Do Barrier Membranes Improve Regeneration of Bony Defects? A Literature Review

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Abstract

Objective: Barrier membranes have been extensively used for bone regeneration. However, their effectiveness is still under investigation. This review was designed to assess whether barrier membranes affect the success of bone graft/bone substitute materials.

Methods: Articles published by November 2012 were collected through electronic searching in MEDLINE, EMBASE and CENTRAL databases. Controlled animal and human prospective studies that had evaluated the efficacy of membranes in membranes in various part of the body except periodontal lesion, extraction socket preservation and maxillary sinus graft, and had more than 4 weeks follow-up period were considered. In addition, in all the included studies complete soft tissue coverage over the defects was achieved. Application of any material other than membrane, bone graft or bone substitute material was lead to exclusion of the article. Obtained results were collected and presented in tables.

Results: A total of 36 studies were selected. Controversy existed in the results of the mentioned articles. In total, 23 studies confirmed the usefulness of membranes.

Conclusion: Evidence suggests that membranes might be useful for bone augmentation. More randomized clinical trials are necessary to achieve applicable results.

Key words: Artificial membrane, Bone regeneration, Bone transplantation, Guided Tissue Regeneration

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Introduction:

Various factors such as trauma, infection, congenital disorders and resection of tumors can cause facial bone defects (1). Reconstruction of these defects has always been a challenge for surgeons. Guided tissue regeneration is a popular technique for this purpose; which, was first introduced by Dahlin et al, in 1988. This method is based on the theory that during wound healing, different cell types with variable numbers migrate towards the wound site at different speeds (2). Membranes may assist bone regeneration by selective inhibition of the migration of some cell types towards the wound site, elimination of inhibitors and preservation of growth factors. Space maintenance is another reason for using these membranes (1). Membranes have two main types of resorbable and non-resorbable. The primary membranes were non-resorbable. These membranes are capable of isolating the bone defects from other tissue cells for a long time. In case of using these membranes, a second (reentry) surgery is usually required to remove the membrane. Additionally, if these membranes are exposed, healing will not occur spontaneously and there would be a risk of bacterial contamination of the exposed membrane and subsequent development of infection (3, 4). e-PTFE, d-PTFE and titanium mesh are among non-resorbable membranes. e-PTFE membranes are considered the gold...
standard for bone regeneration and all the newly introduced membranes have to be compared with e-PTFE.

Resorbable membranes were introduced in order to eliminate the need for the second (reentry) surgery. Such membranes enhance soft tissue healing and integrate into the host tissue. Furthermore, in case of exposure, the membrane is quickly absorbed keeping its microstructure safe from the microbial contamination. Natural or synthetic polymers are used for the fabrication of resorbable membranes. Collagen, dura mater, polyglycolic acid, polylactic acid, polyurethane and their co-polymers are among the materials used for the manufacturing of resorbable membranes. When a collagen membrane is implanted into the human body, it is degraded by the enzymatic activity of macrophages and polymorphonuclears (4).

Space maintenance is a critical factor in bone regeneration. The maintained space facilitates the migration of cells towards the bony defect and protects the newly formed fibrin clot. Additionally, membrane collapse reduces the bone regeneration rate beneath it. Several methods have been recommended to achieve space maintenance. Use of graft materials under the membrane and application of titanium reinforced membranes and titanium mesh are among the suggested techniques (5, 6, 7).

To date, numerous studies have evaluated the efficacy of membranes in regeneration of bony defects. Although Dahlin theory regarding the efficacy of membranes seems logical, several experimental studies have stated otherwise (8, 9). In contrast, a couple of researchers believe that membranes are an effective solution for the challenge of bone regeneration (10, 11). Thus, the available literature yield conflicting results regarding the effect of membranes on bone regeneration.

Some review studies have also evaluated this subject but suffer shortcomings such as unspecified follow up periods and results based on animal experiments only (12). Therefore, the present review study was designed to collect all the relevant previous studies on this subject and report the results. The present study reviewed human and animal experiments published on the efficacy of membranes in local bone regeneration.

Methods:
The present study evaluated the results of controlled human and animal studies. This study answers the question whether the use of membranes has any effect on the amount of bone formation and stability of bone graft materials based on histological, radiographic and clinical findings.

Search tools:
Electronic search was carried out for studies with relevant subjects published by November 2012 using MEDLINE, EMBASE and CENTRAL databases. The searched key words were “bone transplantation” (MeSH), “bone regeneration” (MeSH), “bone substitute” (MeSH), “alveolar ridge augmentation” (MeSH), “artificial membrane” (MeSH), “guided tissue regeneration” (MeSH), “resorbable membrane” (MeSH) and “non-resorbable membrane” (MeSH).

