Bone Healing after Tooth Extraction with or without an Intervention: A Systematic Review of Randomized Controlled Trials

Kushel R. Morjaria, BDS, MSc;* Ron Wilson, PhD;† Richard M. Palmer, PhD, BDS, FDS, RCS‡

ABSTRACT

Objectives: To assess whether the use of a graft and/or membrane post-tooth extraction improves healing of the site dimensionally, radiographically, and/or histologically.

Materials and Methods: MEDLINE and EMBASE and the Cochrane Central register of controlled trials (CENTRAL) were searched up until August 2011. Randomized controlled trials that included and compared healing post-tooth extraction between a control (no intervention) and a graft and/or membrane (test) were selected.

Results: Titles and abstracts of 2,861 papers were screened. A total of 42 papers were selected for full text reading. Nine papers met the eligibility criteria and were selected for further analysis. Because of the varying graft materials used and the different methods of investigation, as well as the variation in follow-up times, a meta-analysis was not possible. The present review found that clinically, there was a range in loss of width in the control sites of 2.46 mm (SD 0.4 mm) to 4.56 mm (SD 0.33 mm) compared to 1.14 mm (SD 0.87 mm) to 2.5 mm (SD 1.2 mm) in the test sites. The range in loss of height in control sites was 0.9 mm (SD 1.6 mm) to 3.6 mm (SD 1.5 mm) compared to a gain of 1.3 mm (SD 2 mm) to a loss of 0.62 mm (SD 0.51 mm) in test sites. Radiographically a range of change in bone height of between 0.51 mm (No SD) to 1.17 mm (SD 1.23 mm) was noted in control sites compared to a change of between 0.02 mm (SD 1.2 mm) and 1 mm (SD 1.4 mm) in test sites.

Conclusion: There is limited data regarding the effectiveness of alveolar ridge preservation therapies when compared to the control. Overall the socket intervention therapies did reduce alveolar ridge dimensional changes post-extraction, but were unable to prevent resorption. Histology did demonstrate a large proportion of residual graft material that may account for some of the difference in alveolar ridge dimensions at follow up.

KEY WORDS: augmentation, bone loss, extraction socket, ridge preservation, systematic review

INTRODUCTION

Grafting and/or guided bone regeneration (GBR) in tooth extraction sockets has been advocated by some clinicians to improve the alveolar ridge dimensions for future restorative treatment. This may be in anticipation of a fixed dental prosthesis to improve the emergence and soft tissue profile under the pontic or the subsequent provision of an implant supported restoration. An alternative application of these techniques is in the management of sockets following the removal of third molars. The resulting osseous defect and loss of clinical attachment distal to the second molars may persist, especially in older patients. In severe cases where the periodontal support of the second molar is already compromised, this may be detrimental to the long-term prognosis of the tooth.

For clinically acceptable wound healing to occur, little intervention is needed for the process to take place in a predictable fashion. The healing process

*Postgraduate student, Department of Restorative Dentistry, Kings' College London Dental Institute, Floor 25 Tower Wing, Guy's Hospital Campus, London, UK; †senior lecturer, Department of Restorative Dentistry, Kings' College London Dental Institute, Floor 25 Tower Wing, Guy's Hospital Campus, London, UK; ‡professor of Implant Dentistry and Periodontology, Department of Restorative Dentistry, Kings' College London Dental Institute, Floor 25 Tower Wing, Guy's Hospital Campus, London, UK

Reprint requests: Professor Richard M. Palmer, King's College London Dental Institute, Floor 25 Tower Wing, Guy's Hospital Campus, London SE1 9RT, UK; e-mail richard.m.palmer@kcl.ac.uk

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post-extraction has been extensively described in the literature, and many of the observations are based on histological examinations using animal models.[1] The healing process in the animal model tends to be faster; therefore, there may be variation in the time frames discussed when using the data to describe the sequence of events post-extraction in humans.[2,3]

The rate of ridge resorption is greatest in the first year, especially within the first 3 months. Variation with regards to bone loss depends on the patient's age at the time of tooth loss as well as marked differences between the maxilla and the mandible. Both local and systemic factors will have an impact on bone loss post-extraction, for example, smoking. There is loss of vertical ridge height which is also more pronounced on the facial aspect. This results in the diminished ridge being more palatally/lingually positioned over time. This situation is exacerbated when there is loss of socket walls or loss of height of the alveolus as a result of a previous disease process or trauma before or during the extraction procedure.

Osteoconduction, osteoinduction, and osteogenesis are terms that may be used to classify the biological properties and clinical effects of graft materials. The understanding of these terms and linking them to the various materials that are currently available may help the clinician to make informed, rational decisions on the choice of graft and/or membrane, based on the desired clinical outcome, as well as the type and size of the residual defect post-extraction.

Osteoconductive materials may stimulate the recruitment and migration of potentially osteogenic cells to the site of matrix formation[4] and provide a framework from which existing bone cells may develop. Polymers, bioactive glass, and hydroxyapatite (natural and synthetic) are examples of purely osteoconductive materials.

The term osteoinduction refers to the property of the material to induce differentiation of undifferentiated cells toward an osteoblastic phenotype. Growth factors such as recombinant human growth factor (Rh BMP-2) and demineralized freeze dried human bone allograft are considered osteoinductive.

Autogenous bone is the only graft material that is considered truly osteogenic. Cells with osteogenic potential include endosteal or cambial osteoblasts, perivascular cells, and undifferentiated stem cells from the bone and bone marrow. Osteogenesis refers to the formation of new bone from living cells transplanted within the graft.

During the normal healing phase post-extraction, the soft tissue cells divide and migrate at a much faster rate than bone cells, so defects tend to fill with soft tissue. The principle of GBR is to prevent the ingrowth of soft tissues, which may otherwise disturb or totally prevent osteogenesis in a defect or wound, and to allow the osteoprogenitor cells to develop bone within a protected space. Some authors also believe that a barrier membrane may also aid clot stabilization,[5] as well as help to protect the wound from mechanical disruption and saliva contamination.

Insertion of graft material into an extraction socket will initiate a host response. This may result in increased inflammatory, macrophage, and osteoclastic activity. Inert biomaterials may cause significant delayed healing effects via interaction with the host tissue, despite the graft appearing to do little except take up space. The effects at the tissue, cellular, and molecular level are dependent on the morphology, chemical composition, porosity, and particle size of the material. The use of a graft and/or membrane may help to foster selective cell and tissue repopulation to restore the alveolar process. The process of normal wound healing may thus be impaired or accelerated depending on the material and whether it contains biomimetic or bioactive molecules.

