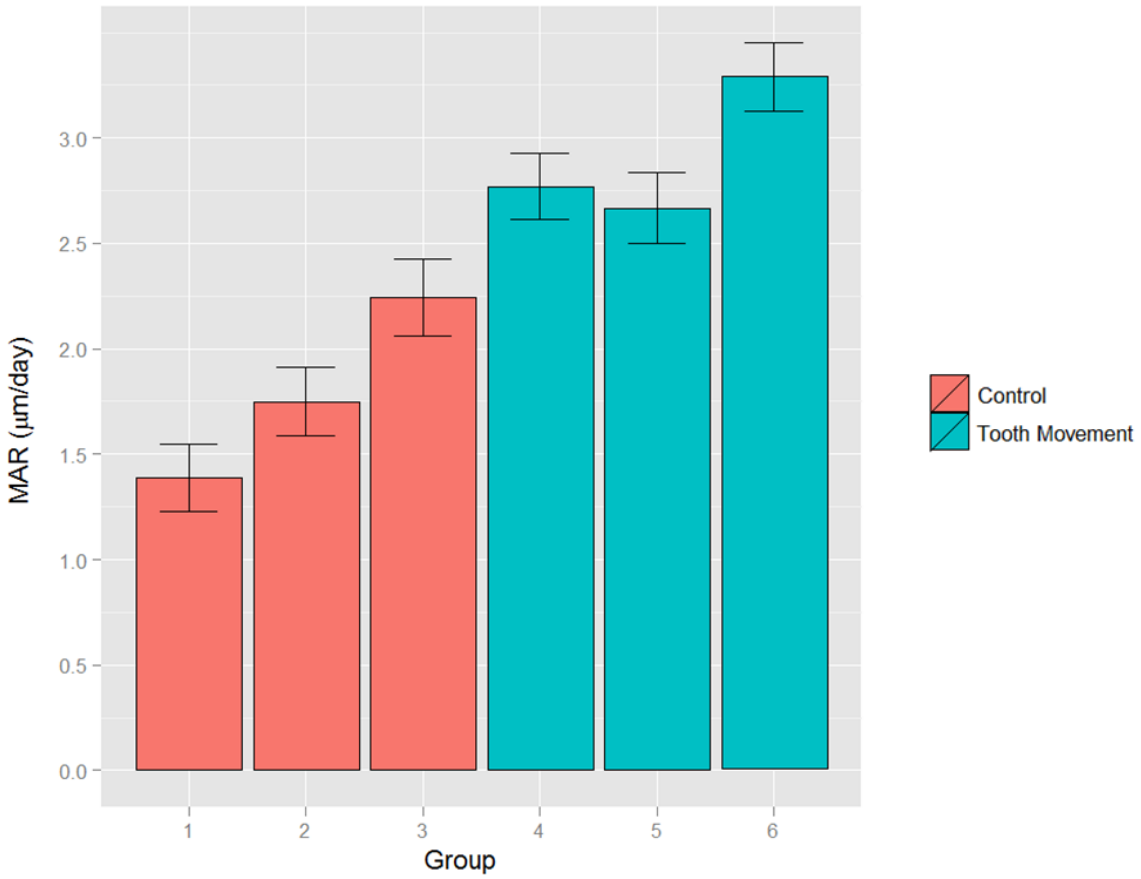

Figure 6: Mineral Apposition Rate. Error bars represent ±1 standard deviation

When the groups were compared with each other (**Error! Reference source not found.**), there was no significant difference in the MAR of group 4 (OTM only) and group 5 (OTM+flap). Similarly, there were no significant differences in the MAR between group 1 (control) and group 2 (flap only).

