Abstract

Title of Thesis: The Effectiveness of Regenerative Therapy in Achieving Complete Hard Tissue Closure of Mandibular Class II Furcations

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Mandibular Class II furcation involvement poses a significant challenge for the treatment and prognosis of mandibular molars. Loss of bone due to advancing periodontal disease in the furcation area with its anatomic configuration leads to continual susceptibility to plaque-related inflammation, breakdown, and attachment loss since adequate debridement and maintenance is difficult. Numerous clinical studies demonstrate regenerative therapies can result in improved overall clinical furation measures with a wide range of clinical success, between 37-91%, for furcation closure. Clinical furcation closure is the most important outcome measurement to ensure proper maintenance by the patient and long-term success of therapy. The purpose of this study was to perform a systematic review of human clinical studies of mandibular Class II furcations treated with regenerative procedures to evaluate hard tissue closure of the furcation, horizontal defect fill (HDF). The search protocol was completed using the OVID database with predetermined inclusion and exclusion criteria, which produced 37 articles for analysis. To be included in this study, surgical re-entry outcome measures for mandibular class II furcations at least 6 months following regenerative therapy in humans had to be reported. Regenerative treatment showed a mean percentage horizontal defect furcation fill ranging

from 34.3-46.4%, when adjusted for pre-treatment means. A subset of 17 studies reported the frequency of complete furcation closure yielding a range of 35.5-52.8% closure. Post-hoc comparisons for the effect on open horizontal defect depth revealed a significant difference between open flap debridement and regenerative theapy: bone replacement graft (BRG), guided tissue regeration (GTR) or combination therapy. Guided tissue regeneration (GTR) and combination therapy (GTR/BRG) were superior to open flap debridement in obtaining hard tissue fill. The BRG group produced imtermediate horizontal defect fill relative to open flap debridement and the GTR and GTR/BRG groups with no significant difference between BRG and the other two regenerative treatment groups. Regenerative therapies, according to summary statistics, yield improvements approaching 50% horizontal defect fill. Early diagnosis and treatment may most likely increase the probability of clinical closure. More studies are necessary evaluating the impact of biologic agents on the predictability of improved clinical outcome measures and furcation closure.

The Effectiveness of Regenerative Therapy in Achieving Complete Hard Tissue Closure of Mandibular Class II Furcations

by
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Preface

Mandibular Grade II furcation involvement poses a significant challenge for the treatment and prognosis of mandibular molars. Loss of bone due to advancing periodontal disease in the furcation area with its anatomic configuration leads to continual susceptibility to plaque-related inflammation, breakdown, and attachment loss since adequate debridement and maintenance is difficult. Hence, regenerative therapy directed towards furcation entrance closure, thereby eliminating the progression of an inaccessible plaque-related inflammatory destruction within the furcation is desired. Guided tissue regeneration is an example of a regenerative technique and utilizes barrier membranes to direct the growth of new bone, cementum, and periodontal ligament at previously diseased sites that have insufficient volumes to support a healthy periodontium. Bone replacement grafts (BRG) have also been used in conjunction with barrier techniques or alone to fill the furcation defects. Combination therapies utilizing bone replacement graft in conjunction with membranes has also been clinically successfully for closure of furcations. There have been numerous clinical studies demonstrating that regenerative therapies can result in an improvement of overall clinical measures with a wide range of clinical success reported between 37% - 91% for furcation closure[36]. When evaluating the success of regenerative therapy, clinical closure of the furcation is truly the most important outcome measurement to ensure proper maintenance by the patient and long-term success of therapy. The purpose of this systematic review is to evaluate hard tissue closure of the furcation as the primary outcome measurement of regenerative therapies

Dedication

This thesis is dedicated to my family – my mother and father, who provided me with the foundation of hard work and values, always supportive and loving, and most importantly, pushed me to be the best; my sister and brother, who always bring a smile to my face and are always there for me. I dedicate this to my fiancé who has been my "rock" through this time and a constant reminder of what is truly important in life.

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BRG – Bone replacement Graft

GTR – Guided tissue regeneration

GTR/BRG – Combination therapy

OFD – Open flap debridement

Introduction

Furcation involvement as a result of advanced periodontal disease has always posed a major clinical challenge to the periodontist. Bacterial invasion and subsequent destruction of the surrounding structures leading to furcation invasion make it inaccessible for proper maintenance and long-term stability of the molar tooth. Furcation involvement is common with an incidence of 35% in mandibular molars and 90% in maxillary molars [1]. Furcation involvement has a significant effect on tooth prognosis. Once the horizontal component at the bifurcation is involved, more than a third of the total periodontal attachment is already lost due to the coronal detachment against the root trunk and progressing into the furcation defect [2]. Using attachment loss as a determinant in prognosis among other important local factors, molars present a unique array of anatomic, technical, and biological factors to consider once the furcation becomes involved. These issues truly make successful surgical treatment and long-term maintenance an often frustrating and difficult task for the clinician.

Several treatments have been attempted to obtain furcation closure garnering bone fill by bone grafts and guided tissue regeneration to improve Grade II furcation lesions [3]. True periodontal regeneration is the histological formation of new bone, new cementum, and a new periodontal ligament over previously exposed root surfaces [4]. Regenerative therapies have been aimed at not only closing the furcation by filling it, but more specifically by attaining a gain in periodontal attachment apparatus to reduce and eliminate the horizontal defect. Most importantly, this contributes to a subsequent decrease in pocket depth as health is achieved by allowing for proper maintenance of the furcation.

Currently, there are multiple classification schemes to measure horizontal and vertical levels of furcation involvement. Glickman (1953) classified the severity of furcation involvement into different grades ranging from I-IV to aid in communication amongst practitioners for treatment purposes [5]. Grade I is incipient, while Grade II has a "definite horizontal component, resulting in a probeable area, but bone remains attached to the tooth so that multiple areas of furcal bone loss, if present, do not communicate." Grade III and IV refer to bony defects that now have no attachment to the furcation area, with a "through-and-through" bone loss pattern. Hamp [6] created a more quantitative system with 3 degrees of furcation involvement. Degree I is defined as horizontal loss less than 3mm, degree II as loss exceeding 3 mm, but not encompassing total width of furcation, and degree III as through-and-through loss in the furcation. The vertical loss was further delineated by Tarnow and Fletcher (1984) into subclasses based upon probeable depth. Classification consisted of subclass A with 0-3mm PD, B with 4-6mm PD, and C with >7mm PD. The extent of furcation invasion is often difficult to diagnose, and therefore a combination of radiographs, clinical probing using a curved Nabers probe, and bone sounding must be utilized simultaneously [7].

