THE OUTCOME OF MAXILLARY SINUS FLOOR AUGMENTATION WITH RECOMBINANT HUMAN BONE MORPHOGENIC PROTEIN 2 VERSUS CONVENTIONAL SINUS GRAFTING PROCEDURES: A SYSTEMATIC REVIEW

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by
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ABSTRACT

Objectives: To study the effect of the recombinant human bone morphogenetic protein-2 (rhBMP-2) on sinus volumetric and histometric changes after sinus floor augmentation compared to a conventional approach utilizing other bone grafting materials, such as autografts, allografts, and xenografts.

Materials and methods: A search of 3 electronic databases, including PubMed/MEDLINE, EMBASE, Cochran Library Central, and a hand search for peer-reviewed journal relevant articles were performed. Relevant articles that were published between the years of 1999-2019 were included in the search. Human clinical trials with data on comparison of sinus volumetric and histometric outcomes with and without the use of rhBMP-2 in sinus grafting procedures, with 10 or more augmentation sites in each study group, and with a follow-up period of at least 3 months, were included. Variables such as the primary outcome (vertical bone level gain) and the secondary outcome (including implant survival rate, bone density, and the histological parametrics) that were recorded for each study was compared and analyzed.

Results: Seven randomized controlled trials (RCTs) were included. The two approaches (conventional bone grafting compared to bone morphogenic proteins (BMPs)) demonstrated comparable effectiveness for both clinical and histomorphometric measures.

Conclusions: This systematic review revealed that the use of rhBMP-2 in maxillary sinus floor augmentation achieved similar clinical and histometric outcomes when compared to conventional sinus grafting procedures after a healing period of at least 3 months or longer. Currently, the concentration and amount of rhBMP-2 utilized to
gain bone formation in maxillary sinus floor augmentation remains unclear and will need further clinical studies completed.
ACKNOWLEDGEMENTS

I would like to thank my mentor, Dr. Susan M. Chialastri, for her support and guidance throughout the project; Dr. Yueh J. Hsiao, for her assistance with refining the manuscript; and my Graduate Periodontology and Oral Implantology faculty, for the knowledge and guidance regarding the topic.
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CHAPTER 1
INTRODUCTION

Dental caries and periodontal disease are the main causes of tooth loss. During the last few decades, missing or lost teeth have been replaced with dental implants, which has become one of the most widely used techniques. Oral rehabilitation with implant-supported prosthesis have shown improved masticatory function and oral specific health-related quality of life compared to removable dentures. However, due to atrophy of the alveolar process, poor bone quality and maxillary sinus pneumatization, placement of implants in the posterior segment of the maxilla may become challenging. Additional surgical augmentation procedures are required to increase bone volume in maxillary sinus to accommodate future implant placements.

Prior to any augmentation procedures, cone beam computed tomography (CBCT) advanced technology has allowed clinicians to become familiar with the anatomy of the maxillary sinus of each individual. Clinicians should be aware of critical anatomical structures and the residual bone height and density of the sinus cavity. Maxillary sinus floor augmentation, most commonly known as a sinus lift, is a surgical procedure which increases the amount of bone in the posterior maxilla by lifting the floor of the Schneiderian membrane and placing a bone graft (Bathla et al., 2018). Sinus augmentation procedures can be classified into two approaches: indirect and direct. Indirect approach, most commonly known as crestal sinus lift, is typically indicated when there is sufficient height to stabilize the implant, and more vertical height is needed to encompass the implant in bone graft. There are several techniques that can be performed with the indirect technique, such as osteotomes, osseodensification (Densah) burs, antral
membrane balloon elevation, or hydraulic lift kits (Gandhi, 2017; Huwais et al., 2018).

The indirect approach works well in single sites but can be utilized in adjacent sites. The crestal approach is a less invasive procedure; however, the detection of a perforation of the sinus membrane is difficult to assess. In the event of a large perforation, clinicians must be capable and confident performing lateral sinus augmentation (Checchi et al., 2010). The direct approach, most commonly known as a lateral window sinus lift, is an invasive procedure which involves creating a window on the lateral wall of the maxilla (Kaufman, 2003). The window allows the clinician to directly visualize and instrument the Schneiderian membrane to the desired vertical height for future implant placements.