Currently, most graft materials appear to have their limitations with regards to maintaining the alveolar ridge and in promoting the regeneration of normal bone architecture. The main problems that may arise include effects on revascularization, persistence of the graft material rather than replacement with host bone, inconsistent performance, inability to restore alveolar ridge height, prolongation of healing time and the small, but important risk of disease transmission (e.g., viral transmission in the case of allogenic bone).[6]

Therefore, there is a need to develop and test graft materials that will predictably enhance the healing of extraction sockets and reduce the subsequent remodeling that may otherwise lead to impairment of appearance and function of the final restoration. The aim of this study was to evaluate the outcome of grafting of extraction sockets compared to natural healing.

Research Question

Is there any benefit in grafting and/or GBR in the management of extraction sockets?

Objectives

1. To assess whether placing a graft and/or membrane post-extraction improves the site dimensionally, radiographically and/or histologically.
2. To assess whether a particular graft and/or membrane is more beneficial than others in improving the healing of an extraction site.
3. To assess if grafting has any beneficial or detrimental effects on post-operative sequelae post-extraction.

METHOD

Criteria for Considering Trials for This Review

1. Randomized controlled clinical trials (RCTs) including split mouth and parallel studies.
2. Patients planned for a dental extraction and a subsequent grafting and/or membrane procedure.
3. Any grafting material and/or membrane that has been approved for dental use. The material may be an active agent, such as bone morphogenetic proteins or platelet rich plasma, or a biomaterial. Autogenous grafts were accepted.
4. Trials with less than 10 test and 10 control sites were not accepted.
5. Trials that measured dimensional changes indirectly using study casts were not accepted.
6. Data for follow up times of greater than one year were not included.
7. Trials were restricted to the English language and humans only.

TYPES OF OUTCOME MEASURES

Primary Outcome Measures

Clinical Measures. To include trials measuring ridge dimensions with and without a flap raised at the time of extraction and at follow up.

Radiographic Measures. To include trials that assess bone density and ridge dimensions radiographically at the time of extraction and at follow up.

Histological Assessment. To include trials that assess bone quantity/quality and residual graft material at follow up.

Secondary Outcome Measures

To review the immediate post-extraction reports within the selected trials for post-operative sequelae and compare the control and the test sites for any secondary outcomes.

Search Methods for Identification of Studies

A search strategy was devised based on extensive discussion between review authors and an independent search strategist. This search strategy was developed for MEDLINE and EMBASE via OVID.

Searched Databases

EMBASE (1980 to August 2011)
OVID MEDLINE (1950 to August 2011)
The Cochrane oral health's group trial register (to August 2011)
The Cochrane central register of controlled trials (CENTRAL) (The Cochrane library to August 2011)

The search strategy developed for MEDLINE and EMBASE using Ovid SP was as follows:

Main search:

1. Tooth Extraction/
2. Extraction*.mp.
3. Tooth Socket/
4. Tooth socket*.mp.
5. 1 or 2 or3 or 4
   (mp = Title, original title, abstract, name of substance word, subject heading word):
6. Graft*.mp.
7. Augmentation* mp
8. Autogenous.mp
9. Allograft.mp
10. Xenograft*.mp
11. Alloplastic*.mp.
12. GBR.mp.
13. Guided Bone Regeneration.mp.
14. BMP*.mp.
15. PRP.mp.
16. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 5 and 16
18. Limit 17 to Humans and English

Cross Referencing

All the selected RCTs and published reviews were cross referenced to ensure a more complete search strategy.

Unpublished Trials

They were not included in the search process.

Handsearching

Handsearching was not carried out.

DATA COLLECTION AND ANALYSIS

Trial Selection

Two independent review authors reviewed the titles and, where available, the abstracts from the search results. Where trials appeared to meet the inclusion criteria, or in cases where there was a lack of information, the full study report was obtained and the reports were read independently by both review authors. All the studies that were selected, but did not meet the inclusion criteria are listed in Supporting Information Table S1. All the selected studies (Table 1) underwent a process of validity assessment, data extraction, and quality assessment.

Data Extraction

Data was extracted using the summary forms independently by one review author (KRM) and verified by the other (RMP). Full details of the study summaries are given in Supporting Information Table S2. Any differences were discussed, with an agreement reached subsequently.

The data extraction forms included:

1. Author, year of publication, and study design
2. Sample characteristics
3. Exclusion criteria
4. Intervention
5. Follow up
6. Diagnostic criteria
7. Findings
8. Comments/conclusions

Assessment of Risk of Bias of Included Trials

A description for randomization was rated as excellent, good, adequate, or poor. A rating of "excellent" demonstrated the allocation of grafting/membrane or control was post-extraction. It also implied good sequence generation. "Good" indicated that the trials were satisfactorily randomized with good sequence generation, but graft allocation post-extraction was unlikely. "Adequate" implied that the method of randomization was not clear, but the allocation of graft material was post-extraction. "Poor" implied that a method of randomization was not stated and graft allocation was pre-extraction.

A description of masking was rated as excellent, good, poor or none. A rating of "excellent" demonstrated that the study stated that the examiner was not involved in treatment provision and that the method of outcome assessment kept the examiner masked. A rating of "good" implied that the study was masked and the examiner was not involved in treatment provision, but the histological or radiological method of outcome assessment may have revealed some residual graft material. "Poor" implied that the examiner was involved in treatment provision.

Assessment of the risk of bias was carried out by both authors independently. The assessment was carried out in duplicate and based on the guidance of the Cochrane handbook of systematic review interventions.[7] The Jadad scale[8] and the CONSORT statement[9] were considered during the formulation of the method for assessing the risk of bias. Details of each trial in terms of a description and judgment were entered into a quality assessment table (Table 2).

The risk of bias was ranked as being high, moderate or low.

1. Low risk of bias: Possible risk of bias which is unlikely to alter reported outcomes
2. Moderate risk of bias: Possible risk of bias which may alter reported outcomes
3. High risk of bias: Possible risk of bias which seriously weakens the confidence in reported outcomes

This was based on the method and timing (pre- or post-extraction) of randomization and whether there was any masking and if so, the adequacy of the masking.

Data Synthesis

The review authors did not formulate a hypothesis with subgroup analysis as no comprehensive meta-analysis was anticipated. This was based on the large variation in the types of intervention included in the search strategy as well as the various methods of assessment of healing post-extraction between trials.