Long-term studies have documented retention after surgical and non-surgical treatment methods of furcated molars affected by periodontal disease. An unfavorable response to therapy of furcated molars is a common theme documented in the periodontal literature, when compared to non-furcated or non-molar teeth. Hirschfeld and

Wasserman [8] followed a group of 600 private practice patients for an average of 22 years following active initial scaling therapy with maintenance appointments every 4 to 6 months. Tooth retention after therapy was dependent on case type, with furcation-involved teeth accounting for 31.4% of total teeth lost. The degree of furcation involvement and multiple therapies for furcations were not compared in this study. Many more teeth were lost in the downhill and extreme downhill groups, as compared to the well-maintained group. A trend was observed towards losing the furcation-involved molars first, with the longest retention of the mandibular cuspids and bicuspids. McFall's study in 1982 followed 100 periodontally-treated patients for an average of 19 years with similar trends in tooth loss[9]. Surgical therapy was provided during the active phase including root amputations, osseous surgeries, and flap debridements. Over half of the total maxillary and mandibular furcated molars (56.9%) were lost during the maintenance period. Maxillary molars closely followed by mandibular molars were lost most after surgical treatment, while mandibular cuspids were the least likely to be lost. Despite the anatomic barriers of proper therapeutic debridement, multiple studies have shown that with maintenance, furcated molars can be retained. However, the longitudinal studies do not contain sufficient data to draw conclusions based on degree of furcation involvement and success of initial non-surgical therapy alone [7]. Depending on the furcation status as well as patient and treatment-related factors, molars continue to be at an increased risk of further attachment loss and eventual tooth loss. The focus now should be at perfecting the regenerative therapies available in bone replacement grafts and guided tissue regeneration techniques for bone fill in the furcation and restoration to health.

Bacterial plaque and the consequent inflammatory process leads to breakdown of the supporting connective tissue and bone starting at the crestal height of bone and leading to attachment loss in the furcation. The pathogenesis of periodontal disease in the furcation is associated with downgrowth of subgingival plaque [10]. Poor subgingival plaque control is often seen with molars due to the inaccessibility of the bacteria within the furcation. It was found that with proper instruction on plaque control, molars with furcation involvement were plaque-free at the margin for a distance of 0.5-2.5mm below the margin corroborating with results found with the use of a round interdental brush and proper hygiene instruction [11]. Submarginal gingivitis was often undiagnosed due to lack of signs of classical inflammation at the gingival margin. However, periodontal probing causing profuse bleeding and pain strongly correlated with presence of submarginal plaque and inflammation. Waerhaug compared the loss of attachment observed on furcal surfaces and outer surfaces of molars and found that there was greater loss on furcal surfaces (62.8%) than outer surfaces (47.3%). The plaque front from the most apical border of plaque to the most coronal attachment fibers for furcal and outer surfaces, is 0.91mm and 0.86mm respectively [10]. The slightly increased distance and observation of measurements of 2mm or greater found in furcations (19 versus 6 sites) were explained by the destructive nature on the attachment fibers from other adjacent root(s) or periodontal abscesses. The goal of furcation therapy is to make subgingival plaque accessible to instrumentation through early diagnosis and direct surgical access to the affected surfaces before further lysis and apical migration of attachment fibers.

Numerous barriers exist anatomically to proper non-surgical and surgical debridement of the furcation lesion. Furcation morphology is a major complicating factor in relation to distance from CEJ, furcation and root shape, and other associated anatomic anomalies. Bower reported furcation diameter to be less than 1mm 81% of the time, with 58% being less than 0.75mm [12]. Another study reported similar numbers by revealing 49% less than 0.75mm in width [13]. The average curette blade width ranges from 0.75-1.1mm, and therefore cannot properly adapt to the furcation entrance resulting in improper instrumentation. Bower also found that concavities were present 100% of the time in furcal aspects of the mesial root with an average depth of 0.7mm, and 99% of the time in the distal root with an average depth of 0.5mm in mandibular molars [14]. Maxillary molars also presented with concavities on the furcal aspects of the mesial, distal, and palatal roots, of average 94%, 31%, and 17% respectively. Due to these anatomic hindrances, the curette alone may not be suitable for adequate planning of the root surface, and narrower tools or ultrasonic tips may be needed as well as proper access to the site for success.

Dunlap and Gher looked at root surface area and separation from the root trunk of the mandibular first molar [2]. When cross-sections were taken in 1mm increments, the mesial root always presented with an hourglass shape due to the mesial and distal concavities, as well as being larger in a B-L dimension and narrower M-D than the distal root. Mean root length in the study was 14.4±1.1mm, and about 50% of the total root surface area was located in the coronal 6mm of root length. The root trunk surface area accounted for the lowest mean when compared to the mesial and distal roots, however still accounted for 30.5% or one-third of the total root surface area. The largest mean surface area occurred at or just below the level of root separation found at 4.0±07mm apical to the CEJ, with no root trunk being longer than 6mm. In the same group of teeth evaluated, buccal and lingual concavities of the mandibular first molar were first found to be at 0.7mm and 0.3mm apical to the CEJ with progressive deepening towards the furcation. Additionally, Wheeler looked at approximate distances where the furcation entrances began and reported the buccal entrance at 3mm apical to the CEJ and the lingual entrance at 4mm apical to the CEJ. The reported measurements can correlate our clinical probing depths with the severity of furcation invasion and amount of remaining attachment that may be present. If probing depths are greater than 5-6mm from buccal and lingual furcation areas of the molar, a through-and-through involvement may be suspected [2, 15]. Once the furcation is diagnosed and probing depths of 5-6mm or greater is observed, less than 50% of the root surface attachment remains as can be deduced by Dunlap's study. This information stresses the early detection, diagnosis, and treatment of periodontally affected molars for preservation of the attachment and prevention of future breakdown at the furcation.

Intermediate bifurcation ridges have also been suspected to be an etiologic agent in plaque accumulation at the furcation. Everett first reported a 73% incidence in mandibular molars, occurring at the bifurcation and crossing from the mesial surface of the distal root to the mesial root primarily in cementum [16]. These ridges may contribute to ineffective plaque control by the patient and complications in root planning during initial therapy by the clinician. Cervical enamel projections and enamel pearls have also been identified as predisposing etiologic agents in furcation involvement. Masters and Hoskins (1964) reported 28.6% on mandibular and 17% on maxillary buccal surfaces of molars, with CEP's occurring in > 90% of isolated mandibular bifurcation involvement [17]. The incidence of CEP's was reported highest in mandibular second molars, followed by maxillary second molars, mandibular first molars, and maxillary first molars. Other reports show a significant correlation between CEP's and furcation invasion[18] when higher grade enamel projections are found, while others show that there is no correlation at all [19]. Connective tissue attachment does not attach to enamel surfaces, and if an enamel projection or pearl is present in the area of the furcation, only a long junctional epithelium will form at best. This attachment may be more susceptible to breakdown by plaque-induced inflammation [20] and may initiate and progress into the formation of a deep constricted pocket [17].