Lateral approached sinus lifts are indicated in sites which typically need more than one implant. The sites are in severely atrophic posterior maxillae, where the sinus has pneumatized and the vertical residual bone height is not enough to stabilize the implant (Bathla et al., 2018).

Different types of biomaterials have been used for maxillary sinus floor augmentation, including autograft, allograft, xenograft, alloplast, and growth factors; the selection of the ideal graft materials has been a subject of controversy over the years. Autogenous bone graft is considered the “gold standard” in augmentation procedures due to its osteogenic, osteoinductive, and osteoconductive characteristics (Sakkas et. al., 2017). Osteogenesis is the development and formation of bone by osteoblasts. Osteoinduction is the process where osteogenesis is induced; including the recruitment and stimulation of immature cells to develop into preosteoblasts. Lastly, osteoconductive surface allows bone growth on its surface and into pores (Albrektsson & Johansson, 2001). Although autogenous bone grafts are considered the “gold standard,” the graft is
associated with risk of donor site morbidity and unpredictable graft resorption. Therefore, various bone substitutes of biologic or synthetic origin are used to simplify the surgical procedure by diminishing the need for bone harvesting. Bone formation and regeneration using these bone substitutes involves complex cellular interactions in the signaling pathway.

Bone morphogenetic proteins (BMPs) are a group of naturally formed multifunctional growth factors found in human body and are part of the transforming growth factor-β (TGF-β) superfamily. The role of the TGF-β superfamily is to control the physiologic response and maintenance of metabolic homeostasis in the bone tissues (Guo & Wang, 2009). BMPs play an important role involving tissue morphogenesis, regeneration, cell differentiation, and healing processes. There are over 30 identified BMPs; only a small number are known for their osteoinductive qualities – BMP-2 and BMP-7 (Diaz-Sanchez et al., 2015). BMP-7 is a strong inducer of osteogenic differentiation of mature adipose stem cells; which has been shown to stimulate undifferentiated cells to produce mineralized tissue. Whereas, BMP-2 is a potent osteogenic factor that promotes differentiation of mesenchymal stem cells into osteoblasts and chondroblasts (Tash et al., 2014). Since the BMPs’ osteoinductive ability was discovered, researchers have been focusing on the therapeutic application of specific BMP isoforms, 2 and 7, in regenerative therapy. In a study by Krishnakumar, rhBMP-2 was documented mainly for the treatment of fractures, and rhBMP-7 mainly for non-union fractures and osteonecrosis (Krishnakumar et al., 2017).

Based on radiographic, histological, and clinical evaluation, the osseous bone defects displayed successful healing of segmental bony defects; these bony defects
resulted from trauma, infection or any malignancies. Bowers showed histologic success in regenerating a significant amount of periodontal attachment, which included new bone, new cementum, and connective tissue, by integrating osteogenin BMP-2 into the bone grafting material in humans with intrabony defects (Bowers et al., 1991). Other studies had also shown successful application of BMP-2 in repairing defects around implants with peri-implantitis and regenerating bone which helps re-establish implant osteointegration (Sigurdsson et al., 1997). With advanced molecular biology techniques, recombinant human BMP-2 (rhBMP-2) has been made available for therapeutic use due to its ability to rapidly trigger the differentiation of osteoblasts. These stem cells differentiate into osteoblasts and begin to form trabecular bone and/or cartilage; at the same time, angiogenesis (blood vessel formation) is observed (Schmitt et al., 1999). BMPs have crucial role in maintaining adult tissue homeostasis, such as the maintenance of joint integrity, the initiation of fracture repair, and vascular remodeling (Wang et al., 2014).