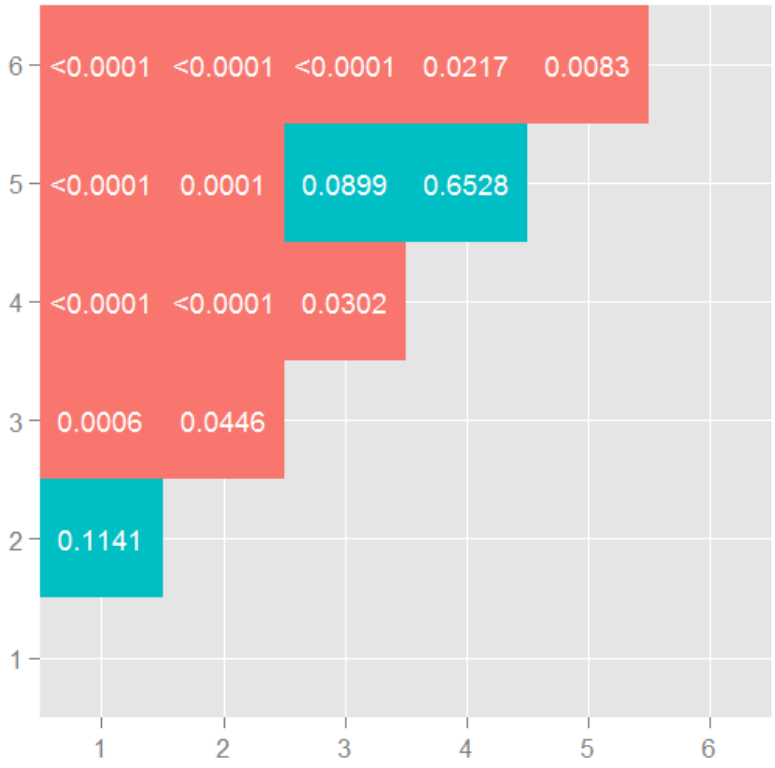

Figure 7: Differences between groups. Red colour represents that the differences were statistically significant at the 5% significance level. The *p* values are also included for each pair.

Discussion

The Effect of Corticotomy on MAR

Flurochrome labelling is a well-recognised method of measuring the MAR which represents the anabolic production of osteoid matrix by osteoblasts[31]. The aim of this study was to investigate the dynamic response of the alveolar bone to corticotomy-facilitated OTM using flurochrome bone labelling. More specifically, the purpose was to examine the effect in the

buccal bone in response to a buccally directed OTM as this replicates clinical case reports whereby the dental arches are expanded in conjunction with the corticotomy procedure[32].

Our study showed that there is a statistically significant increase in the MAR when the corticotomy procedure was applied in conjunction with OTM, as opposed to OTM alone. This can be explained by an increase in the rate of bone turnover resultant to the local injury. Described by Frost as the RAP effect in which the speed of wound healing is increased above normal levels, in bone there is an up-regulation of the remodelling process which may persist for as long as the causative stimulus remains. The reason behind RAP seems to be protective in nature, accelerating vital processes and thus reducing the time required for healing[18].

The effect of mucoperiosteal flap on MAR

In contrast to the corticotomy procedure, raising a mucoperiosteal flap has been suggested as a means to up-regulate RAP in bone and hence increase the rate of OTM. Yaffe *et al* have used high resolution microradiography to demonstrate massive resorption of the alveolar bone in response to mucoperiosteal flap surgery. The effects are magnified when both lingual and buccal flaps are raised as opposed to when the surgery is performed on the buccal aspect only[33]. Binderman *et al* have also demonstrated, using micro-radiographic and histological methods, that periodontal surgery stimulates a cascade of signals suggestive of RAP by up-regulating osteoclastic activity to resorb the cortical lamina of the alveolar bone. The resultant osteopenia allows the bone to be more susceptible to orthodontic forces[22].

Extrapolating from the studies of Yaffe *et al*[33] and Binderman *et al*[22], a significant increase in MAR should be observed in the OTM+flap group compared to the OTM only group. However, the results are conflicting in that the difference in the MAR between OTM only and OTM+flap was not statistically significant. This may be due to the high magnitude of force applied which was chosen intentionally as the effects of hyalinisation and subsequent root resorption were also planned to be evaluated; the results of this component will to be published as a future report. With a more physiological force, different results may be observed. Nevertheless, the same trend was seen in the no appliance groups and there was no significant difference between the control group and flap only.