Accessory and lateral pulp canals that are also located in the furcal region have also been linked to furcation invasion. Pulpal disease or inflammation must always be ruled out when looking at isolated furcation defects for proper therapy and resolution. Different studies report accessory canals ranging from 27-76% [21-23] of maxillary and mandibular molars, suggesting that pulpal disease may affect the surrounding periodontium.

Besides the anatomic component of molar furcations that assist in harboring bacterial biofilm, the inability of operators to adequately access and remove all root accretions is another barrier to defect resolution. Bacterial endotoxin is a major virulence factor found in plaque contributing to periodontal disease present on the root surface. Hence, one of the goals of scaling and root planing is to decrease and remove endotoxin from the involved root surface as shown by Jones and O'Leary when compared to nontreated controls [24]. Calculus is another major contributing factor that must be removed by root instrumentation to prevent a secondary site of bacterial accumulation. Scaling and root planing of furcation teeth are much harder than single-rooted teeth, even with an open flap approach. When comparing the open and closed approaches, Caffesse found greater residual calculus was left behind following a closed scaling and root-planing session (S/RP) and greatest at the levels of the CEJ or anatomic grooves, fossae, and furcations [25]. The probing depth ranges also directly correlated with amount of residual calculus. When PD ranges 1-3mm, open and closed were equally effective. When PD ranges from 4-6mm, 43% were calculus-free with S/RP, and 76% when combined with an open flap. Once the pocket depths were greater than 6mm, both closed and open techniques produced poor results, 32% and 50% calculus-free respectively. Multiple authors have compared the two approaches only looking at effective calculus removal in the furcation area under a stereomicroscope [26, 27]. Results show superior root instrumentation with open root planing, providing evidence for surgical therapy. When operator experience was simultaneously evaluated, Fleisher concluded that open surgical access and operator experience leads to better calculus removal [28]. However, complete calculus removal from the furcation is limited with conventional procedures alone as observed in pocket depths greater than 4mm.

In the past, the furcation diagnosis often meant a hopeless diagnosis and led to extractions. Currently, multiple treatments exist from non-surgical therapy with scaling and root planing, to surgical therapies including open flap debridement, gingivectomy and apically-positioned flaps, osseous surgery, root amputation or tooth resection, and tunneling procedures. Due to the inability to remove all of the toxic accretions from the root surfaces, surgical therapy is preferred to increase the chance of success. Longitudinal studies of the past revolved around the goal of resection of the gingival tissues and underlying bone in order to apically position and allow for proper maintenance. Osteoplasty and ostectomy is done to eliminate bony defects by creating ramps and reduce the horizontal defect depth by allowing for apical adaptation of gingival tissues[29]. McFall reported earlier lost over 50% of the total molars with diagnosis of furcal involvement during the maintenance period ranging up to 19 years after treatment with osseous resective surgery[9]. Tunneling procedures have been advocated in the past for full exposure of the furcation for advanced Grade II/III defects when roots are divergent for proper brush maintenance, extended root length, and optimal plaque control by the patient. However, it has been shown that these teeth are more prone to root caries and prone to repocket in the future [6]. Odontoplasty of the coronal portion of the tooth is often recommended and often completed simultaneously with surgery in order to improve access for plaque control. Root resection, hemisection, and bicuspidization are all aggressive options to eliminate the furcation. Endodontic and restorative failures are additional expenses and concerns for the clinician and the patient when these therapies are considered [7].

Given the limitations of osseous resective procedures, there has been a trend toward regenerative and implant therapies. Increased success and availability of regenerative and implant techniques have placed the above described resective therapies down the list of ideal treatment options. Bone grafting, guided tissue regeneration, and combination therapy have gained popularity and are now considered treatments of choice for Grade II furcated molars to rebuild the supporting structures that have been lost due to periodontal disease. Guided tissue regeneration (GTR) is defined by the utilization of barrier membranes alone to direct the growth of new bone, cementum, and periodontal ligament at previously diseased sites that have insufficient volumes to support a healthy periodontium. Bone replacement grafts (BRG's) have also been used alone to fill the defect, or in conjunction with membranes also called combination therapy. There have been numerous studies and reviews demonstrating that regenerative therapies can result in an improvement of overall clinical measures with a wide range of success reported between 37-91% (Evans 1996). McClain and Schallhorn compared barrier regeneration of ePTFE membranes with and without composite osseous grafting, showing increased success with combination therapy [30]. Bowers used combination therapy with an ePTFE membane and demineralized freeze-dried bone allograft in a 24-month study on mandibular Grade II furcation defects. The study reported 74% complete clinical closure, with 68% being reduced to Grade I. Furcation closure was more frequent with early Grade II furcations, and closure was least frequent when vertical or horizontal bone loss exceeded 5mm. Although success was found in advanced defects, the severity of furcation involvement will continue to affect the prognosis of regenerative therapy and long-term maintenance.

Bone fill in the furcation is a clinical measure that surgeons associate with success on re-entry. However, periodontal regeneration is confirmed by histologic analysis of new bone, cementum, and periodontal ligament over previously diseased root surfaces as shown apical to a calculus notch. Harris first demonstrated this in a furcation defect in a case report demonstrating the histologic success of combination guided tissue regenerative therapy using allograft composite graft and absorbable membrane [31]. Histologic regeneration has also been demonstrated by Ridgway, Mellonig, and others by taking tooth en-bloc sections utilizing combination therapy with beta-TCP graft, rh-PDGF-BB growth factor, and collagen membrane [32, 33]. Combination therapy using xenograft bovine bone graft and collagen membrane was also shown histologically to regenerate new attachment and others in furcation defects [34]. Bone replacement grafts alone have also demonstrated the same principles of periodontal regeneration with histologic evidence by Camelo *et al* using dFDBA and rh-PDGF-BB[35]. Multiple trials using different bone grafts with/without membranes, and often using growth factors to enhance cell migration to the defect site, have revealed true periodontal regeneration at the site of Grade II furcation defects and demonstrated proof that growth of a new periodontal apparatus is possible.