Treatment outcomes after enhancement of the vertical bone height in the maxillary sinus are well-documented and reported in numerous research articles. The different treatment modalities include but are not limited to autogenous block or particulate grafts, combination of autograft and allograft, xenograft, and biologics materials. According to Esposito et al. (2009), autogenous bone has been considered as the gold standard for augmenting bone with a very high success rate; however, the major limitation is the amount of autogenous bone available from the donor site, which may require another donor surgical site to obtain more autogenous bone making the overall surgery more invasive. Autogenous grafts are osteogenic, osteoinductive and
osteconductive; the graft contains osteoblasts, induces bone formation, and acts as a scaffold. Allografts, xenografts, and alloplasts are osteoconductive; the grafts function as a scaffold. Biologics, such as rhBMP-2, are osteoinductive and induces and enhances new bone formation (Nappe et al., 2016). According to Galindo-Moreno et al. (2018), allograft exhibited faster turnover and quicker decrease in biologic action after six months compared to xenograft. Another study stated that allograft presented with a significantly higher amount of de novo bone percentage than the xenograft. Alloplastic materials, made up of beta-tricalcium phosphate or hydroxyapatite, are typically used to decrease the risk of any human disease or prion transmission from a bovine derived source (Nappe et al., 2016).

Animal studies have shown that the high osteogenic activity of rhBMP-2 combined with absorbable collagen sponge (ACS) seemed to produce similar bone apposition results as autogenous bone (Wada et al., 2001; Lee et al., 2013). Similarly, another goat study concluded that the sinuses implanted with rhBMP-2/ACS demonstrated a greater radiopacity and induced an increased formation of vital bone (Nevins et al., 1996). In another study, bone augmentation with rhBMP-2 in rhesus monkeys revealed a substantial amount of calcified bone matrix to marrow spaces ratios according to the histomorpheic analysis. The results indicated that BMP-2 can bring about osseous regeneration in bony defects (Boyne, 1996). Furthermore, human studies demonstrated that the administration of rhBMP-2 with ACS in a maxillary sinus floor procedure produced new bone growth. This study displayed histological evidence of new bone growth and matured activity in the rhBMP-2 induced bone in all of the eleven patients that were evaluated (Boyne et al., 1997). Therefore, the objective of this
comprehensive review is to present current evidence on the effect of rhBMP-2 to enhance the vertical alveolar bone height in the posterior part of the maxillary sinus floor augmentation compared to other conventional bone grafting techniques without additional growth factors or other biologics, both clinically and histologically.
CHAPTER 2

MATERIALS AND METHODS

A search of 3 electronic databases, including PubMed/MEDLINE, EMBASE, Cochran Library Central, and a hand search for peer-reviewed journal relevant articles were performed. Relevant articles that were published between the years of 1999 to 2019 were included in the search. When searching the databases the following was used: (“growth substance[mh] OR growth factor[mh] OR biologic factors[mh] OR biologics[tiab] OR BMP2[tiab] OR bone morphogenic protein[mh] OR rhBMP-2[tiab] AND maxillary sinus[mh] OR maxillary sinus augmentation[tiab] OR sinus floor augmentation[tiab] OR sinus augmentation[tiab] OR sinus lift[tiab] OR sinus elevation[tiab]”) and was given 1,627 results. Eleven hand-searched articles were found from dental and implant-related journals between the year of 1999 to 2019.

The PICO (patient, intervention, comparison, outcome) question that was asked was as following:

P: Healthy patients without smoking history receiving maxillary sinus augmentation;

I: Human clinical trial of 10 or more augmentation sites in each group with data on sinus volumetric/ histological outcomes in sinus grafting procedures with at least 3-month follow-up period;

C: The effect of rhBMP-2 combined with other grafting materials on the volumetric/ histometric changes after sinus floor augmentation compared with bone grafting materials without an addition of biologic agents;

O: Differences in the of vertical bone level (VBL) gain, bone density, and histometric outcomes of the grafted sinus in preparation for future implant placements.
The studies were chosen based on inclusion criteria: human clinical trials that contained data comparing volumetric and/or histometric outcomes of the sinus with and without the use of rhBMP-2 in sinus grafting procedures; at least 10 or more augmentation sites in each study group; and with a follow-up period of at least 3 months. Case reports and systematic reviews were excluded; however, the references were screened for any relevant articles that could potentially be used for this review.