Several reasons may explain why this was observed: firstly, the rats in Binderman's study were sacrificed 21 days after the surgical flap procedure whereas the rats in our study were sacrificed seven days after appliance insertion and surgical intervention. A shorter duration was chosen because previous research has shown that the ideal time frame to evaluate optimal double flurochrome labelling in rats is 7-14 days and the bone turnover in a rat is believed to be approximately six days[24,34]. The RAP effect from a flap procedure may not be apparent at the seven day mark and may require more time for activation and up-regulation in the rat model. Different results may be observed at a later time point.

An alternative explanation may be that the level of RAP response from a flap-only procedure is not strong enough to enable rapid OTM[20]. Binderman has shown histologically that there are extensive resorptive areas in the PDL aspect of the alveolar bone and many osteoclasts are seen at the bone surface on the inner aspect of the alveolar bone when a coronal flap is raised. Despite such evidence, the procedure was not carried out within the context of OTM. Rather, the study was carried out to determine the alveolar bone resorption following a coronal versus an apical approach in a mucoperiosteal flap surgery in the rat mandible[22]. Therefore, although the catabolic events are upregulated, the resultant effects may not be resilient or pervasive enough to accelerate OTM.

Jong[25], using the same rats that were used in this study measured, the inter-cuspal distance of the first molar tooth and although the measurement for the OTM+flap was higher than OTM, it was not statistically significant. Sebaoun has also stated that raising a flap cannot evoke RAP and decortication is required to induce a RAP effect although this was not tested in their study[20]. The present results along with those of Jong and Sebaoun support the notion that injury to the cortical bone is critical in inducing the RAP effect in order to accelerate the rate of OTM.

Increase in MAR with OTM

The results from this study demonstrated a surge in the MAR of the alveolar bone in response to OTM when compared with the control group. This observation may be explained by the findings of Verna *et al* which demonstrated micro-cracks in the alveolar bone in pigs in response to OTM[35]. This type of injury, albeit small, takes place in osseous tissue which

amplifies the RAP phenomenon when compared with soft tissue injury. Despite there being no intentional injury to the bone, OTM itself involves injury to the osseous tissue via micro-cracks in the alveolar bone thus up-regulating bone remodelling in the vicinity of the tooth.

Apart from micro-cracks, other mechanisms whereby regional osteopenia takes place due to OTM include the 'stress shielding effect' in which the orthodontic force creates an environment shielding some areas of the bone from mechanical stress[36]. Such areas experience a reduction in occlusal loading below the critical threshold required for the maintenance of normal architecture. Milne *et al* used finite element methods to demonstrate that the region of osteopenia is in the inter-radicular region.

Limitations of the current study

Due to the tipping force applied to the tooth, the distribution of force along the length of the PDL would not be consistent, with increased force towards the coronal aspect of the root. Accordingly, we would expect the MAR to be uneven along the length of the root. In order to reduce the error associated with the tipping movement, we chose the longest consistent parallel lines of calcein and alizarin red for quantification.

Acquiring sections from the methylmethacrylate was technique sensitive. Unlike paraffin, the procedure of embedding in methylmethacrylate is irreversible but provides a supporting medium comparable to the hardness of bone which makes it optimal for flurochrome analysis[37]. The sections were fragile and had a tendency to rip from manipulation. Enough sections were made for analysis however more sections to analyse from each animal would have enhanced the results.

The region of interest spanned 2mm mesially and 1mm distally from the crown of the maxillary 1st molar tooth. It would have been valuable to discern any differences in the MAR in more specific and narrow regions of interest; for example, dividing the region into 1mm segments. Smaller regions may provide information on where the RAP tapers off and decreases in relation to the location of the corticotomy cuts. Such information and its extrapolation may enable clinical application in terms of differential anchorage and also the use of temporary anchorage devices (TADS) where bone injury is created.