Furcation closure with hard tissue fill is truly the most important clinical determinant for evaluating success in grafting and regenerative therapies to properly ensure maintenance by the patient and long-term success. A past review by Evans *et al* have tried to report clinical closure of the furcation by defining it as a reversion to a Grade I furcation defect or lack of horizontal probing depth, which was measured as <1mm in a previous analysis comparing bone replacement grafts, or $\geq 50\%$ defect fill [36]. However, percentage defect fill within a three-dimensional space of a furcation depending on the morphology of the hard tissue fill may not necessarily correspond to a furcation reversion to Class 0 or 1. When comparing GTR against OFD, Jepsen and Eberhard concluded that complete furcation closure was unpredictable due to the sparse data and limited reporting available [37]. Many trials only evaluate mean probing depth reductions, which may not directly correlate with adequate bone fill to close the Grade II furcation defect that was initially present.

The purpose of this review is to systematically evaluate how often hard tissue furcation closure is truly achieved by surgical re-entry confirmation in periodontal Grade II furcation defects by comparing bone replacement grafts, guided tissue regeneration, and combination therapies. Due to the wide ranges of success and therapies compared with no clear conclusions reported concerning furcation closure, this systematic review will offer more information on clinical expectations and parameters of successful regeneration. This will allow the practitioner to make an educated evidence-based decision about long-term prognosis and therapy for Grade II furcated mandibular molars.

Materials and Methods

Searching protocol:

The Medline OVID database was searched for experimental trials to include in the systematic review. The objective was to identify articles in the English language where regenerative therapy was used for the treatment of mandibular Class II furcations.

The search strategy for Medline via OVID database utilized multiple fields in list form and is listed below in detail:

Database: Ovid MEDLINE(R) 1948 to Present with Daily Update
Search Strategy:
----
1 Furcation Defects/ (626)
2 furcation*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (1227)
3 1 or 2 (1227)
4 graft.mp. or Transplants/ (180231)
5 grafting.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (42385)
6 Guided Tissue Regeneration, Periodontal/ or GTR.mp. (2470)
7 regeneration.mp. or Bone Regeneration/ (82572)
8 regenerative therapy*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (595)
9 Guided Tissue Regeneration/ (1017)
10 Bone Transplantation/ or bone graft.mp. (25390)
11 allograft.mp. or Transplantation, Homologous/ (85577)
12 intrabony.mp. (587)
13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (337589)
14 3 and 13 (480)

The search strategy was completed on OVID search, as in Figure 1. Only articles in English were considered for review. Furcation defect(s) and Furcation were key search terms to narrow down the studies by defect type. These studies were cross-matched with a variety of regenerative terminology as listed in #4-12. The total number of studies from this initial search revealed 468 potentially relevant studies. The selection of studies for inclusion into this systematic analysis after abstract and full-text reviews is shown in Figure 1. For the 468 articles that the OVID search produced, abstracts were reviewed and excluded if they were not consistent with study duration, surgical re-entry was not performed, and did not look at clinical outcome parameters.

Study selection:

Eligibility into the study in the systematic review included

- randomized clinical trials and controlled case series
- minimum 6-month follow-up of patients
- data available for mandibular molar Grade II furcation treatment
- **outcome measurements made at surgical re-entry**

The various interventions that were analyzed for comparison included open flap debridement, guided tissue regeneration, bone replacement graft, and combination therapy consisting of a wide range of biomaterials. No study was excluded based on the therapies compared. Of the 468 articles, 61 articles were considered for full-text review. Any studies that looked at growth factors in combination with furcation therapy were excluded, but will be looked at separately. Refer to Table 1 for detailed descriptions of excluded studies after full-text review. The thorough search process yielded 37 studies to be included for statistical analysis in this systematic review. The search was exhausted and checked by two examiners separately to confirm the final studies to be included in the review. The same second examiner also abstracted data and confirmed correct data from the included studies to eliminate any errors in extraction and statistical calculation.

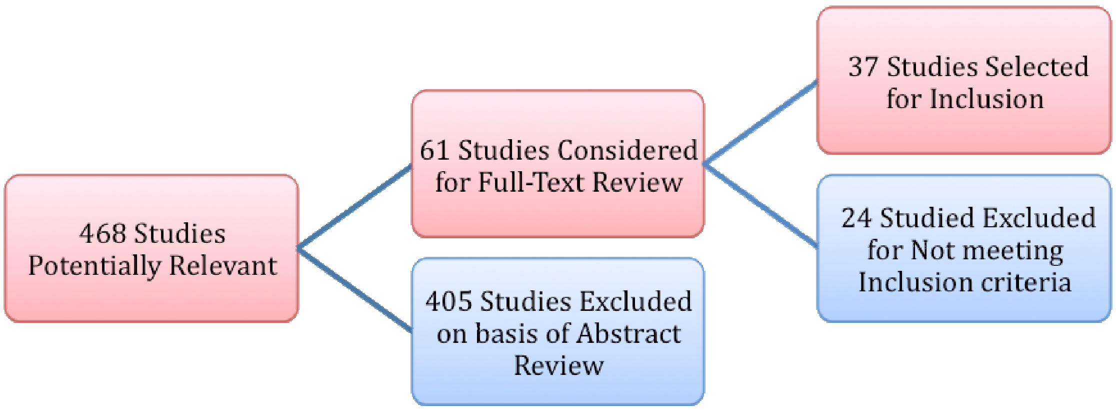

Figure 1: Study Selection Process

Breakdown of Excluded Studies	
Reference	**Reason for Exclusion**
Hoffman 2006, Howell 1997, Jepsen 2004, Lekovic 2003, Meyle 2004, Nevins 2003	Use of Growth Factors (EMD, PRP, GEM21s)
Flores-de-Jacoby 1991, van Steenberghe 1989	Not in English
Anderegg 1991, Flanary 1991, Ling 2000, Vest 1999, Yamanouchi 1995,	Combined Data with non-Grade II mandibular molar defects, wrong defect type
Garrett 1994, Mellonig 1976, Sepe 1978, Snyder 1983, Vernino 1999, Akbay 2005	Inadequate or No Data provided
Camelo 2000, Pontoriero 1988, Van Swol 1993	No surgical re-entry or inadequate re-entry duration
Yukna 1997, Tsao 2006	Longitudinal Report Data Reported in prior study

Table 1 : References of excluded studies and reasons for exclusion for analysis

Outcome Measures and Statistical Analysis:

The primary outcome measurement compared was change in open horizontal probing defect depths to evaluate clinical bone fill at the level of the furcation. Other variable measurements included changes in open vertical probing, closed horizontal probing, soft tissue probing depth reductions and clinical attachment level gain. Table 2 provides the included studies with details of study design and surgical arms, with outcome parameters that were available for analysis. Multiple treatment arms were treated as separate entities and classified according to four different treatment groups:

1) Open flap debridement (OFD),

2) Guided tissue regeneration (GTR),

3) Bone replacement graft (BRG),

4) Combination therapy

The statistical analysis was completed to compare differences in soft tissue measurements, as well as open hard tissue measurements, among the four treatment groups. The soft and hard tissue pre-treatment and post-treatment mean differences were converted to percentage defect fill. The treatment groups were compared against each other to conclude which regenerative therapy produces greatest bony defect fill horizontally and vertically.