The CONSORT (Consolidated Standards of Reporting Trials) checklist focuses how the randomized controlled trials were designed, analyzed, and interpreted (2010). Using the CONSORT guideline checklist, the quality of the randomized control trials (RCTs) were selected for the following parameters: sequence generation, randomization methods, allocation concealment method, masking of the examiner (blinding), incomplete outcome data adequately addressed, and free of selective outcome reporting. The risk of bias was categorized in different degrees: low risk if all the criteria were met, moderate risk when only one criterion was missing, and high risk if two or more criteria were missing. Demographic information was recorded for each study, including the study design, sample size, technique used, number of augmented sites, doses of rhBMP-2, types of grafting materials, and follow-up period. Additional variables, if there were any, recorded for each study were the primary outcome (VBL gain) and the secondary outcome (including SR, bone density, and the histological parametrics).
CHAPTER 3

RESULTS

The screening process was shown in the PRISMA flowchart (Figure 1).

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) was developed for the reporting of systematic reviews and meta-analyses (2015).
Electronic and hand searches yielded 1,632 articles, of which 473 articles were excluded, since those studies examined animals. The remaining 1,154 articles were selected for full-text evaluation after screening their titles and abstracts; of which 1,147 articles were excluded since those studies were older than 1999, case reports with less than 10 subjects, and no data reported for statistical analysis. Seven articles (Boyne et al., 2005; Triplett et al., 2009; Kao et al., 2012; Froum et al., 2013; Froum et al., 2014; Kim et al., 2014; Kim et al., 2015) were included in this systematic review. The main features, data, and conclusions of the included studies were summarized in Table 1.
Table 1. Features, data and conclusions of the included articles.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>Age/ Gender</th>
<th># of Test sites</th>
<th># of control sites</th>
<th>Follow-up (months)</th>
<th>Test group intervention/dose</th>
<th>Control group intervention</th>
<th>Survival Rate %</th>
<th>VBL gain (mm)</th>
<th>Bone density (mg/cm²)</th>
<th>% of vital bone</th>
<th>% of residual biomaterials</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyne et al. (2005)</td>
<td>48</td>
<td>Avg. 55.2 F - 29 M-19</td>
<td>T1:17 T2:18</td>
<td>13</td>
<td>CT scan taken 4 months after augmentation and 6 months after loading</td>
<td>rhBMP-2/ACS 1.50 mg/ml (T1) 0.75 mg/ml (T2)</td>
<td>Autograft (N = 7) / Autograft + allograft (N=6)</td>
<td>79%</td>
<td>10.16 ± 4.70 (T1) / 9.47 ± 5.72 (T2) / 11.29 ± 4.12</td>
<td>10.29 ± 77 (T1) / 84 ± 50 (T2) / 350 ± 243</td>
<td>NA</td>
<td>NA</td>
<td>The higher of the rhBMP-2 concentrations was deemed the most effective for maxillary sinus floor augmentation procedures.</td>
</tr>
<tr>
<td>Triplett et al. (2009)</td>
<td>160</td>
<td>23-76 F - 71 M-89</td>
<td>82</td>
<td>77</td>
<td>CT scans taken 6 months after augmentation and 6 months after implant placement</td>
<td>rhBMP-2/ACS 1.50 mg/ml (N = 82)</td>
<td>Autograft (N = 42) / Autograft + allograft (N = 35)</td>
<td>87% / 87%</td>
<td>7.83 ± 3.52 / 9.46 ± 4.11</td>
<td>200±283 (mg/cm³)</td>
<td>NA</td>
<td>NA</td>
<td>Significant overall bone height gain occurred in both of the treatment groups. The crestal bone loss was comparable between the 2 groups.</td>
</tr>
<tr>
<td>Kao et al. (2012)</td>
<td>22</td>
<td>34-67 F - 9 M-13</td>
<td>11</td>
<td>11</td>
<td>Core samples taken after 6-9 months after sinus augmentation</td>
<td>rhBMP-2/ACS 1.50 mg/ml mixed with deproteinized bovine bone in an 80/20 ratio</td>
<td>Deproteinized bovine bone</td>
<td>NA</td>
<td>NA</td>
<td>16.04±7.45 / 24.85±5.82 (N = 10)</td>
<td>15.70±4.97 / 39.70±7.27 (N = 10)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Froum et al. (2013)</td>
<td>21</td>
<td>NA</td>
<td>T1:10 T2:11</td>
<td>11</td>
<td>CT scan taken 6-9 months after sinus augmentation</td>
<td>5.6 ml rhBMP-2/ACS + MCBA (T1) 2.8 ml rhBMP-2/ACS + MCBA (T2)</td>
<td>MCBA</td>
<td>NA</td>
<td>NA</td>
<td>25.3±15.3 (T1) / 21.5±11.6</td>
<td>10.5±12.9 (T1) / 23.2±12.9</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