Clinical Application

As with all animal studies, extrapolation to human clinical responses should be undertaken with caution as morphologically, rat bone has limited trabecular bone on the buccal side[38]. Nonetheless, as this study aimed to investigate the effects of moving a tooth to the limits of the bony envelope, using a buccally directed force was deemed as most appropriate. As with all animal studies, extrapolation to human clinical responses should be done with caution. The increase in MAR cannot and should not be extrapolated directly into a reduction in treatment duration. Based on studies of OTM, it can be postulated that an increase in MAR would be associated with an increase in the rate of OTM as there is less resistance from the osseous tissue but further studies are required before establishing quantitative guidelines for clinical application.

Further Studies

The high force in the current study was chosen deliberately to investigate hyalinisation and root resorption. Currently there is no evidence based force level to study OTM on rats[39], however different levels of forces ranging from 20-60cN have been researched by other investigators in the literature. Repeating the same experiment with a medium and low force would provide an insight into the optimal force to be employed clinically. Time dependent studies whereby the rats are sacrificed at different time points to observe how the MAR is affected would also provide useful information regarding when the RAP initiates and tapers off. Similarly, the extent of bony injury required to create a RAP phenomenon will be useful in determining its clinical use. In particular, the effects of the different grafting materials available when used in conjunction with the corticotomy surgery will provide a platform for clinical use.

Conclusion

- When no OTM is involved, there is a trend of increasing MAR with the raising of a mucoperiosteal flap and corticotomy procedure.
- When OTM is involved, raising a flap does not significantly increase the MAR beyond the levels of OTM, therefore, we conclude that injury to the cortical bone is essential in increasing the MAR and thus OTM.
- OTM itself increases MAR and we postulate this to be a result of microdamage to the alveolar bone in the vicinity of the tooth undergoing OTM.

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10. CONCLUDING REMARKS

With an increasing number of adults seeking orthodontic treatment, understanding methods that are able to decrease the duration in fixed appliance is essential for the orthodontist. The first study titled "Accelerating orthodontic tooth movement with the aid of periodontal surgery – what the practitioners are thinking" showed that despite 82% of orthodontists stating that a reduction in treatment time was at least important – if not very important or extremely important – for their patients, only 11.5% of orthodontists had experience with the technique. Furthermore, more than half of the orthodontists surveyed would not recommend corticotomy procedure to their patients. Over 90% of periodontists believed that there were side effects associated with the procedure and the lack of research on this topic was the most important reason behind the reluctance to recommendation by orthodontists and periodontists.

Strengthening the body of research on the topic of corticotomy facilitated orthodontics was the aim of the second article titled "Dynamic response of the alveolar bone to corticotomy-facilitated orthodontic tooth movement". In contrast to previous studies that have predominantly used static methods to investigate bone remodelling, a dynamic method of double fluorescent bone labelling was employed. By depicting the bone turnover at two separate time points on a rat, it was determined that there is a trend of increasing MAR when raising a mucoperiosteal flap and applying the corticotomy procedure. However, when OTM is involved, raising a mucoperiosteal flap does not significantly increase the MAR beyond the levels of OTM. This demonstrates that the injury to the cortical bone is essential in increasing the MAR and thus OTM.

The results from the present study validate that bony injury to the cortical bone is critical in initiating the regional acceleratory phenomenon. The next logical step in the study of corticotomy-facilitated OTM would be a randomised clinical trial to demonstrate the clinical efficacy. A sufficient number of adult patients with similar malocclusions would need to be recruited and this may be difficult. However, a smaller scale study involving impacted canines that already require the raising of a flap may shed light regarding its efficacy on human subjects.

11. APPENDICES

Appendix 1: Procedure for resin embedding from IMVS (SA Pathology) Bone and Joint Research Laboratory

Set Up

1. Make enough alcohol solutions
2. Ensure there is enough MMA, PEG-400 (hardener) and perkadox (initiator)

Method

1. Fixation 70% ethanol – 24hrs
2. Dehydration

Ethanol concentration	Time under vacuum (days)
70%	1
85%	1
85%	1
95%	1
100%	1
100%	1

3. Defat/removal of ethanol – Acetone – 2 days with lid on
4. Infiltration

Solution	Time under vacuum (days)
MMA	1
MMA (100%) and PEG-400 (10%w/v)	14

5. Embedding – MMA (100%) + PEG-400(10%) + initiator (perkadox 16, 0.4% w/v) – approximately 2 days in oven at 37°C with lids on tight and in a container of water. Ensure containers are not floating, use weights to keep blocks secure. 2 days approximately is the time period for full polymerisation.