Since furcation defect characteristics are often correlated with clinical outcomes, all measures were submitted to an analysis of covariance, adjusting for pretreatment means. All outcome variables were submitted to an analysis of covariance, adjusting for mean pretreatment measurements, using a least-squares regression model (JMP9, Cary, NC). Post-hoc comparisons of treatment groups were made using a Tukey-Kramer HSD test at an alpha level ≤ 0.05.

Frequency of furcation closure:

Furcation closure with the regenerative therapies at the time of surgical re-entry in the included studies was reported in 17 out of the 37 total studies included in this review. The total numbers reported completely closed or converted to a Grade I furcation was considered for analysis and data by treatment provided is shown in Table 7. Table 8 provides the calculations of percentage frequency of closure for each of the four treatment groups.

Reference	**Re-entry, mos**	**Design**	**N1**	**Intervention**	**N2**	**Intervention**	**Outcomes**	
							Soft Tissue	**Hard Tissue**
GTR								
Da Costa-Noble 1996	6	RCT	8	Elastin-Fibrin Matrix			PD	HPDD
Demolon 1994	12	RCT	22	ePTFE			PD, HPD	VPDD, HPDD
Garrett 1990	12	RCT	15	Dura mater			PD	VPDD, HPDD
Lekovic 1998	6	RCT Split-mouth	14	CTG			PD, CAL	VPDD, HPDD
Machtei 1994	12	RCT	30	ePTFE			PD, CAL	HPDD
Machtei 2003	12	RCT	19	Goretex			PD, CAL	VPDD, HPDD
Zahedi 2003	12	CCS	40	DPPA-CL Collagen			PD, CAL	VPDD, HPDD

Table 2: Studies Included for Analysis and Outcome Measures Available

Reference	Re-entry, mos	Design	N1	Intervention	N2	Intervention	Outcomes	
							Soft Tissue	Hard Tissue
OFD/GTR								
Lekovic 1991	6	RCT, Split-mouth	12	OFD	15	CTG	PD, CAL	VPDD, HPDD
Lekovic 1989	6	RCT, Split-mouth	12	OFD	12	ePTFE	PD, CAL	VPDD, HPDD
Mellonig 1994	6	RCT, Split-mouth	11	OFD	11	Goretex	PD, CAL	VPDD, HPDD
Paul 1992	6	RCT, Split-mouth	14	OFD	14	Collagen	PD, CAL	VPDD, HPDD
Prathibha 2002	6	RCT, Split-mouth	10	OFD	10	Tefgen	CAL	VPDD, HPDD
Wang 1994	12	RCT, Split-mouth	12	OFD	12	Collagen	PD, CAL	HPDD
OFD/BRG								
Kenny 1988	6	RCT, Split-mouth	23	OFD	23	Porous HA	PD	VPDD. HPDD
Pepelassi 1991	6	RCT, Split-mouth	13	OFD	13	Composite graft	PD, CAL, HPD	VPDD, HPDD
OFD/Combination								
Houser 2001	6	RCT, Split-mouth	13	OFD	18	Bio-Oss/Bio-Guide	PD, CAL, HPD	VPDD, HPDD

Table 2: Studies Included for Analysis and Outcome Measures Available

Reference	Re-entry, mos	Design	N1	Intervention	N2	Intervention	Outcomes	
							Soft Tissue	Hard Tissue
GTR/GTR								
Blumenthal 1993	12	RCT, Split-mouth	12	Collagen	12	ePTFE	PD, CAL, HPD	VPDD, HPDD
Bouchard 1993	12	RCT, Split-mouth	12/11	CTG	12/11	ePTFE	PD, CAL, HPD	VPDD, HPDD
Couri 2002	6	RCT, Split-mouth	13	DFDBA + ePTFE	13	DFDBA + MGCSH	PD, CAL	VPDD, HPDD
Dos Anjos 1998	6	RCT, Split-mouth	15	Cellulose	15	ePTFE	PD, CAL	VPDD, HPDD
Pruthi 2002	12	RCT, + Split-mouth	17	ePTFE	17	Collagen	PD, CAL	VPDD, HPDD
Scott 1997	6	RCT, Split-mouth	12	LAMBONE	12	ePTFE	CAL	VPDD, HPDD
Villaca 2004	12	RCT, Split-mouth	10	ePTFE	10	Modified ePTFE	PD, CAL	VPDD, HPDD
Yukna 1996	11.1	RCT, Split-mouth	27	OFD	27	Collagen	PD, CAL	VPDD, HPDD
Yukna 1996 (cont)	11.1	RCT, Split-mouth	32	Collagen	32	ePTFE	PD, CAL	HPDD
Yukna 1992	12	RCT, Split-mouth	11	ePTFE	11	FDDMA	PD, CAL	VPDD, HPDD

Table 2: Studies Included for Analysis and Outcome Measures Available

Reference	Re-entry, mos	Design	N1	Intervention	N2	Intervention	Outcomes	
							Soft Tissue	Hard Tissue
GTR/Combination/OFD								
Belal 2005	12	RCT	10	OFD	10	PGA/PLA	PD, CAL	HPDD
					10	PGA/PLA + HA		
					10	CTG		
					10	CTG + HA		
Tsao 2006	6	RCT	9	OFD	9	MBA	PD, CAL	VPDD, HPDD
					9	Collagen		
Lekovic 1990	6	RCT, Split-mouth	15	PTF membrane	15	PTF membrane + PHA	PD, CAL	VPDD, HPDD
Luepke 1997	6	RCT, Split-mouth	14	Resorbable membrane	14	Resorbable membrane + DFDBA	PD, CAL, HPD	VPDD, HPDD
SImonpietri-C 2000	6	RCT, Split-mouth	15	Cellulose	15	Cellulose + ABB	PD, CAL	HPDD
Wallace 1994	6	RCT, Split-mouth	7	ePTFE	10	ePTFE + DFDBA	PD, CAL	VPDD, HPDD
GTR/BRG								
Yukna 2001	6	RCT, Split-mouth	27	ePTFE	27	Bioactive glass	PD, CAL, HPD	VPDD, HPDD
BRG/BRG								
Yukna 1994	6-12	RCT, Split-mouth	15	HTR polymer	15	AOC	PD, CAL	VPDD, HPDD
BRG/Combo								
Lyons 2008	9	RCT	9	PLA + DFDBA	11	DFDBA	PD, CAL, HPD	HPDD
Combo/Combo								
Lamb III 2001	9	RCT	12	Non-porous Teflon	12	Porous Teflon	PD, CAL, HPD	VPDD, HPDD
Yamaoka 1996	12	RCT, Split-mouth	15	ePTFE + DFDBA	15	DUIS + DFDBA	PD, CAL, HPD	VPDD, HPDD