#, number; Avg., average; F, females; M, males; T, test group; MCBA, mineralized cancellous bone allograft; ErhBMP, Escherichia-coli-produced rhBMP-2; BCP, β-tricalcium phosphate-coli-produced rhBMP-2; BCP, β-tricalcium phosphate; HA, hydroxyapatite; NA, not available.

*values calculated by the authors
Table 1. (continued) Features, data and conclusions of the included articles.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>Age/ Gender</th>
<th># of Test sites</th>
<th># of control sites</th>
<th>Follow-up (months)</th>
<th>Test group intervention/ dose</th>
<th>Control group intervention</th>
<th>Survival Rate %</th>
<th>VBL gain (mm)</th>
<th>Bone density (% of vital bone)</th>
<th>% of residual biomaterials</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froum et al. (2014)</td>
<td>20</td>
<td>NA</td>
<td>T1:12 T2:12</td>
<td>12</td>
<td>CT scan taken 6–9 months after augmentation</td>
<td>5.6 ml rhBMP-2/ACS + MCBA (T1) 2.8 ml rhBMP-2/ACS + MCBA (T2)</td>
<td>MCBA</td>
<td>NA</td>
<td>12.2±4.3 (T1)/12.5±3.9 (T2)/10.6±3.4</td>
<td>NA</td>
<td>NA</td>
<td>The results showed bone height gain was significantly greater in the treatment groups compared with the control in short term.</td>
</tr>
<tr>
<td>Kim et al. (2014)</td>
<td>41</td>
<td>Avg. 52.4 F-19 M-22</td>
<td>20</td>
<td>21</td>
<td>CT scan and panoramic film taken 6 months after augmentation</td>
<td>ErhBMP-2 0.67 ml in 1.50 mg/ml buffer + 1 g BCP</td>
<td>Deproteinized bovine bone</td>
<td>NA</td>
<td>13.41±2.26/12.39±3.18</td>
<td>NA</td>
<td>24.1±53.1/19.7±10.8*</td>
<td>Sinus augmentation with ErhBMP-2 carrying BCP carrier did not enhance bone regeneration compared to graft alone.</td>
</tr>
<tr>
<td>Kim et al. (2015)</td>
<td>127</td>
<td>Avg. 53.54 F-34 M-93</td>
<td>65</td>
<td>62</td>
<td>CT scan and panoramic film taken 3 months after augmentation</td>
<td>1 mg/ml ErhBMP-2 (0.5–2.0 mg/sinus) + 0.5–2.0 g HA</td>
<td>Inorganic bovine bone</td>
<td>NA</td>
<td>NA</td>
<td>16.10±10.52/8.25±9.47</td>
<td>58.64±14.61/62.31±14.57</td>
<td>Low-dose ErhBMP-2 with HA was effective and significantly enhanced vital bone formation in early stages of healing.</td>
</tr>
</tbody>
</table>

#, number; Avg., average; F, females; M, males; T, test group; MCBA, mineralized cancellous bone allograft; ErhBMP, Escherichia-coli-produced rhBMP-2; BCP, b-tricalcium phosphatecoli-produced rhBMP-2; BCP, b-tricalcium phosphate; HA, hydroxyapatite; NA, not available.

*values calculated by the authors
The results of risk of bias assessment for included RCTs were summarized in Table 2. Four studies were considered to have a moderate risk of bias and three studies were considered to have a high risk of bias.
Table 2. Risk Assessment of publication bias for the included studies.