Appendix 2: Questionnaires distributed to orthodontists and periodontists.

Australian Society of Orthodontists

THE UNIVERSITY of ADELAIDE

SURVEY OF CORTICOTOMY ASSISTED ORTHODONTIC TREATMENT IN GRADUATE ORTHODONTIC AND PERIODONTIC PROGRAMS AND ORTHODONTIC AND PERIODONTIC PRACTICES IN AUSTRALIA AND NEW ZEALAND

By completing this anonymous questionnaire, you are consenting for the information collected to be used as part of a doctorate thesis and journal publication.

Year of Graduation/Prospective Year of Graduation as an Orthodontist: _____

University where specialist qualification was/is to be attained: _____

Are you actively involved in University Teaching/Research?

- ☐ Yes
- ☐ No

City of Main Practice: _____

State of Main Practice: _____

1. **Have you heard or read about corticotomy-facilitated orthodontic tooth movement or periodontally accelerated osteogenic orthodontics or Wilckodontics?**

   ☐ Yes → go to question 2

   ☐ No → go to question 3

   ☐ Unsure → go to question 3

2. **Where did you <u>first</u> hear or read about the procedure?**

   ☐ At a conference

   ☐ Journal Article

   ☐ Colleague

   ☐ Patient

   ☐ Other_____

3. **Corticotomy-facilitated orthodontics is believed to accelerate the rate of tooth movement by eliminating the lag phase of tooth movement due to a transient state of osteopenia. The clinical procedure involves raising a full thickness flap and surgically placing small cuts with a bur into the cortical alveolar bone. Would you recommend this procedure to any of your patients?**

   □ never → go to question 5

   □ hardly ever → go to question 4

   □ occasionally → go to question 4

   □ fairly often → go to question 4

   □ very often → go to question 4

4. **If you were to recommend the procedure to patients, what type of cases would you limit the corticotomy procedure to? (tick all that apply)**

   □ Adult Patients Only

   □ Ankylosed Tooth

   □ Impacted Canine

   □ Patient susceptible to root resorption

   □ Other _____

5. **For what reasons would you decide against recommending the corticotomy procedure? (tick all that apply)**

   □ I don't know enough about the procedure

   □ The research is still limited

   □ It's too invasive

   □ I don't believe it will accelerate the treatment time or confer the advantages claimed to the patients

   □ Other_____

6. **What would make you feel more likely to recommend this procedure to your patients? (tick all that apply)**

   □ Further research

   □ Continuing Education

   □ I will wait until it becomes more 'mainstream' within the profession

   □ Assurance that there are no adverse side effects

   □ Other_____

7. **Have you undertaken the treatment with any patients in your practice? If so how many cases in *total (per year)* have you undertaken with the aid of corticotomy?**

   □ I have not undertaken any cases → go to question 9

   □ Less than 5 → go to question 8

   □ Between 5 and 10 → go to question 8

   □ More than 10 → go to question 8

8. **Do you believe that there was a reduction in the total treatment time?**

   □ Yes → How would you quantify this reduction in percentage ____

   □ No

9. **How important do you believe that the reduction in treatment time is for patients?**

   □ Extremely important

   □ Very important

   □ Important

   □ Not very important

10. **Are you using any other methods to reduce the treatment time for your patients and if so please state the method.**

    □ No

    □

    Yes_____

    _____

11. **Comments:**

Thank you for your participation

Australian Society of Orthodontists

THE UNIVERSITY of ADELAIDE

SURVEY OF CORTICOTOMY ASSISTED ORTHODONTIC TREATMENT IN GRADUATE ORTHODONTIC AND PERIODONTIC PROGRAMS AND ORTHODONTIC AND PERIODONTIC PRACTICES IN AUSTRALIA AND NEW-ZEALAND

By completing this anonymous questionnaire, you are consenting for the information collected to be used as part of a doctorate thesis and journal publication.