TABLE 1 Summary of Each Trial Included in the Present Review

TABLE 1A Third Molar Trials (All Radiological Trials)

Author/Year/Design	Number and Age of Patients	Site	Material	Follow Up	Method
Throndson and Sexton[10] Year 2002 Spit mouth design	20 patients (14 completed the study) 31 years (No standard deviation provided)	Bilateral third molars	Bioactive glass	3/6/12 months Customized stent used for reference (RINN holder used)	Clinical attachment: Measured presurgery and 3/6/12 months. Distal aspect of 7 used as reference for CEJ to bone crest measurement Radiographic assessment: Periapicals presurgery/6 and 12 months to assess alveolar bone height
Munhoz et al.[11] Year 2006 Split-mouth design	39 patients 15–25 years (no mean or standard deviation given)	Bilateral third molars	Composite xenogenic bone graft with a collagen membrane	60 days and 180 days Positioners used to provide standardization of the radiographs. Measurements repeated for both groups to check for interexaminer agreement	Radiographic assessment Periapicals Distal aspect of 7 used as reference for CEJ to bone crest measurement

TABLE 1B Non-Third Molar Trials

Group 1

Clinical Trials

Author/Year/Design	Number and Age of Patients	Site	Material	Follow Up	Method
Lekovic et al.[13] Year 1998 Split mouth design	16 patients 52.6 years (SD 11.8 years)	Two non-molar extractions per patient	Glycolide and lactide polymer membrane	6 months Reviewed 2 weeks and 1/2/3/6 months Examiner was not involved in treatment provision	Titanium pins placed on buccal aspect and used as fixed reference point to assess external vertical, internal vertical and horizontal dimensions

TABLE 1 ***Continued***

Group 2

Clinical and Histological Trials

Author/ Year/Design	Number and Age of Patients	Site	Material	Follow Up	Method
Lasella et al.[14] Year 2003 Parallel study	24 patients 51.5 years (SD 13.6 years)	One or two non molar extractions with the sites having at least one adjacent tooth 12 test sites 12 control sites	Mineralized freeze dried bone allograft hydrated in 50 mg/mL solution of tetracycline and a collagen membrane	4 or 6 months Reviewed weekly until soft tissue closure An acrylic stent used as a reference for vertical measurements after raising a flap. Difference in readings >1 mm were repeated and <1 mm were averaged	Clinical: Vertical (mid buccal, mesial and distal) and horizontal ridge measurements. Socket wall and soft tissue thickness assessed Two examiners not involved in treatment provision Histology % cellular bone % acellular bone % trabecular space (2.7 × 6 mm core)
Barone et al.[15] Year 2008 Parallel study	40 patients (26–69 years) (No mean or SD given)	Single non molar extraction sockets with adjacent teeth 20 test sites 20 control sites	Porcine corticocancellous bone and collagen membrane	7–9 months Reviewed monthly after the first week Measurements were taken by one examiner using a stent as a reference via surgical exposure	Clinical Vertical (mid buccal, mesial and distal) and horizontal ridge measurements Examiner not involved in treatment provision Histology Total bone volume (%) Connective tissue (%) Residual graft material (%)

TABLE 1 ***Continued***

Group 2

Clinical and Histological Trials

Author/Year/Design	Number and Age of Patients	Site	Material	Follow Up	Method
Aimetti et al.[16] Year 2009 Parallel study	40 patients 51.27 years (SD 8.4 years) Within the groups Test: 50.8 years (SD 8.4 years) Control: 51.8 years (SD 8.6 years)	Single anterior maxillary extraction sockets 22 test sites 18 control sites	Medical grade calcium sulfate hemihydrate	3 months Reviewed weekly for one month and each month until implant placement. Acrylic stent used to provide a reference for measurements	Clinical Crestal height/buccopalatal width and marginal bone levels Examiner not involved in treatment provision Histology % woven bone vs. lamellar bone (2.5 × 7 mm core)
Pelegrine et al.[17] Year 2010 Parallel study	13 patients (30 extraction sites) Mean age: 47.5 years (SD 10.3 years)	Up to four anterior maxillary teeth requiring extraction per patient 15 Test (7 subjects) 15 Control (6 subjects)	Autologous bone marrow (from the iliac crest)	6 months (measurements taken at implant placement) No further discussion regarding follow up Masking not discussed	Clinical assessment: Titanium screw placed on the lingual aspect as a reference to allow assessment vertically of EVM and IVM (IVM = socket fill) and horizontally (CHM) Vestibular and palatal thickness loss were also assessed. Histological assessment 7 × 2 mm core

TABLE 1 ***Continued***

Group 3

Radiological and Histological Trials

Author/Year/ Design	Number and Age of Patients	Site	Material	Follow Up	Method
Fiorellini et al.[18] Year 2005 Parallel study	80 patients 65 pts: 1 site 15 pts: 2 sites 47.4 years (No SD given)	Maxillary premolars, incisors and canines only	Four groups: (Number of patients in each group) A: 0.75 mg/mL Rh BMP-2 with ACS (mean dose 0.9 mg BMP) (22) B: 1.5 mg/mL Rh BMP-2 with ACS (mean dose 1.9 mg BMP) (21) C: Control (no intervention) (20) D: Placebo group (ACS and dilutent for Rh BMP-2 alone) (17) (BMP: Bone morphogenetic protein) (ACS: Collagen sponge: carrier. Bovine type 1 collagen)	4 months Reviewed clinically 2/14 days and 1/2/3/4 weeks post-op Post-op periapicals at baseline and 2/3/4 months No details of computerized tomography (CT) protocol. Three independent masked CT examiners	Radiographic assessment: (CT Scan) Within 4 days after extraction and 4 months after baseline. To assess bone width at different levels along the length of the socket Socket height, density and volume also assessed Histology: (Qualitative only) Presence of cortical and/or trabecular bone, thickness of trabeculae, presence of lamellar/woven bone and residual collagen matrix.

Group 4

Histological Trials

Author/Year/Design	Number and Age of Patients	Site	Material	Follow Up	Method
Froum et al.[19] Year 2002 Parallel study	19 patients 30 sites 59.4 years (SD 11.9 years)	17 Mandibular teeth 13 Maxillary teeth (various sites)	10 sockets Bioactive glass (BG) (300–355 μm particle size) 10 sockets demineralized freeze dried allograft (DFDBA) (cortical bone from bone bank) (250–500 μm particle size) 10 sockets control (no graft)	6–8 months (2 × 7 mm bone core for histology at surgery for implant placement)	Comparing % vital bone % connective tissue % residual graft material between BG/DFDBA/Control

SD = standard deviation.