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Randomization</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Examiner masked (blinding)</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>All patients accounted for at end of study</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Incomplete outcome data adequately addressed</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Free of suggestion of selective outcome reporting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Estimated potential risk of bias</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
All the studies, except Froum et al. (2013 & 2014), reported the age range and the gender of the study participants. In addition, the seven studies performed computed tomography (CT) scan within 3 to 9 month period after sinus floor augmentation to evaluate the volumetric changes. Boyne et al. (2005) and Triplett et al. (2009) were the only studies that reported the survival rate (SR) of the implants.

In this review, two different types of rhBMP-2 were utilized. All the studies used rhBMP-2 derived from mammalian cells, and Kim et al. (2014) and Kim et al. (2015) used Escherichia coli-produced rhBMP-2 (ErhBMP-2). Considering the grafting materials, Boyne et al. (2005) and Triplett et al. (2009) introduced rhBMP-2 with absorbable collagen sponge (ACS) (rhBMP-2/ACS) to augment maxillary sinuses as experimental group and autogenous graft in combination with allogeneic grafts as control group. Kao et al. (2012) used rhBMP-2/ACS mixed with deproteinized bovine bone as test group and deproteinized bovine bone alone as control group. Froum et al. (2013 & 2014) studies used rhBMP-2/ACS mixed with mineralized cancellous bone allograft (MCBA) as test group and MCBA alone as control. Kim et al. (2014) used hydroxyapatite (HA) and beta-tricalcium phosphate (BCP) at a ratio of 30:70 as the carrier of ErhBMP-2 solution in test group and BCP alone as control group. Kim et al. (2015) utilized low dose ErhBMP-2 soaked with HA for the experimental group and inorganic bovine bone xenograft for the control group.

In the Boyne et al. (2005) study, by 4 months postoperatively, the mean vertical bone height changes were less in the 0.75mg/mL concentration of rhBMP-2 group than the 1.50mg/mL concentration group. At 4 months postoperative, new bone density was statistically different among the treatment groups, more bone density in the group with
1.50mg/mL. A standard density block was utilized to assess the bone density of the newly induced bone in two areas of interest. After 36 months of functional loading, the dental implant survival rates were 79% in the bone graft, 81% in the treatment group using 0.75mg/mL and 88% in the treatment group using 1.50mg/mL.

In the Triplett et al. (2009) study, by 6 months there was a significant amount of new bone that was formed in each group. No marked differences were found in the histologic parameters evaluated between the two groups. Histologically, the new bone generated was comparable to the native bone in density and structure in both groups. The success rate for the rhBMP-2/ACS group was 79%, and 201 of 251 implants placed in the bone graft group and 199 of 241 implants placed in the rhBMP-2/ACS group were integrated, retained, and functional at 6 months after loading. No adverse events were deemed related to the rhBMP-2/ACS treatment. The dental implant survival rate was 87%, the same for both test and control groups after 6 months of implant placement.

Kao et al. (2012) found that there were no healing complications in both treatment groups. After 6 to 9 months of healing, all implants achieved primary stability. Bone biopsies were taken for histologic examination, which showed that all graft sites with rhBMP-2/ACS + Bio-Oss and Bio-Oss alone healed without inflammation and uneventfully. Newly formed mineralized bone consisted of a mixed type of bone that included woven bone and matured bone structure.

In the study Froum et al. (2013) conducted, the analysis showed that there was no statistically significant difference in new bone between MCBA+ACS (T1) and MCBA (control) or between MCBA+rhBMP-2+ACS (T2) and control. There was a statistically
significant difference in new bone between T1 and T2. For residual graft, there was a statistically significant difference between T1 and control but not between T2 and control.

In Froum et al. (2014), two time points where selected for measurements of height: The results indicated that height of the grafted sinus was significantly greater in the treatment groups compared with the control. However, by the second time point, there were no statistically significant differences. Three weeks post-surgery bone volume measurements showed similar statistically significant differences between test and controls. However, test group 1 with the greater dose of rhBMP-2 showed a statistically significant greater increase compared with test group 2 and the control. All three groups had similar volume and shrinkage. By examining the cross-sectional slices of the CBCT, the bone density of the grafted sites was measured in Hounsfield units (HU). Density measurements varied from the above results, with the control showing statistically significant greater density at both time points. By contrast, the density increases over time in both rhBMP groups was similar and statistically higher than in the control group.