Year of Graduation/Prospective Year of Graduation as Periodontist: _____

University where specialist qualification was/is to be attained: _____

Are you actively involved in University Teaching/Research?

- ☐ Yes
- ☐ No

City of Main Practice: _____

State of Main Practice: _____

1. **Have you heard or read about corticotomy-facilitated orthodontic tooth movement or periodontally accelerated osteogenic orthodontics or Wilckodontics?**

   ☐ Yes → go to question 2

   ☐ No → go to question 3

   ☐ Unsure → go to question 3

2. **If you have answered *yes* to the above question where did you first hear about the procedure?**

   ☐ At a conference

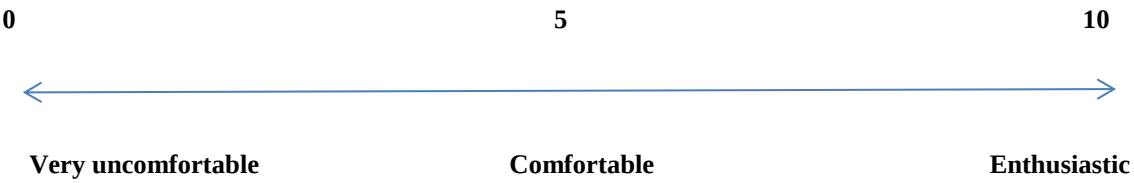
   ☐ Journal Article

   ☐ Colleague

   ☐ Patient

   ☐ Other_____

3. **Corticotomy-facilitated orthodontics is believed to accelerate the rate of tooth movement due to a transient state of osteopenia. The clinical procedure involves raising a full thickness flap and surgically placing small cuts with a round bur into the cortical alveolar bone. If an orthodontist colleague referred you a patient for the procedure described above, how comfortable would you feel about carrying out the procedure? (please mark on the scale below)**



4. **As a Periodontist, do you believe that there are side effects to this procedure?**

   □ No

   □ Yes → Please elaborate

   _____

5. **For what reasons would you decide against undertaking the corticotomy procedure if a referral was made from an orthodontist colleague? (tick all that apply)**

   □ I don't know enough about the procedure

   □ The research is still limited

   □ It's too invasive

   □ I don't believe it will accelerate the treatment time or confer the advantages claimed to the patients

   □ Other _____

6. **What would make you feel more open to undertaking this procedure? (tick all that apply)**

□ Further Research

□ Continuing Education

□ I will wait until it becomes more 'mainstream' within the profession

□ Assurance that there are no adverse side effects

□ Other_____

7. **Have you undertaken the treatment with an orthodontist colleague in your practice? If so how many cases in *total (per year)* have you undertaken?**

□ I have not undertaken any cases

□ Less than 5

□ Between 5 and 10

□ More than 10

8. **Comments**

Thank you for your participation

Appendix 3: Raw data of the double fluorescent labelling and subsequent mineral apposition rate.