Selection of studies:
Titles of studies found using the mentioned key words were evaluated and those irrelevant to our subject were excluded. Abstracts of selected articles were assessed in terms of the following inclusion criteria:

1. Bony defects in various part of body
2. Controlled animal and human studies that had used membranes and bone graft
3. Full soft tissue coverage over the defect after the surgery
4. A follow up period of 4 weeks or longer

The exclusion criteria were:

1. Uncontrolled studies
2. Use of any material other that graft and membrane in the defect
3. Use of membrane in periodontal lesions, extraction socket preservation, peri-implantitis, or maxillary sinus graft

During the process of article selection, journal’s name, authors’ names, and date of publication were eliminated to reduce the reviewer bias and each article was allocated a code.

Data extraction:
To collect data, forms specifically designed for this purpose were used. Data regarding type of membrane, bone graft/bone substitute material, number and species of understudy samples, data analysis method, duration of follow up period, and results were collected.
Data analysis:
Defects covered with membrane in studies were considered as the test and those without membrane coverage were considered as the control group. The obtained results were collected and presented in tables.

Results:
Of a total of 4,025 articles obtained through electronic search with key words in databases and also through hand search of journals, 36 met the inclusion criteria and were selected for our study. The process of article selection is demonstrated in Figure 1.

Figure 1. The process of selection of searched articles

Characteristics of studies, application results and complications of the performed therapeutic intervention are summarized in Tables 1 to 5 based on the type of bone graft used (autogenous, allogenous, xenogenous, alloplastic material).

In sixteen studies membranes were used with autogenous bone grafts. In 10 of them membranes were effective (6,10,14,16-18,20-22,24). The remaining studies failed to find a significant difference in bone regeneration between case and control groups (8,9,13,15,19,23).

Evidence of bone formation, reduced bone graft resorption and integration of graft into the recipient site in these studies were indicative of the efficacy of intervention in the test group. In one of these studies, the membrane was effective only when covering the defect and after its removal, severe bone resorption occurred (15).

Another study introduced membrane exposure as a risk factor compromising the success of bone regeneration and reported a case of severe bone graft resorption and lack of continuity between the graft and the recipient site in situations where the membrane had been exposed (18).

In one article, membranes were used over allogenous bone grafts. This study found higher height index in case groups (11).

In ten articles, membranes were used with xenogenous bone graft, and 8 of them proved effectiveness of the membranes by observing increased bone formation and decreased bone resorption (26-30,32,33,34). However, the remaining articles did not found any significant differences between case and control groups (25,31).
Table 1. Qualitative data obtained from reviewing human and animal studies which had used autogenous bone graft