In the Kim et al. (2014) study, all the sites healed with no inflammation or complications. The radiographic analysis using three-dimensional reconstruction software revealed that the volume of the bone increased, but the difference was not statistically significant in either group. Between the two groups, comparing the volumetric changes also showed no significant difference. Although, there were different healing patterns that were observed through histologic analysis, none of the histometric parameters differed significantly between the groups.
Lastly, in the Kim et al. (2015) study, at 3 months after the sinus augmentation, core biopsies were obtained and analyzed histomorphometrically. The mean new bone formation with rhBMP-2/HA and bovine xenograft augmentation was 16.10% and 8.25%, respectively. The soft tissue and residual graft areas showed no significant differences between the groups. With regard to safety, no significant difference between the two groups was observed; there was no significant increase in the amount of rhBMP-2 antibodies in the serum after rhBMP-2/HA grafting.
CHAPTER 4

DISCUSSION

The studies that reported the amount of grafted vital bone using rhBMP-2 ranged from 16% to 25% compared to conventional grafting ranged from 17% to 25%. The two studies that analyzed the survival rate of implants in the grafted sinus with rhBMP-2 ranged from 81% to 87% compare to 79% to 87% survival rates in grafted sites without rhBMP-2. The results of this current review demonstrated that the use of rhBMP-2 in human maxillary sinus floor augmentation did not show a significant difference on dimensional or histometric outcomes after 3 months or more of healing, in comparison with conventional surgical procedures. This review evaluated the amount of vital bone formed after three or more months after sinus floor augmentation procedures by analyzing previously published histomorphometric data. Histomorphometric analysis is essential for evaluation of new and early bone formation in which the bone density is insufficient for computed tomography evaluation. No significant difference was detected regarding the percentages of vital bone formation and residual bone grafting materials. This implies that in maxillary sinus floor augmentations, rhBMP-2 achieved similar histometric outcomes when compared to conventional sinus grafting procedure.

Furthermore, it is worth noting the histomorphometric findings are only based on 4 studies (Kao et al., 2012; Froum et al., 2013; Kim et al., 2014; Kim et al., 2015) and with a 3- to 9-month follow-up. Among these four studies, one study used MCBA (Froum et al., 2013), another one used xenograft (Kao et al., 2012), one used BCP (Kim et al., 2014), and the last study used hydroxyapatite granules (Kim et al., 2015) as the carriers for rhBMP-2.
Kim et al. (2015) reported that the hydroxyapatite alone functioned successfully as a carrier for rhBMP-2 to improve the fusion rate according to the increase in the rhBMP-2 dose. As carriers of rhBMP-2, those bone substitutes can maintain the graft volume during wound closure and provide mechanical strength until woven bone is induced by rhBMP-2 and changed to lamellar bone. In contrast, Boyne et al. (2005) and Triplett et al. (2009) utilized absorbable collagen sponge, which did not maintain porous structural integrity by covering soft tissue and external force during bone regeneration. Kao et al. (2012) reported that new bone formation was compromised when a deproteinized bovine bone was used as a carrier.

Triplett et al. (2009) also reported significantly higher bone density in the bone graft group compared with the rhBMP-2/ACS treatment group at 6 months postoperatively. The bone density of the grafted sites was examined by analyzing the cross-sectional slices of the CBCT and measuring the Hounsfield units (HU). Density measurements varied from the above results, with the control showing statistically significant greater density at both time points. However, the induced bone density in the rhBMP-2/ACS group was significantly higher than the bone graft group at 6 months after functional loading. The authors concluded that the bone density around implants after functional loading in augmented sinus with rhBMP-2/ACS performed as well as that of the bone graft group. It may be concluded that a higher density of mineralized tissue shown in CT scan/radiograph at early stage of healing does not necessarily equate to higher amount of mature bone; because, the radiopaque/mineral property of the grafting materials might contribute to overestimation of bone quality. In the Boyne et al. (2005) and Triplett et al. (2009) studies, the experimental groups had no mineralized materials
grafted into the sinus; however, in the Froum et al. (2014) study, they grafted a relatively smaller amount of allograft into the sinus in the treatment group while a larger amount of allograft used for the control. Therefore, special precaution should be taken when interpreting the results of this parameter.