Group	Rat	Slide	Distance(μm)	Area(μm^2)	Area/Distance (μm)	20xMag	Average(μm/day)
6	1	1	626.7	66730	106.5	28.3	3.54
		2	1031.2	85716	83.1	22.1	2.76
		3	864.9	65912	76.2	20.3	2.53
		4	633.0	48987	77.4	20.6	2.57
		5	760.4	88451	116.3	30.9	3.87
	2	1	861.0	101375	117.7	31.3	3.91
		2	546.1	51522	94.3	25.1	3.14
		3	728.2	68672	94.3	25.1	3.14
		4	825.1	73051	88.5	23.6	2.94
		5	1100.1	123666	112.4	29.9	3.74
	3	1	916.9	80542	87.8	23.4	2.92
		2	1123.8	118618	105.6	28.1	3.51
		3	796.0	75285	94.6	25.2	3.14
		4	823.9	94178	114.3	30.4	3.80
		5	985.2	119671	121.5	32.3	4.04
	4	1	685.4	26360	38.5	10.2	1.28
		2	1111.6	106012	95.4	25.4	3.17
		3					
		4					
		5					
	5	1	1224.6	146428	119.6	31.8	3.98
		2	1003.2	89654	89.4	23.8	2.97
		3	1158.9	107917	93.1	24.8	3.10
		4	1014.6	101289	99.8	26.6	3.32
		5	1474.3	143626	97.4	25.9	3.24
	6	1	352.5	15307	43.4	11.6	1.44
		2	787.7	96757	122.8	32.7	4.08
		3	1233.0	183230	148.6	39.5	4.94
		4	1115.1	158712	142.3	37.9	4.73
		5	948.9	99880	105.3	28.0	3.50
							3.31
5	1	1	1376.8	104666	76.0	20.2	2.53
		2	641.6	47190	73.6	19.6	2.45
		3	883.9	76235	86.3	22.9	2.87
		4	1107.9	104384	94.2	25.1	3.13
		5	1403.1	142125	101.3	26.9	3.37
	2	1	413.6	20713	50.1	13.3	1.67
		2	367.1	19864	54.1	14.4	1.80
		3					
		4	536.0	29920	55.8	14.8	1.86
		5					
	3	1	646.4	60844	94.1	25.0	3.13
		2	479.7	37871	79.0	21.0	2.63
		3	451.1	41802	92.7	24.7	3.08

		4	403.8	25476	63.1	16.8	2.10
		5	493.4	74400	150.8	40.1	5.01
	4	1	761.9	78923	103.6	27.6	3.44
		2	619.1	60865	98.3	26.1	3.27
		3	962.8	62115	64.5	17.2	2.15
		4	237.3	13865	58.4	15.5	1.94
		5	651.3	50576	77.7	20.7	2.58
	5	1	1075.4	84085	78.2	20.8	2.60
		2	717.4	68404	95.4	25.4	3.17
		3	592.4	41401	69.9	18.6	2.32
		4	453.8	40520	89.3	23.8	2.97
		5	532.5	42254	79.3	21.1	2.64
	6	1	462.2	33872	73.3	19.5	2.44
		2	405.2	25501	62.9	16.7	2.09
		3					
		4					
		5					
4	4	1	674.0	104249	154.7	41.1	5.14
		2	517.5	33022	63.8	17.0	2.12
		3	1026.2	57048	55.6	14.8	1.85
		4	388.3	38751	99.8	26.5	3.32
		5	723.4	66407	91.8	24.4	3.05
	5	1	847.0	99929	118.0	31.4	3.92
		2	702.8	71954	102.4	27.2	3.40
		3	644.1	39653	61.6	16.4	2.05
		4	546.7	28617	52.3	13.9	1.74
		5	783.0	90120	115.1	30.6	3.83
	6	1	716.2	31787	44.4	11.8	1.48
		2	787.4	90911	115.5	30.7	3.84
		3	1207.9	148563	123.0	32.7	4.09
		4	557.8	30997	55.6	14.8	1.85
		5	770.2	52383	68.0	18.1	2.26
	7	1	993.5	64432	64.9	17.3	2.16
		2	1035.1	82947	80.1	21.3	2.66
		3	1318.3	105453	80.0	21.3	2.66
		4	717.5	49227	68.6	18.2	2.28
		5	756.6	57076	75.4	20.1	2.51
	8	1	632.9	32837	51.9	13.8	1.73
		2	1112.0	68377	61.5	16.4	2.04
		3	693.8	63061	90.9	24.2	3.02
		4	596.6	29494	49.4	13.2	1.64
		5	501.0	34106	68.1	18.1	2.26
	9	1	503.3	54009	107.3	28.5	3.57
		2	1057.8	123337	116.6	31.0	3.88
		3	956.4	91286	95.4	25.4	3.17
		4	1269.1	85217	67.1	17.9	2.23