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and species of understudy samples/Site of defect</th>
<th>Type of membrane/type of bone graft material/graft source</th>
<th>Data analysis technique/Duration of follow up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberius P. et al, (1992)(10)</td>
<td>28 rats Calvarium, mandible e-PTFE mandible/ Fibula</td>
<td>Histology</td>
<td>12 weeks</td>
<td>Bone graft was more active in the case group and caused an increase in the cancellous component. Less volumetric loss was observed in the test group.</td>
</tr>
<tr>
<td>Dongieux JW. et al, (1998)(13)</td>
<td>4 dogs Mandible Collagen e-PTFE/ Mandible</td>
<td>Clinical, Histology</td>
<td>10 weeks</td>
<td>The change in bone volume compared to baseline was 45.7% in the collagen, 31.5% in the e-PTFE and 40.0% in the control group. The differences were not significant.</td>
</tr>
<tr>
<td>Lundgren AK. et al, (1997)(14)</td>
<td>8 rabbits Mandible / skull Polylactide, glycolide</td>
<td>Clinical, Histology, Histomorphometry</td>
<td>12 weeks</td>
<td>The mean volume of the augmented bone was 148.1 ± 23.2 mm³ in the test and 119.6 ± 12.2 mm³ in the control group. This difference was statistically significant.</td>
</tr>
<tr>
<td>Rasmusson L. et al, (1999)(15)</td>
<td>9 rabbits Tibia bone e-PTFE/ Calvarium</td>
<td>Clinical, Histology, Histomorphometry</td>
<td>8, 16, 24 weeks</td>
<td>While maintained, the membrane had a protective effect on the graft but after membrane removal, severe bone resorption was observed.</td>
</tr>
<tr>
<td>Antoun H. et al (2001)(8)</td>
<td>12 humans Maxilla/Mandible e-PTFE/ Mandible</td>
<td>Clinical, Histology</td>
<td>CT scan</td>
<td>The difference in width augmentation between the test and control groups was not statistically significant (mean width 3.7 mm in the test and 2.9 mm in the control group). A significant difference was noted in horizontal bone resorption between the test (mean of 0.3 mm) and the control (mean of 2.3 mm) group.</td>
</tr>
<tr>
<td>Donos N. et al, (2002)(16)</td>
<td>51 rats Maxilla Mandible e-PTFE/ Iliac bone</td>
<td>Histology</td>
<td>Planimetric assessment</td>
<td>After 6 months, maxillary grafts in the test and control groups suffered severe bone resorption and lack of continuity between the graft and the recipient site.</td>
</tr>
</tbody>
</table>
In mandible, grafts covered with membrane did not suffer resorption and well integrated into the adjacent tissues. In the control group, varying degrees of resorption and integration were observed.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rats</th>
<th>Site</th>
<th>Membrane</th>
<th>Planimetric assessment</th>
<th>Days</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donos N. et al, (2002)(17)</td>
<td>30</td>
<td>Mandible</td>
<td>e-PTFE/Mandible</td>
<td>Planimetric assessment</td>
<td>0, 12, 15, 30, 60, 180, days</td>
<td>After 180 days, gradual resorption and loss of integrity was observed between the graft and the adjacent tissues in the control group. In the test group, area beneath the membrane was completely filled with bone and a complete continuation was observed between the graft and the adjacent tissue.</td>
</tr>
<tr>
<td>Donos N. et al, (2002)(18)</td>
<td>20</td>
<td>Maxilla</td>
<td>e-PTFE/Mandible</td>
<td>Planimetric assessment</td>
<td>15, 30, 60 and 90 days</td>
<td>In situations where the membrane had been exposed and also in the control group, severe bone graft resorption and lack of continuity between the graft and the recipient site were observed. In cases where membrane was not exposed, the graft was in continuity with the adjacent structure and no resorption occurred.</td>
</tr>
<tr>
<td>Salata LZ. et al, (2002)(19)</td>
<td>14</td>
<td>Mandible</td>
<td>e-PTFE/Radial bone</td>
<td>Planimetric assessment</td>
<td>6, 24 weeks</td>
<td>After 24 weeks, the mean amount of new bone in defects was $3.33 \pm 0.83$ mm in the test and $2.69 \pm 1.00$ mm in the control group. The difference was not statistically significant.</td>
</tr>
<tr>
<td>Jardini MAN. et al, (2005)(21)</td>
<td>60</td>
<td>Mandible</td>
<td>e-PTFE/Calvarium</td>
<td>Planimetric assessment</td>
<td>7, 14, 21 and 45 days</td>
<td>Severe bone graft resorption in the control group and extensive bone regeneration in the test group were observed.</td>
</tr>
<tr>
<td>Gielkens PFM. et al, (2008)(9)</td>
<td>192</td>
<td>Mandible</td>
<td>Poly (DL-lactide-e-caprolactone)/Collagen/e-PTFE</td>
<td>Microradiography/Micro-CT</td>
<td>2, 4, 12 weeks</td>
<td>No significant difference was detected between the test and control groups in terms of bone remodeling, resorption or integration of the graft into the recipient site.</td>
</tr>
</tbody>
</table>
Comparison of collagen membranes with and without cross-links in studies yielded controversial results. One study stated that cross-linking is a favorable property (27) while another one could not find a significant difference in this regard (29). Kim SH et al, in their study applied a double-layer collagen membrane and observed less graft resorption and higher density of the newly formed bone (30).

In two articles, membranes were placed over alloplastic materials, and both of them reported usefulness of the membranes (35,36).

In seven articles, different graft materials were used in case and control groups. In 3 of them, membranes increased bone regeneration and decreased bone resorption (37,38,42). Interestingly, in one study membranes caused decreased bone regeneration in comparison with defects without membranes (7). In another study, the maintenance of bone graft volume was dependent on membrane stability over defect during healing period (39). Von Arx et al
showed that defects filled with autogenous graft and covered with e-PTFE membranes had more bone regeneration compared with defects filled with allogenic graft or alloplastic material and covered with the same membrane (42). In remaining articles no significant difference was seen between case and control groups regarding the amount of bone formation (40,41).