Both studies (Boyne et al., 2005 and Triplett et al., 2009) reported that the majority of implant failures occurred before prosthetic loading and resulted from inadequate bone quality during the osseointegration phase. Therefore, a possible longer healing period (>6 months) might be necessary before implant placement to achieve better bone quality. Kim et al. (2015) reported that the amount of new bone formation 3-months after sinus augmentation using rhBMP-2 can reduce the conventional 6-month waiting period by 50%. The effect of utilizing rhBMP-2 in sinus floor augmentation on vital bone formation might be attained at the very early stage of the healing period, but this difference possibly will diminish after 6 to 9 months post-operation. However, future clinical studies should be conducted to determine the ideal healing time and surgical protocol when using rhBMP-2 to augment the maxillary sinus.

Froum et al. (2013) and Kim et al. (2014) reported the difference of percentage of vital bone formation between the sites with perforated and non-perforated sinus membranes. Froum et al. (2013) reported that more bone formation in perforated sinuses was associated with higher dosage of rhBMP-2/ACS. In contrast, Kim et al. (2014) showed less bone formation in perforated sinuses with the treatment of BMPs. The authors considered that the perforated Schneiderian membrane might compromise the osteoinductive capacity of rhBMP-2. At this moment, the effect of membrane perforation on vital bone formation in maxillary sinus floor augmentation with the use of rhBMP-2
remains unclear and will need further research conducted. Although there is not a significant difference between the rhBMP-2 group and control group, there is a lack of human clinical trials to investigate potential indications, such as limited residual bone height or long span grafted area, of the use of rhBMP-2 in sinus floor augmentation procedures. The residual bone height between bone crest and sinus floor has been associated with long-term implant success and prognosis (Pjetursson et al., 2009). The use of biologic agents such as BMP-2 might potentially enhance positive surgical outcomes due to its angiogenesis and osteogenesis characteristics.

Serious complications, such as swelling or infection, could occur after the use of rhBMP-2 in grafting procedures. Kim et al. (2014) and Kim et al. (2015) reported minor complications, which included post-operative bleeding, pain and swelling. Boyne et al. (2005) and Triplett et al. (2009) indicated the morbidity associated with bone graft harvesting to use autogenous bone had a significantly greater incidence of oral edema, ecchymosis, pain, arthralgia, abnormal gait, sinusitis, skin rash, and erythema than the rhBMP-2/ACS group. The post-operative facial edema might result from an influx of fluid and cells into the treatment site during the initial phase of the wound healing.

Reviewing the seven articles, there were various degrees of heterogeneity and publication bias. Within the selected studies, there were several confounding factors such as – the study designs, follow-up periods, the grafting materials and the types and concentrations of rhBMP-2. The studies analyzed compared rhBMP-2 to other grafting materials where there could be a difference in the concentration of the rhBMP-2 that is used. Since most of the articles in this review were either moderate or high in terms of the risk of bias, the data should be analyzed cautiously.
CHAPTER 5

CONCLUSION

This review revealed that the use of rhBMP-2 in maxillary sinus floor augmentation achieved similar clinical and histological outcomes when compared to conventional sinus grafting procedures, after a healing period of 3 to 9 months. Additionally, vital bone formation utilizing rhBMP-2 in sinus floor augmentation might be achieved at the very early stage of the healing period, but this difference possibly will diminish after 6 to 9 months post-operative. However, there have been other studies that have shown the post-operative pain and other patient-reported outcomes that were improved using rhBMP-2 as compared to autogenous bone, whether the bone was harvested with an intraoral or extraoral approach. At this moment, the concentration and amount of rhBMP-2 utilized to gain bone formation in maxillary sinus floor augmentation remains unclear and will need further clinical studies to determine the ideal healing time and surgical protocol.
REFERENCES CITED