TABLE 2 Quality Assessment Summary

Trial	Randomization	Outcome Assessor Masked	Withdrawals	Bias Score (Randomization + Masking)	Risk of Bias
Third molar					
Throndson and Sexton[10]	Poor	None	Yes (unable to contact patients for follow up)	2 + 3 = 5	High
Munhoz et al.[11]	Adequate	None	None	1 + 3 = 4	High
Non third Molar					
Group 1					
Lekovic et al.[13]	Excellent	Excellent	None	−1 + 0 = −1	Low
Group 2					
Lasella et al.[14]	Good	Good	None	0 + 1 = 1	Low
Barone et al.[15]	Good	Good	None	0 + 1 = 1	Low
Aimetti et al.[16]	Adequate	Good	None	1 + 1 = 2	Moderate
Pelegrine et al.[17]	Poor	None	None	2 + 3 = 5	High
Group 3					
Fiorellini et al.[18]	Poor	Good	None	2 + 1 = 3	Moderate
Group 4					
Froum et al.[19]	Excellent	Good	None	−1 + 1 = 0	Low

KEY: Risk of bias: (−1 to 1 = low, 2 to 3 = moderate, 4 to 5 = high).
Randomization:
Good sequence generation: 0
Poorly randomized: 1
No method stated: 2
(Randomization after extraction: −1)
(Randomization rating: −1 = Excellent, 0 = Good, 1 = Adequate, 2 = Poor).
Masking:
Examiner not involved in treatment provision: 0
Examiner masked but in some cases difficult e.g., residual graft in histology and radiology: 1
Poor Masking: 2 No Masking: 3
(Masking rating: 0 = Excellent, 1 = Good, 2 = Poor, 3 = None).

RESULTS

Description of Trials

From the initial search result of 2,861 papers, 2,217 papers were rejected on the title alone and a further 602 papers were rejected based on the abstract. The remaining 42 trials were selected for reading of the full text based on the title and abstract. Nine trials were subsequently included in the present review. Figure 1 includes all the trials selected for the reading of the full text, including the main reason for the rejection of 33 trials.

Of the nine trials included, two were based on third molar sites (Throndson and Sexton;[10] Munhoz et al.[11]). They were both prospective radiological trials. Munhoz et al.[12] included the same subjects as Munhoz et al. and provided additional 2-year follow-up data not included in this review.

The remaining seven trials were prospective and were divided into clinical trials (group 1; Lekovic et al.[13]), clinical and histological trials (group 2; Lasella et al.;[14] Barone et al.;[15] Aimetti et al.;[16] Pelegrine et al.[17]), radiological and histological trials (group 3; Fiorellini et al.[18]), and a histological trial (group 4; Froum et al.[19]).

Three trials had a split-mouth study design[10,11,13], and six trials had a parallel study design.[14–19] Table 1 provides an overview of each selected trial, including a description of subjects and sites as well as the type of graft material used and the method of assessment used during the extraction phase and at follow up.

EXCLUSION CRITERIA USED IN SELECTED TRIALS

Site-Related Exclusion Criteria

Throndson and Sexton[10] and Munhoz et al.[11] only included bilaterally impacted mandibular third molars in their trials; however, there was variation between the two studies as regards the excluded sites. Munhoz et al.[11]

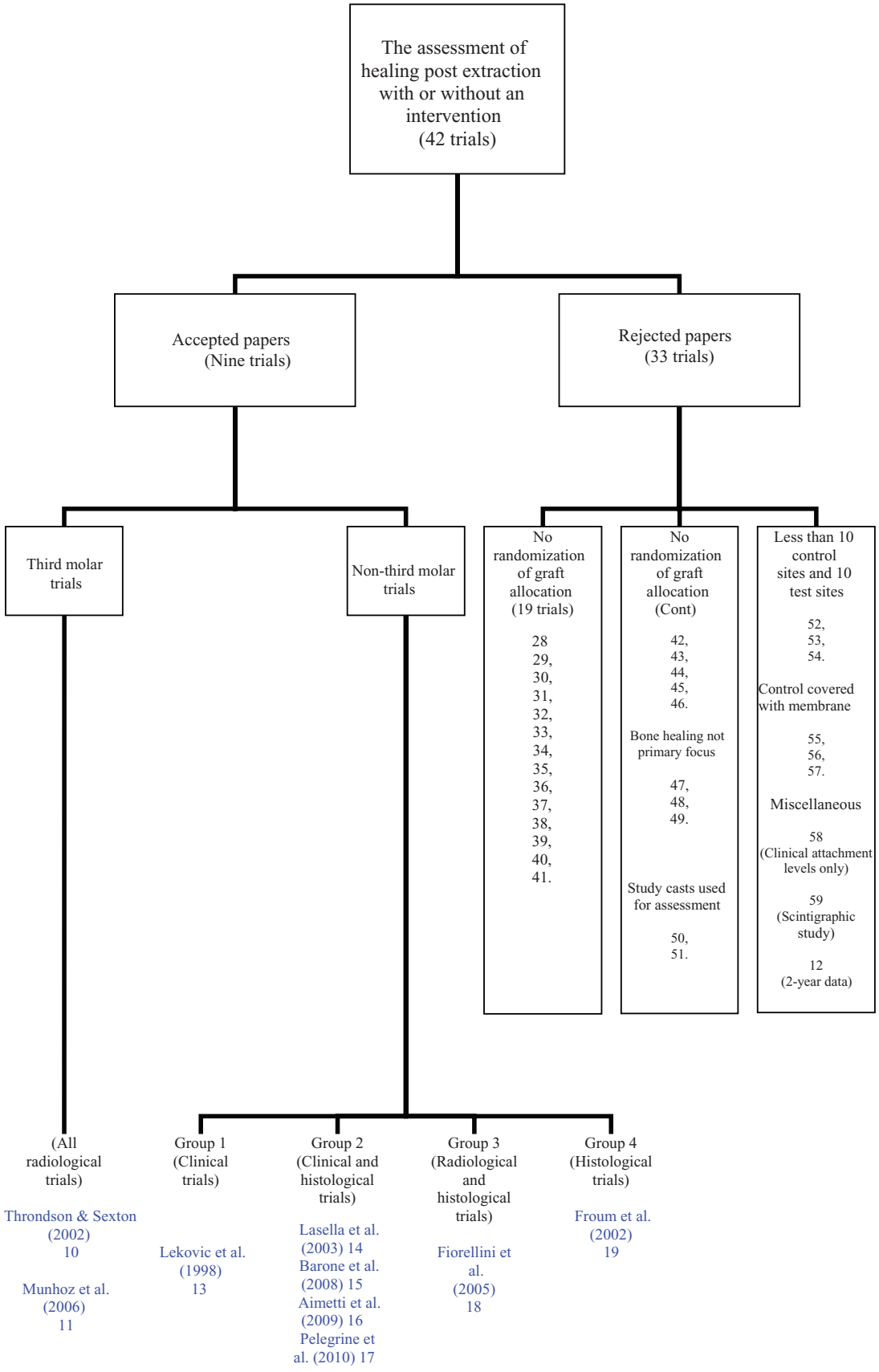

Figure 1 A summary of the outcome of the trials that were initially selected.

excluded subjects if the impacted third molars were not in a symmetrical position according to the classification of Winter[20] and Pell and Gregory[21] Throndson and Sexton[10] excluded all erupted third molars and all bilateral third molars whose relative position to each other were "not similar." Munhoz et al.[11] excluded sites with poorly positioned adjacent second molars.