Table 2: Studies Included for Analysis and Outcome Measures Available

Results

Table 3 provides adjusted and non-adjusted effect for initial defect mean measurements with an analysis of covariance, using a least-squares regression model. Table 4 provides overall means and highlights which treatment group performed best for each clinical outcome variable. Table 5 and 6 provide the mean ± standard deviation for each outcome measure separately by treatment group (Open Flap Debridement, Guided Tissue Regeneration, Bone Replacement Graft, and Combination therapy) separated out by hard tissue measurements and soft tissue measurements. Figure 2 illustrates the overall trend for regenerative therapies of open hard tissue defect fill measures as compared to open flap debridement.

Open Horizontal Defect Depth

For horizontal defect fill, the results revealed a significant main effect for treatment ($F = 9.6$, $p \leq 0.0001$). Post-hoc comparisons revealed a significant difference between the open flap debridement group and the other three regenerative therapies. Additionally, there was no significant difference between guided tissue regeneration, bone replacement graft, and combination therapy, or between open flap debridement and bone replacement graft. Hence, BRG therapy was an intermediate treatment between OFD and GTR/Combination therapies.

Open Vertical Defect Depth

Similar to open horizontal defect depth, an association was found with initial probing depth and defect resolution. Therefore, an analysis of covariance adjusting for the mean pretreatment vertical probing depth was completed using a least-squares regression model

(JMP9, Cary, NC). For vertical fill, the results revealed no significant effect for treatment ($F = 1.69$, $p \leq 0.1858$). However, when an unadjusted ANOVA analysis was performed, there was a significant effect for treatment, with post-hoc comparisons of treatment groups using Tukey-Kramer HSD test, at an alpha level ≤ 0.05, showing that the BRG group revealed a significant difference compared to the other three treatment groups.

Closed Probing Depth (Vertical)

For closed vertical probing depth, the same calculations with adjustment for mean pretreatment initial probing depth with a least-squares regression model revealed a significant effect for treatment ($F = 16.74$, $p \leq 0.0001$). Post-hoc comparisons of treatment groups made using Tukey-Kramer HSD test at an alpha-level ≤ 0.05 further revealed a significant difference between open flap debridement and the remaining three regenerative groups. Comparisons between treatment groups revealed that there was no significant difference between the BRG, OFD, and Combination groups, nor between the OFD and BRG treatment groups. As with open horizontal defect fill, this shows that BRG therapy was an intermediate treatment between OFD and GTR/Combination therapies.

Closed Horizontal Probing Depth

For closed horizontal probing depth, the same calculations with adjustment for mean pretreatment initial probing depth with a least-squares regression model revealed a non-significant effect for treatment. Post-hoc comparisons of treatment groups made using Tukey-Kramer HSD test at an alpha-level ≤ 0.05 further revealed no significant difference between the four treatment groups.

Clinical Attachment Level

For clinical attachment level, the same calculations with adjustment for mean pretreatment initial clinical attachment levels with a least-squares regression model revealed a non-significant effect for treatment. ($F = 1.54$, $p \leq .23$) Post-hoc comparisons of treatment groups made using Tukey-Kramer HSD test at an alpha-level ≤ 0.05 further revealed no significant difference between the four treatment groups.

Furcation Closure:

Table 7 displays the reported furcation closure data available. From the total 37 included studies, only 17 studies reported incidence of furcation closure or conversion to Class I at surgical re-entry. Total numbers are listed for each study and sorted by treatment group. Table 8 shows frequency of closure for each treatment. Guided tissue regeneration was the treatment group with greatest number of defects (n=293) available for analysis, with open flap debridement with the least number of defects (n=56). When comparing percentage of furcation closure, bone replacement grafts had the highest frequency of furcation closure of 52.5%, followed by combination therapy with 45.9%. Open flap debridement had the lowest frequency of closure of 7.1%.

	Non-Adjusted Effect Test			Adjusted Effect of Initial Pre-treatment Measurements		
	F ratio	DF	P value	F ratio	DF	P value
Hard Tissue						
Horizontal Defect Fill	8.58	4	<.0001*	9.63	3	<.0001*
Vertical Defect FIll	3.44	3	0.0260*	1.69	3	0.1858
Soft Tissue						
Probing Depth Reduction	7.78	3	0.0002*	16.74	3	<.0001*
Clinical Attachment Level Gain	2.10	3	0.1139	1.54	3	.2255
Horizontal Probing Depth Reduction	1.79	3	0.1981	1.10	3	0.3852
***P<.05 statistically significant**						

Table 3: ANOVA Effects of Treatment Group Non-adjusted and Adjusted for pre-treatment means by Analysis of Covariance

Treatment Group	**Hard Tissue Measurements % Defect Fill**		**Soft Tissue Measurements % Defect Resolution/Fill**		
	Horizontal Defect Fill	Vertical Defect Fill	Vertical Probing Depth Reduction	Clinical Attachment Level Gain	Horizontal Probing Depth Reduction
Open Flap Debridement	15.49 [B]	19.90 [B]	22.16 [B]	7.58 [A]	8.90 [A]
Guided Tissue Regeneration	39.13 [A]	32.01 [B]	42.21 [A]	23.13 [A]	42.55 [A]
Bone Replacement Graft	34.33 [A,B]	71.44 [A]	34.84 [A,B]	21.98 [A]	40.35 [A]
Combination Therapy	46.36 [A]	36.75 [A,B]	40.91 [A]	25.99 [A]	46.46 [A]

[A,B]: not connected by the same letter are significantly different

Table 4: Overall Outcome Means for Treatment Group

Treatment Group	**Horizontal Defect Fill**	**Std Dev**	**Vertical Defect Fill**	**Std Dev**
Open Flap Debridement	15.49 [B]	11.26	19.90 [B]	24.11
Guided Tissue Regeneration	39.13 [A]	20.52	32.01 [B]	29.49
Bone Replacement Graft	34.33 [A,B]	13.73	71.44 [A]	10.01
Combination Therapy	46.36 [A]	15.50	36.75 [A,B]	34.31