		5	640.6	64513	100.7	26.8	3.35
3	1_B	1	429.0	41435	96.6	25.7	3.21
		2	634.5	34606	54.5	14.5	1.81
		3	461.9	27354	59.2	15.8	1.97
		4					
		5					
	2	1	266.2	9361	35.2	9.4	1.17
		2	422.4	19244	45.6	12.1	1.51
		3					
		4					
		5					
	3	1	378.9	28073	74.1	19.7	2.46
		2					
		3					
		4					
		5					
	4	1	135.7	5034	37.1	9.9	1.23
		2	193.2	14515	75.1	20.0	2.50
		3	189.5	10089	53.3	14.2	1.77
		4	396.7	25203	63.5	16.9	2.11
		5	466.9	31052	66.5	17.7	2.21
	5	1	426.4	50235	117.8	31.3	3.92
		2	623.5	42076	67.5	18.0	2.24
		3	781.1	74786	95.7	25.5	3.18
		4	483.3	29277	60.6	16.1	2.01
		5	629.3	31519	50.1	13.3	1.67
	6	1	529.6	36500	68.9	18.3	2.29
		2	785.1	66818	85.1	22.6	2.83
		3	728.2	83462	114.6	30.5	3.81
		4	457.0	16123	35.3	9.4	1.17
		5					
2	2	1	230.3	8090	35.1	9.3	1.17
		2	238.6	8050	33.7	9.0	1.12
		3	506.3	17604	34.8	9.2	1.16
		4	527.1	20661	39.2	10.4	1.30
		5	557.2	34777	62.4	16.6	2.08
	3	1	1143.7	50450	44.1	11.7	1.47
		2	946.2	33584	35.5	9.4	1.18
		3	421.3	33192	78.8	21.0	2.62
		4	422.0	26768	63.4	16.9	2.11
		5	450.9	14415	32.0	8.5	1.06
	4	1	465.9	35144	75.4	20.1	2.51
		2	306.7	15594	50.8	13.5	1.69
		3	597.8	35655	59.6	15.9	1.98
		4	719.4	36463	50.7	13.5	1.69
		5	526.1	52569	99.9	26.6	3.32

	5	1	419.3	11820	28.2	7.5	0.94
		2					
		3	696.6	29138	41.8	11.1	1.39
		4	301.6	17047	56.5	15.0	1.88
		5	405.9	20234	49.9	13.3	1.66
	6	1	694.5	40470	58.3	15.5	1.94
		2	689.2	55991	81.2	21.6	2.70
		3	760.6	50245	66.1	17.6	2.20
		4	648.8	39067	60.2	16.0	2.00
		5	484.1	24676	51.0	13.6	1.69
	7	1	349.9	23503	67.2	17.9	2.23
		2					
		3	363.1	15318	42.2	11.2	1.40
		4	229.2	6198	27.0	7.2	0.90
		5					
							1.76
1	1	1	454.6	10769	23.7	6.3	0.79
		2	454.2	22371	49.3	13.1	1.64
		3	741.8	48993	66.0	17.6	2.20
		4	695.2	45837	65.9	17.5	2.19
		5	356.1	13151	36.9	9.8	1.23
	2	1	531.1	14833	27.9	7.4	0.93
		2	740.4	31764	42.9	11.4	1.43
		3	408.5	15749	38.6	10.3	1.28
		4	724.2	50248	69.4	18.5	2.31
		5					
	3	1	1058.7	41144	38.9	10.3	1.29
		2	768.9	47483	61.8	16.4	2.05
		3	671.4	43682	65.1	17.3	2.16
		4	1005.3	59440	59.1	15.7	1.97
		5	796.2	51031	64.1	17.0	2.13
	4	1	505.9	15611	30.9	8.2	1.03
		2	221.7	9664	43.6	11.6	1.45
		3	394.3	10857	27.5	7.3	0.92
		4	476.5	24159	50.7	13.5	1.69
		5	179.6	4607	25.7	6.8	0.85
	5	1	580.2	16556	28.5	7.6	0.95
		2	179.6	4601	25.6	6.8	0.85
		3	304.7	6354	20.9	5.5	0.69
		4	388.7	13704	35.3	9.4	1.17
		5	814.7	38835	47.7	12.7	1.58
	6	1	177.5	4341	24.5	6.5	0.81
		2	659.3	18312	27.8	7.4	0.92
		3	931.5	31504	33.8	9.0	1.12
		4	684.3	27089	39.6	10.5	1.32
		5					