Froum et al.[19] excluded sites where more than 2 mm of buccal plate had been lost and in situations where the socket had three walls or less post-extraction. Aimetti et al.[16] excluded extraction sockets with less than four intact walls post-extraction. Pelegrine et al.[17] excluded any sites with severe bone loss with no further details provided. In contrast, Fiorellini et al.[18] excluded any sockets with more than 50% buccal bone remaining. The majority of studies excluded all molar extractions.[13–18]

Two studies did not include mandibular extraction sites.[17,18] Three studies excluded sites with no adjacent teeth.[14–16] Three trials excluded potential extraction sites with infection.[10,14,16]

Age-Related Exclusion Criteria

Throndson and Sexton[10] excluded any patients under the age of 25. Lasella et al.[14] and Barone et al.[15] stated that they excluded subjects below 18 years of age.

Smoking-Related Exclusion Criteria

Five trials excluded smokers entirely.[10,11,16,17,19] Barone et al.[15] included smokers who smoked less than 10 cigarettes a day. In cases where patients had smoked in the past, Froum et al.[19] accepted only non-smokers into the trial if they had not smoked for at least 6 months. Smoking was not mentioned in three trials.[13,14,18]

Medical History

Four trials excluded patients with any systemic disorders.[11,13,15,17] Three trials excluded all diabetics, subjects suffering from autoimmune dysfunction, and patients on prolonged cortisone therapy.[16,17,19]

Lasella et al.[14] excluded subjects with diseases affecting the periodontium, and Aimetti et al.[16] excluded subjects prescribed treatment that would affect bone healing.

Pregnant women were excluded in three trials,[11,16,17] and lactation was excluded in one study.[16]

Froum et al.[19] excluded patients who had antibiotics in the last 6 months, as well as subjects who had chemotherapy. Lasella et al.[14] and Barone et al.[15] excluded all subjects who had used NSAIDs long term. Four trials stated they excluded subjects with known allergies to any materials and medication used.[10,13,14,19]

Risk of Bias (Table 2)

Having combined the results for randomization and masking, Three trials were considered to have a high risk of bias,[10,11,17] as there was no evidence of masking and no method of randomization discussed. Munhoz et al.[11] was the only trial that was described as having a high risk of bias that allocated the graft post-extraction.

Two trials were considered to have a moderate risk of bias.[16,18] Both trials demonstrated that the examiners were masked, but the method of randomization was not clear. Both trials that were described as having a moderate risk of bias allocated the graft post-extraction.

The remaining four trials were considered to have a low risk of bias. The trials with a low risk of bias demonstrated good sequence generation (coin toss;[13,14] computer-generated randomized list;[15] envelopes prepared by a statistician[19]) and evidence of masking. The examiners involved in the trials that were described as having a low risk of bias were not involved in treatment provision. From these four trials, only Lekovic et al.[13] and Froum et al.[19] allocated the graft post-extraction.

Reasons for Extraction

Apart from the third molar trials, only two trials discussed the reasons for extraction. Aimetti et al.[16] provided a number of reasons (e.g., caries, retained roots, periapical abscesses, etc.). Froum et al.[19] stated that the extractions were for periodontal or prosthetic reasons. Lekovic et al.[13] stated that the patients in the trial were undergoing periodontal therapy, suggesting that a proportion of the teeth extracted were periodontally involved.

Preparation of Sockets

Sockets were prepared with some variation between trials. Flaps were raised prior to extraction in seven trials.[10,13–15,17–19] Aimetti et al.[16] did not raise a flap except at 3 months. There was no mention of flap elevation by Munhoz et al.[11] Sockets were perforated with a round bur by Froum et al.[19] and Fiorellini et al.[18] Primary closure was achieved in six trials.[10,13,15,17–19]

Graft Material

Because of the varying nature of the graft material used, each trial is listed separately in Table 1. Included within this summary table are the methods and follow-up times for assessment of the extraction sites included within the selected trials. Interestingly, Pelegrine et al.[17] was the only selected trial to use an autogenous graft. This study group used autologous bone marrow harvested from the iliac crest.

Table 1 demonstrates the considerable variation between the trials and highlights the heterogeneous nature of the trials included in this systematic review. None of the trials were the same and all used different graft materials except two trials that used bioactive glass.[10,19] The two trials that used bioactive glass were different in both site and method of assessment. Throndson and Sexton[10] was a radiographic lower third molar trial that also assessed clinical attachment levels, whereas Froum et al.[19] was a histological trial that incorporated various sites in the maxilla and mandible.

Post-Operative Care

All the trials prescribed antibiotics or analgesia either pre- or post-operatively except for three trials.[10,11,17] Froum et al.[19] did not mention analgesia as part of the post-operative protocol. Only three trials discussed denture adjustment or modification of denture use.[13,15,19] The use of chlorhexidine gluconate mouthwash was described by all trials except Munhoz et al.[11] and Pelegrine et al.[17]

Follow Up

When referring to follow-up times, this is the time point at which the assessment of the site was performed after a period of healing. There were many occasions during these trials that patients were followed-up intermittently from both a radiographic and a clinical perspective. For the breakdown of follow-up times for each study and an exact final time point at which the sites were evaluated and compared to the initial extraction phase, please refer to Table 1. The final assessment and follow-up times varied between 3 months[16] and 1 year.[10] The remaining trials had follow-up times of 6 months[11,13,14,17] or between 6 and 9 months,[15,19] except Lasella et al.[14] with a follow up time of 4 or 6 months and Fiorellini et al.[18] with a follow up time of 4 months.

Clinical Outcomes (Five Trials with a Total of 133 Patients)

Of the nine selected trials, five trials included a clinical component as part of their investigation.[13–17]

The range of dimensional changes clinically at the control sites was between 2.46 mm (SD 0.4 mm) and 4.56 mm (SD 0.33 mm) for loss in width. Within the test sites, there was a range of a loss in width between 1.14 mm (SD 0.87 mm) and 2.5 mm (SD 1.2 mm). As regards changes in bone height, there was a range in vertical bone loss of between 0.9 mm (SD 1.6 mm) and 3.6 mm (SD 1.5 mm) in the control sites; for the test sites, there was a range of a gain of 1.3 mm (SD 2 mm) to a loss of 0.62 mm (SD 0.51 mm). Overall, the differences in change in alveolar ridge dimensions were shown to be significant between test and control, except for Lasella et al.[14] for the difference in dimensional changes for ridge width ($p = 0.052$).