[A,B]: not connected by the same letter are significantly different

Table 5: Hard Tissue Defect Fill Mean Measurements for Treatment Group

Treatment Group	% Vertical Probing Depth Reduction	Std Dev	% Clinical Attachment Level Gain	Std Dev	% Horizontal Probing Depth Reduction	Std Dev
Open Flap Debridement	22.16 [B]	11.27	7.58	15.53	8.90	17.72
Guided Tissue Regeneration	42.21 [A]	14.24	23.13	17.00	42.55	19.18
Bone Replacement Graft	34.84 [A,B]	8.63	21.98	17.34	40.35	29.51
Combination Therapy	40.91 [A]	13.85	25.99	16.32	46.46	17.18

Table 6: Soft Tissue Defect Fill Mean Measurements for Treatment Group

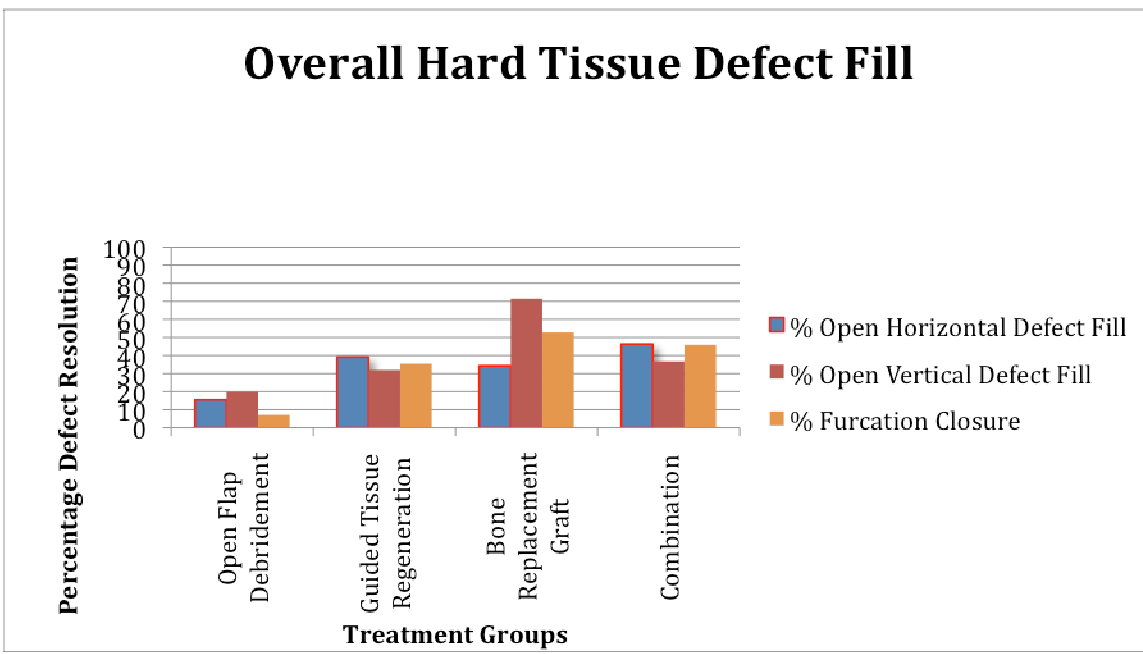

Figure 2: Overall Measures of Hard Tissue Closure and Defect Fill

Reference	Treatment Group*	Convert to Class 0	Convert to Class 1	# Total
Belal 2005	1	0	2	10
	2	4	8	20
	4	8	7	20
Bouchard 1993	2	6	N/A	22
Blumenthal 1993	2	0	N/A	24
Da Costa-Noble 1996	2	2	4	8
Garrett 1990	2	3	N/A	15
Houser 2001	1	N/A	1	13
	4	N/A	14	18
Mellonig 1994	1	0	N/A	11
	2	1	N/A	11
Pepelassi 1991	1	0	N/A	13
	3	0	N/A	13
Scott 1997	2	9	N/A	24
Taheri 2009	3	0	8	10
	4	0	7	8
Tsao 2006	1	0	1	9
	3	0	3	9
	4	0	2	9
Yukna 1996	0	0	N/A	27
	2	9	N/A	91
Yukna 1992	2	0	N/A	11
Yukna 1994	3	1	17	30
Yukna 2001	2	1	18	27
	3	1	17	27
Yamaoka 1996	4	1	N/A	30
Zahedi 2003	2	12	27	40
***Treatment Group: 1) Open Flap Debridement, 2) Guided Tissue Regeneration, 3) Bone Replacement Graft, 4) Combination Therapy**				

Table 7: Data of Furcation Closure (Hard tissue)

Treatment Group	# Conversion to Class 0 or 1/# total	Percentage of Closure
Open Flap Debridement	4/56	7.1
Guided Tissue Regeneration	104/293	35.5
Bone Replacement Graft	47/89	52.8
Combination Therapy	39/85	45.9

Table 8: Frequency of Furcation Closure by Treatment Group

Discussion

Grade II furcations have always posed a clinical challenge due to the mandibular molar's anatomy as well as the limitations imposed regarding adequate debridement with the instruments available to the practitioner. Due to the wide anatomical variance in root trunk lengths, depth and location of concavities, and convergence and divergence of the roots, the furcation defect is a difficult area to quantify. Once bone loss occurs at the level of the furcation entrance, it becomes a three-dimensional defect space with a multitude of confounding factors relating to molar furcation anatomy and inability to instrument properly. Surgical re-entries are the only true way to determine clinical success because it is visual confirmation of hard tissue fill and success of guided tissue regeneration techniques.

Early diagnosis and management of furcations improves successful periodontal defect resolution as shown by Bowers *et al*. Clinical management and prognosis of the furcated molar is truly dependent on how advanced the defect has invaded horizontally. Bowers showed that with increases in horizontal attachment levels, especially when probing depth was 5mm or greater, there was an associated decrease in clinical closure [38]. Therefore, open horizontal probing depth was used as a primary outcome measure which is translatable to the percent furcation defect fill and was analyzed to evaluate anticipated hard tissue fill expected with our different regenerative therapies. Percentage defect fill using open horizontal defect depths gives the most translatable measure to bring into clinical practice and the effect was found to be significant when adjusting for the initial pretreatment mean probing depth measurements.