Radiological Outcomes (Three Trials with a Total of 139 Patients)

Of the nine selected trials, only three trials included a radiological assessment as part of their investigation.[10,11,18]

Radiographically a range of change in bone height of between 0.51 mm (no SD) and 1.17 mm (SD 1.23 mm) was noted in the control sites. The test sites demonstrated a range of change in bone height of between 0.02 mm (SD 1.2 mm) and 1 mm (SD 1.4 mm). The difference in alveolar bone height changes at follow up were assessed to not be significant between the test and control sites for both Throndson and Sexton[10] and Munhoz et al.[11] The p value provided by Throndson and Sexton[10] was 0.038. Our analysis of the data provided a p value of 0.05 (borderline non-significant). This would then correlate with the description by the authors of a lack of a significance difference (0.17 mm between test and control sites according to Throndson and Sexton[10]). Because of the loss of six subjects during the study, the final sample size of this trial was small.

Fiorellini et al.[18] divided the sites into four groups. Two groups consisted of either 0.75 mg/mL or 1.5 mg/mL Rh BMP with ACS (collagen sponge) and the remaining two groups consisted of a placebo (ACS alone) and a control (no intervention). The follow-up period was 4 months. A baseline CT imaging was taken 4 days after treatment. This was to take into account the radiodensity of the collagen sponge and provide a more

TABLE 3 Summary of Histology Results

Trial	Graft Material	% Vital Bone	%Connective Tissue	% Residual Graft
Lasella et al.[14] 4 or 6 months follow up	Mineralized freeze dried bone allograft and a collagen membrane (No *p* values given)	T: 28% (SD 14%) C: 54% (SD 12%)	Not available	T: 37% (SD 18%)
Barone et al.[15] 7 to 9 months follow up	Corticocancellous porcine bone and a collagen membrane	T: 35.5% (SD 10.4%) C: 25.7% (SD 9.5%) ($p < 0.05$)	T: 36.6% (SD 12.6%) C: 59.1% (SD 10.4%) ($p < 0.05$)	T: 29.2% (SD 10.1%)
Aimetti et al.[16] 3 months follow up	Medical grade calcium sulfate hemihydrate	T: 58.8% (SD 3.5%) C: 47.2% (SD 7.7%) ($p < 0.0001$)	Not available	Not available
Pelegrine et al.[17] 6 months follow up	Autologous bone marrow	T: 45.47% (SD 7.21%) C: 42.87% (SD 11.33%) ($p = 0.36$)	Not available	Not available
Froum et al.[19] 3 months follow up	Bioactive Glass (T1) Demineralized freeze dried allograft (T2) (No SDs provided)	T1: 59.5% T2: 34.7% C: 32.4% ($p = 0.074$)	T1: 35.3% T2: 51.6% C: 67% ($p = 0.006$)	T1: 5.5% T2: 13.5% ($p = 0.001$)

SD = standard deviation.
NOTE: Trabecular bone volume has been provided by Barone et al.[15] and Aimetti et al.[16] and has been included in Table 3 as vital bone.

accurate baseline image against which the final results could be assessed. There was no significant difference between groups for change in radiodensity. As regards bone height and width changes, there was a significant difference between the 0.75 mg/mL group and the control for width change at the top of the socket (coronal 25%). There was a significant difference in height and width change when comparing the control and the 1.5 mg/mL group except near the base of the socket for width change. The median bone width increased in all groups at the top of the socket except the control and the difference was significant ($p < 0.05$). The greatest difference in change in mean alveolar ridge dimension between the treated and untreated sites was 2.7 mm (this was for width change at the top of the socket (1.5 mg/mL: 3.27 mm [SD 2.53 mm] and control: 0.57 mm [SD 2.56 mm]). Fiorellini et al.[18] noted that the adequacy of bone volume for implant placement was three times greater in the middle part of the socket in the 1.5 mg/mL group when compared to the control and placebo sites (6 mm × 12 mm considered the minimum bone volume for adequate implant placement). The statistical analysis showed good correlation between CT examiners.

In contrast to the findings of Fiorellini et al.,[18] Munhoz et al.[11] found a significant difference in change in bone density between test and control.

Histological Outcomes (Six Trials with a Total of 216 Patients)

Six trials included a histological examination within their study.[14–19] Only Froum et al.[19] and Barone et al.[15] appear to have consistently used a stent/template to aid core retrieval from the experimental site. Froum et al.[19] was the only trial that primarily assessed histological outcomes.

The histological data is presented in Table 3. Fiorellini et al.[18] did not provide any quantitative data regarding histological outcomes and is therefore not included in Table 3.

The only direct comparison between graft materials can be made between DFDBA and bioactive glass as they were both examined within the same trial.[19] A true comparison cannot be made between trials as highlighted by the variation in results of the histological outcomes for the untreated controls. Also an in-depth analysis comparing graft materials histologically is outside the remit of this review.

POST-OPERATIVE SEQUELAE

Post-operative sequelae were not mentioned in three trials.[14,15,19] Post-operative healing was uneventful in two trials.[16,17] Lekovic et al.[13] mentioned that no infection or membrane exposure was noted.

Throndson and Sexton[10] reported that three patients experienced wound dehiscences at the grafted site after 1 week, which resolved by the second week. Less pain was reported at the grafted site. Alveolar osteitis was noted in three of the non-grafted sites and none in the grafted sites.

Munhoz et al.[11] described that 7 days after surgery, 12.8% and 2.5% of the control group experienced pain and infection respectively compared to 17.9% and 7.7% of the test group.

Fiorellini et al.[18] provided a summary of 250 events that were reported. 75% of the subjects had oral edema, 68% discussed experiencing mouth pain and 46% experienced oral erythema. It was noted that there were more episodes of edema and erythema in the treatment groups with no further details provided.

IMPLANT PROVISION

All the trials in the non-third molar studies, except for Lekovic et al.,[13] included patients that were scheduled for an implant-supported restoration.[14–19]

The final follow-up time provided was, in these trials, the point at which the relevant measurements/histological cores were obtained. The osteotomy site was then subsequently prepared for implant placement.

DISCUSSION

Currently, there is no consensus on grafting immediately post-extraction. RCTs used to form a systematic review may provide clinicians with a more evidence-based approach to the decision-making process, as opposed to what can only be described as an opinion-based approach.

The aim of this review was to assess whether grafting of an extraction socket is advantageous and whether any particular graft and/or membrane was shown to be more effective. With implant provision becoming more widespread, the need to anticipate and preempt post-extraction bone loss has become an even greater concern among clinicians. Post-extraction grafting produces potential added risks of post-operative complications and greater cost to the patient with possibly no added value or justification for subsequent restorative treatment.

The present review included all published RCTs, which evaluated sites treated post-extraction with a graft and/or membrane compared to sites with no intervention. Two trials were third molar extraction studies. As both third molar trials were primarily radiological studies, it was deemed appropriate to group them together. They provided a good split mouth model with biologically more comparable extraction sites for testing. The main group of studies did not fit as neatly together and were further subdivided into trials examining clinical outcome only, clinical and histological trials, a radiological and histological trial, and a histological trial. Although these subgroups overlap, in terms of method of analysis used (e.g., histology is part of three of the four subgroups), it allowed an assessment of whether two trials were able to be analyzed together and whether further statistical analysis between studies was possible. It also improved the opportunity for qualitative discussion of the data, despite there being different methods of outcome assessment at extraction and follow up, as well as there being different types of graft material under investigation.

Several studies excluded sites with missing socket walls or those with diminished socket wall height.[16–19] The various site exclusion criteria discussed provided a standardization between test and controls sites and improved the comparability of the data within each trial. However, the selective approach to site inclusion is not representative of the average clinical situation, where partial or total loss of socket walls may have occurred. This may be as a result of pre-existing bone loss or may occur during the extraction itself, despite the best efforts of the clinician to remove the tooth as atraumatically as possible.

Except for three trials,[14,16,18] none of the other trials selected carried out sample size calculations. In general, samples were small to moderate in size, with five trials consisting of less than 30 subjects. Three of the four remaining trials did not exceed 40 subjects. Fiorellini et al.[18] had the largest sample size and included 80 subjects. Despite their limitations, the results shown should provide useful clinical information and indications.

CLINICAL OUTCOMES

Five trials provided clinical outcome data. Lekovic et al.[13] did demonstrate a significant difference in alveolar ridge dimensional changes between test and control sites.

Overall, there was approximately 1 mm less vertical resorption and 2 mm more bone fill in the test group according to this study. The average residual ridge width was noted as being approximately 6 mm in the test and 3 mm in control sites. Overall, a difference in bone loss of 3 mm between the test and control sites is likely to have a considerable impact on future restorative treatment. This study group stated that this will be particularly beneficial for implant provision where a wider diameter implant may be considered. Interestingly, the clinical photographs published did not illustrate much of a difference in horizontal dimension between the test and control sites at follow up.

Lasella et al.[14] was only able to demonstrate a significant difference in alveolar dimensional changes between test and control in the vertical dimension. The large vertical gain of 1.3 mm (SD 2 mm) mid bucally in the test group, when all the other alveolar dimensions in both groups had experienced resorption, may have been due to overfilling of the test sites (the proportion of residual graft material was 37%). The difference in bone resorption mesially and distally in the vertical dimension, although shown to be significant, was only 0.9 mm and 0.7 mm respectively. These small clinical differences in resorption are unlikely to have a major impact on the final restorative outcome. The methodology was not ideal with regards to the horizontal measurements being taken prior to raising a flap and the vertical measurements being taken after raising a flap. Horizontal measurements after the flap was raised would have been more accurate. There was a range with regards to follow-up assessment times and this would have an impact on the overall comparability of the data.

Barone et al.[15] demonstrated a greater amount of bone loss in the control sites when compared to the test sites and the difference was statistically significant. Approximately, a 2 mm difference in bone loss was noted horizontally and in the vertical dimension at the buccal and lingual aspects. This may be attributed to the persistence of residual graft material combined with the relatively long follow up period.

Aimetti et al.[16] showed a significant difference in bone loss between test and control sites for buccal crestal bone height and buccopalatal width. In real terms, the greater amount of resorption in the control sites (0.7 mm and 1.2 mm respectively) is small and it is unlikely to have a significant impact on the final restorative outcome.

Pelegrine et al.[17] was the only study group to include an autogenous graft. They demonstrated a significant difference between test and control sites for change in external vertical dimensions and ridge width. There was no statistically significant difference in socket fill. Where a statistical difference had been shown, the mean difference was less than 1.5 mm. When this is taken into consideration, along with some of the large standard deviations demonstrated (e.g., change in ridge height for the test sites was 0.62 mm [SD 0.51 mm]), the impact of the intervention resulting in a consistent clinically significant difference may be questioned. The authors did state, however, that grafting or ridge expansion was required in five of the control sites prior to implant placement, and no further intervention was required prior to implant placement in the test sites.

RADIOLOGICAL OUTCOMES

Three trials provided radiological outcome data. The Munhoz et al.[12] paper published in 2011 was the same trial as that was published in 2006, but with 2-year follow-up outcomes included. These data have not been incorporated into this review as Munhoz et al.[11] included the initial 6-month results.

Throndson and Sexton[10] and Munhoz et al.[11] did not demonstrate any significant difference between test and control sites for alveolar bone height changes at the final follow up (1 year and 6 months, respectively). Munhoz et al.[11] noted a significant difference in bone density at follow up ($p < 0.05$). However, the test sites had the radiograph taken before the graft was placed; therefore, the radiodensity of the graft would not have been taken into account. It would therefore be difficult to compare the two groups as the graft material may have contributed to the significant difference in radiodensity between the two groups.

Fiorellini et al.[18] had the benefit of a larger sample (80 patients), encompassing eight study centers and the use of 3D tomography. CT allows a useful three-dimensional assessment, but it may lack sufficient resolution. For example, Razavi et al.[22] concluded that one

potential limitation of CT was the inability to resolve bone thickness (<1 mm) and thin bone may be encountered in many extraction sockets. The Fiorellini group took the baseline CT 4 days after extraction and grafting of the test sites and they were unable to demonstrate a significant difference in bone density at 4 months post-extraction. This was the only trial that accounted for the change in radiographic density due to the grafted material by taking the radiographic image after the graft was placed. They did demonstrate a consistent significant difference when a concentration of 1.5 mg/mL Rh BMP-2 was used. However, the mean differences between test and control sites for change in bone height and width overall was generally less than 2 mm. The large standard deviations reported would indicate that in some situations the impact of the higher concentration of Rh-BMP-2 would have been minimal clinically. This fact must be weighted up with the cost of using BMPs for this application and recent reports within the literature of greater inflammation and subsequent swelling associated with the use of higher concentrations of BMPs.[23]

HISTOLOGICAL OUTCOMES

Six trials included histology as part of the study. There was a lack of consistency between trials regarding the use of a stent to aid core retrieval from the extraction site. The consistent use of a stent would have helped to increase the chances of core retrieval from completely within the grafted site and avoid sampling of an unaffected area. The biggest concern demonstrated by the trials that included a histological investigation was both the large amount of residual graft material and the variation in the amount of vital bone noted in the test sites. Except for Lasella et al.,[14] all the trials demonstrated a greater percentage of vital bone within the test sites.

Froum et al.[19] was the only study that analyzed two materials histologically as well as a control. The results demonstrated that there was almost three times less residual graft material for bioactive glass when compared to demineralized freeze dried allograft. This demonstrates the large variation as regards resorption between graft materials. The presence of residual graft material may disturb the process of osseointegration when considering subsequent implant placement. The possibility of the unresorbed graft material behaving like a foreign body and enhancing a developing inflammatory lesion must also not be overlooked. Despite the potential problems with grafting, some trials have shown a high percentage of direct contact between bone and implant as well as a lack of graft particles contacting the implant surface.[24,25] These trials demonstrated that unresorbed graft particles did not compromise the osseointegration of the implants.