According to this review, guided tissue regeneration and combination therapies yielded the highest defect fill closure in open horizontal defect depth. Guided tissue regeneration can fill the furcation defect horizontally 39.13%±20.52% average, while combination therapy can fill 46.36%±15.50% average with hard tissue fill. Bone replacement graft group yielded 34.33%±13.73% defect fill, while the open flap debridement group yielded 15.49%±11.26% defect fill. Results show that combination therapy is consistently most effective in improving outcome measures followed by guided tissue regeneration and bone replacement grafts. Open flap debridement has been repeatedly shown to be inferior in improvement of clinical outcome variables, including open horizontal defect fill. This only confirms the conclusions of past studies and reviews, which looked at primarily soft tissue measurements in assessing defect resolution. Murphy and Gunsolley came to the conclusion that GTR enhanced outcomes and augmentation material additionally seemed to enhance outcomes, compared to open flap debridement in their systematic review of studies with GTR and surgical control arms [39]. More importantly, the evidence shows that independent of initial pretreatment horizontal probing depths, hard tissue furcation defect fill is achievable.

Clinical attachment level gains, closed horizontal probing depth, and open vertical probing defect fill were not shown to be significantly different when an analysis of covariance was done adjusting for pretreatment means with a least-squares regression model. This shows that surgical treatment is not highly correlated with gains in clinical attachment level, and therefore may not the best measure to use in comparing different regenerative therapies against each other. Since this is a closed measurement, the probe will stop where the tissue attachment allows. If healing is mostly done by repair and a long junctional epithelium and not with true regeneration in the defect, the clinical probing is not an accurate form of measure for clinical success. Therefore, surgical reentry to confirm hard tissue fill may be the only way to know that true attachment is present. Most of our included studies did not report closed horizontal probing depths, and the lack of data may have influenced our comparative results.

According to Wheeler's Dental Anatomy, the average labiolingual dimensions of a mandibular first molar at the cervical line is 9.0 mm and a mandibular second molar is 8.8mm. The pre-surgical horizontal probing depths included in this analysis ranged from 3-8.4mm, or 30-90% bone loss in a bucco-lingual dimension at the level of the furcation. In addition, the greatest root surface area occurs at 4-7mm apical to the CEJ, correlating at the level of root separation about 4.0±0.7mm as shown by Dunlap *et al*. Also, close to 50% of the total attachment occurs in the coronal 6mm of the total root length. From a maintenance aspect, the only way to properly retain these furcated molars is to close the furcation with hard tissue fill to gain clinical attachment level coronally where a majority of the attachment occurs. True regeneration in the form of bone, cementum, and a periodontal ligament is most desired after surgical grafting therapy and considered to be the most resilient against future periodontal breakdown. Long junctional epithelium forms by repair due to the rapid apical migration of epithelial cells down the root surface, and does not lead to the reformation of lost structures due to the periodontal disease. This is where the idea of guided tissue regeneration arose in order to retard the epithelial cells from infiltrating the defect site and give preference to other cells for regeneration of bone, cementum, and PDL. Our results only further validate the regenerative techniques available, showing guided tissue regeneration and combination therapy to be most clinically successful.

Bone replacement grafts serve as a scaffold for space maintenance and future tissue regeneration, whether alone or in combination with a barrier. When comparing overall mean vertical bony defect fill among treatment groups, the bone replacement graft yielded highest defect fill and was statistically different from the remaining three treatment groups. No statistical difference existed between the combination and bone replacement group in this comparison. This evidence confirms that the use of bone replacement graft may be a vital part of regenerative therapy for clinically significant vertical bone fill of the furcation. The space-making capacity of bone graft materials alone or in combination with a barrier most likely allows for long-term maintenance of vertical space for eventual bony regeneration. Bone replacement grafts achieved the highest rate of furcation closure of 52.8%, while the combination group achieved second highest rate of closure of 45.9%. Furcation closure data closely correlate with the trend seen with our other clinical outcome variables.

Clinicians are confronted with the decision whether to treat or to extract teeth with furcation involvement. Implants are not completely devoid of complications, especially from periimplantitis-related and prosthetic concerns. Due to the complicating factors involved with adequate root instrumentation of the furcation, including critical needs for proper surgical technique and operator proficiency, the choice of treating a furcated molar must be made with patient-related and prognostic-related factors in mind. This systematic review provides an evidence-based foundation to help guide clinicians in the decision to treat patients with Grade II furcated mandibular molars. This review provides percentages in defect fill that can give the practitioner a range of expectations based on treatment therapy. The evidence shows that one can attain hard tissue closure, as previously shown by Bowers *et al* demonstrating a linear relationship of predictability of hard tissue closure with decreasing horizontal probing depths [38]. It was revealed that with regenerative therapy over a wide range of defect severity but independent of that initial pretreatment variable, the frequency of closing the furcation horizontally was achieved on average approached 50%, and is confirmed by percentage frequency of closure data. Past evidence shows that horizontal defects extending past 5mm in probing depth rarely close, and the data in the included studies show a wide range of defects from 3-8.4mm. Due to the wide range of defect severity, 50% defect fill is most likely underestimating the probability of complete closure for those defects probing less than 5mm. It can be concluded that regenerative therapies are viable surgical options for Grade II furcated mandibular molars in routine clinical practice.

Currently, there is growing interest in biologic agents in the field of dentistry and there may be a substantial benefit in producing increased defect fill in Grade II furcations. More prospective studies using different growth factor agents such as Emdogain, PRP, and PDGF-bb are necessary in order to confirm the ability of biologic mediators to enhance the histologic and clinical outcomes. Future evidence may validate their safety and use in routine regenerative therapy despite the added financial burden. Ultimately, the decision falls on the clinician to recommend regenerative therapies if permitting, after proper diagnosis, treatment planning, and overall patient and long-term maintenance considerations.

Conclusions

1) Combination therapy and guided tissue regeneration groups were superior to open flap debridement, and differences are statistically significant when comparing defect fill, open horizontal defect, and closed vertical probing depth. Bone replacement graft was intermediate to OFD and GTR/Combination groups with no significant differences between BRG and these treatment groups.

2) Open Hard Tissue measurements: Combination therapy yielded greatest overall means in open horizontal defect fill, with an average of 46.46% ± 15.50% defect fill, closely followed by guided tissue regeneration. This confirms that the use of a barrier alone or in combination with a graft material leads to highest probability of bony defect fill in the furcation.

3) Reporting the frequency of furcation closure by hard tissue fill at surgical re-entry was inadequate (17/37 studies reported). Nonetheless, amongst the 17 studies reporting, the highest frequency of closure was seen in the bone replacement graft group, closely followed by combination therapy and then by guided tissue regeneration. Open flap debridement reported the least frequency of closure. These results closely correlate with the percent open hard tissue defect fill.

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