The impact of greater connective tissue in the control sites, which was demonstrated by Froum et al.[19] and Barone et al.[15] to be statistically significant, is also worth considering. Although it may imply less mineralized tissue, connective tissue has an important role to play. It includes a number of different cells incorporated into a matrix consisting of ground substance and fibers. A proportion of cells within connective tissue are involved in the host defense mechanism (i.e., includes macrophages and lymphocytes), which may contribute to reducing the risk of infection post-extraction.

POST-OPERATIVE CARE AND SEQUELAE

Munhoz et al.[11] provided a direct comparison for post-operative sequelae between test and control. The sites that were not treated with a graft were less painful and had a lower incidence of infection post-operatively.

The results of Throndson and Sexton[10] demonstrated that grafting can increase the risk of wound dehiscences, but they also described a higher incidence of dry socket and pain in the non-grafted sites. The reason for this difference between the control and test sites remains unclear.

It is impossible to draw any valid conclusion on the post-operative protocol and how this would have affected the results. As well as the varying nature of the different graft materials used, there was also a lack of reporting of post-operative sequelae within some studies as well as a variation in site management and post-operative protocols between trials.

STATISTICAL ANALYSIS, QUALITY OF EVIDENCE, AND POTENTIAL BIASES

The statistical analyses overall were generally deemed appropriate. In the three trials of split-mouth design, each treatment was assigned to a single extraction site. Therefore, the unit of analysis was the site as well as the patient. In the remaining parallel studies, the site and the subject were treated as the same.

Pelegrine et al.[17] included subjects with multiple sites under investigation. Each subject had either all test

sites or control sites. Multiple sites within each subject could then be averaged to allow a subject-based analysis. Although this method of analysis was deemed appropriate, the concern in this case was that the trial consequently appeared to be underpowered which would cast doubt over the reliability of the statistical significant differences demonstrated. Froum et al.[19] and Fiorellini et al.[18] also included subjects with more than one site under investigation. Froum et al.[19] did not discuss the incorporation of an adjustment for repeated measures within each subject. As regards Fiorellini et al.,[18] the statistical analysis was subject-based but it was not clear how data from subjects with two sites were dealt with. This would increase the risk of a type I statistical error in both cases.

The quality of evidence within the trials that fulfilled the acceptance criteria was good in the case of the non-third molar trials, with a low to moderate risk of bias except for Pelegrine et al.,[17] which was assessed to have a high risk of bias (no method of randomization and no evidence of masking given).

There may have been a greater risk of bias in some trials when compared to other trials classified within the same risk of bias group. For example, graft allocation may have been pre-surgery and in some instances masking may be more difficult (e.g., evidence of residual graft material in the case of histology).

Lekovic et al.[13] was likely to have had the lowest risk within the group of trials classified as having a low risk of bias. This was the only trial with an "excellent" rating for both randomization (which included graft allocation post-extraction) and masking.

The risk of bias was considered to be higher in the two third molar trials, due to a lack of information regarding the method of randomization and there being no evidence of the examiners being masked. It was also noted that Throndson and Sexton[10] lost six patients at follow up. They stated that if a patient could not be followed up for the entire year, their data was not included for the purposes of reporting clinical attachment levels or levels of osseous fill, but was included for the discussion of the immediate post-surgical course.

Not including patients lost at follow up is not ideal and depending on the missing data, may or may not provide an accurate representation of the final outcome. An intention-to-treat analysis was not included in this trial, but would have provided a good opportunity to include all the subjects in the study, with some adjustments for any missing data.

PREVIOUS REVIEWS

There have been two previous reviews close to this subject.[26,27] The review published by Van der Weijden et al.[26] reported bone changes following extraction without an intervention. The review published by Ten Heggeler et al.[27] was based on the effect of socket preservation in non molar sites and included trials that compared untreated control sites. Ten Heggeler et al.[27] did not include any histological analysis and, therefore, were unable to question whether a proportion of the difference in alveolar ridge dimensions at follow up was possibly due to unresorbed graft material. We agree with their conclusions that because of the heterogeneous nature of the human trials available, it is very difficult to draw robust conclusions.

LIMITATIONS

Part of the limitations of the review are the selection of only published trials and those that were in the English language. This introduces language and publication bias. It is also clear that the research question may have been more focused on, for example, solely the clinical element of the trials or restricting the inclusion criteria to include trials that included specific extraction sites, e.g., non third molar trials only, or only one type of graft material. This was not possible because of the lack of randomized control trials that attempted to answer the research question.

As described earlier, overall the samples sizes within the selected trials were relatively small and this would have reduced the power of the studies. It was noted that only three trials included a power test. A meta-analysis was not possible due to the variation in graft materials used, methods of assessment and the variation in follow times between each selected trial.

CONCLUSION

There is limited data regarding the effectiveness of alveolar ridge preservation therapies when compared to a control. This limits the ability to draw any robust conclusions. Overall the socket intervention therapies did reduce alveolar ridge dimensional changes post-extraction, but were unable to prevent resorption. Trials that included a histological component did demonstrate a large proportion of residual graft material, which may

account for some of the difference in alveolar ridge dimensions at follow up. When the trials took into account the radiodensity of the graft material, there was no difference in changes in radiographic density between the intervention and control. A comparison between interventions was not possible due to the variation in methods of assessment and follow up times as well as a variation in site management protocols between trials. Lekovic et al.[13] and Fiorellini et al.[18] demonstrated promising results with regards to alveolar ridge preservation, most significantly with regards to alveolar ridge width, when using glycolide and lactide polymer membranes and higher concentrations of bone morphogenetic proteins respectively, but further randomized controlled trials are necessary to confirm these findings.

CLINICAL RELEVANCE

This review demonstrates the need to consider grafting post-extraction carefully and whether the added cost to the patient relative to the final outcome is justified.

The histological studies have shown that it is possible that a large proportion of the difference in resorption when comparing grafting and simple healing may be due to unresorbed graft. As regards implant provision, the amount of residual graft material may have a direct impact on primary stability and subsequent successful osseointegration.

IMPLICATIONS FOR FUTURE RESEARCH

The possibility of more robust conclusions and comparisons between interventions are more likely if there are more randomized trials available, which are more homogenous in nature and have larger sample sizes. A greater number of homogenous trials would also facilitate a meta-analysis which would enable an evaluation of the outcome of the combination of results from several trials.

A particular problem with grafting studies when comparing with a control is the difficulty in masking the examiner. This is something that will always be an issue when trying to reduce bias unless more resorbable materials become available in the future.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Supporting Information Table S1. Rejected papers.
Supporting Information Table S2. Summary tables of selected trials.