**Table 2. Qualitative data obtained from reviewing human and animal studies which had used allogenous bone grafts**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and species of understudy samples/Site of defect</th>
<th>Type of membrane, type of bone graft material/graft source</th>
<th>Data analysis method/duration of follow up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordh M. et al, (1998)(11)</td>
<td>21 rats Cranium e-PTFE/Femur, Tibia</td>
<td>Histology, immunohistochemistry 12-20 weeks</td>
<td>The height (the ratio of newly formed bone to the remaining graft material) after 20 weeks was 0.28±0.05 in the test and 0.00 ± 0.00 in the control group. The differences were statistically significant.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Qualitative data obtained from reviewing human and animal studies which had used xenogenous bone grafts**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and species of understudy samples/Site of defect</th>
<th>Type of membrane, type of bone graft material/graft source</th>
<th>Data analysis method/duration of follow up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khoshkhoon ejad AA. et al, (2006)(25)</td>
<td>12 rabbits Calvarium Collagen/Deproteinized bovin bone mineral</td>
<td>Histology, Histomorphometry 1, 2 months</td>
<td>Percentage of regenerated bone was 22.41±1.32% in the test and 22.95±2.18% in the control group. This difference was not statistically significant.</td>
<td></td>
</tr>
<tr>
<td>Queiroz TP. et al, (2006)(26)</td>
<td>30 rabbits Parietal bone Bovine bone matrix membrane/ Lyophilized bovine bone</td>
<td>Histology 15, 30, 60 days</td>
<td>Immature bony islands partially filled the control group defects. In the test group defects, the newly formed bone was more mature and greater in amount.</td>
<td></td>
</tr>
<tr>
<td>Zubery Y. et al, (2007)(27)</td>
<td>12 dogs Mandible GLYM, BCM/ Deproteinized bovine bone mineral</td>
<td>Histology, Histomorphometry 8, 16, 24 weeks</td>
<td>Both membranes were effective in bone regeneration. In areas of contact with bone, all GLYM sites had been ossified.</td>
<td></td>
</tr>
<tr>
<td>Kim M. et al, (2008)(28)</td>
<td>6 dogs Mandible Collagen/ Deproteinized bovine bone mineral</td>
<td>CT scan 2, 4 months</td>
<td>Use of membrane enhanced bone regeneration. Percentage of new bone formation in the layer immediately below the surface was 14±20% in the control group, 27±15% in the CM test group, and 36±9% in the CCM test group. The difference between each test and control group was statistically significant but the difference between the two test groups was not statistically meaningful.</td>
<td></td>
</tr>
<tr>
<td>Bornstein MM. et al, (2009)(29)</td>
<td>17 pigs Calvarium CM CCM/ Deproteinized bovine bone mineral</td>
<td>Histology Histomorphometry 4 months</td>
<td>Grafts covered with membrane showed less bone resorption compared to controls. In the double-layer collagen group less bone resorption and higher bone density were observed compared to the single layer</td>
<td></td>
</tr>
<tr>
<td>Kim SH. et al, (2009)(30)</td>
<td>36 rabbits Parietal bone Single-layer collagen Double-layer collagen /bovine porous bone mineral</td>
<td>Histology Histomorphometry 3, 6, 9, 12, 18, 24, 36, 48, 60 and 72 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rothamel D. et al. (2009)(31)  6 dogs Mandible Collagen/ Deproteinized bovine bone Histology Histomorphometry 6 months Percentage of newly formed bone was 56.8±16.7% in the control and 56.0±12.4% in the test group. This difference was not statistically significant.

Sammartino G. et al. (2009)(32)  45 humans Mandible Collagen/ Bovine porous bone mineral Radiography Clinical Histology 3, 6, 9, 12, 18, 24, 36, 48, 60, 72 months Membrane was helpful for the prevention of a second-molar periodontal defect.

Bernabe PFE. et al. (2011)(33)  64 rats Tibia Decalcified cortical osseous membrane/ Bovine organic bone graft Histology Histomorphometry 3 months The new bone area fraction was 12.35±4.08% in the control and 52.44±11.88% in the test group. This difference was statistically significant.

Artzi ZVI et al. (2012)(34)  9 cats Maxilla Collagen/ Bovine bone mineral Histology Histomorphometry 3, 6 months After 6 months, bone area fraction was 21.6 ±10.7% in defects without membrane and 30.2%±5.7% in defects with membrane. The differences were statistically significant.

Table 4. Qualitative data obtained from reviewing human and animal studies which had used alloplastic material

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and species of understudy samples/Site of defect</th>
<th>Type of membrane, type of bone graft material/graft source</th>
<th>Data analysis method/duration of follow up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schliephake H. et al., (1994)(35) 5 minipigs Mandible Iliac bone Polylactic/HA</td>
<td></td>
<td>Histology, Microradiography 5 months</td>
<td>HA blocks covered with membrane showed complete bony penetration. In the control group, less bone ingrowth in an irregular pattern was observed.</td>
<td></td>
</tr>
<tr>
<td>Lee JS. et al., (2012)(36) 5 dogs Mandible</td>
<td>e-PTFE/ BCP</td>
<td>Histology Histomorphometry 8 weeks</td>
<td>Bone regeneration height was 3.52±0.69 mm in the BCP, 3.51±0.16 mm in the CCP, 3.96±2.86 mm in the membrane + BCP and 5.45±0.25 mm in the membrane + CCP group.</td>
<td></td>
</tr>
</tbody>
</table>

BCP: Biphasic calcium phosphate
CCP: Cyanoacrylate-Combined Calcium Phosphate

Table 5. Qualitative data obtained from reviewing human and animal studies comparing 2 or more bone grafts/ bone substitute material

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and species of understudy samples/Site of defect</th>
<th>Type of membrane/graft source</th>
<th>Data analysis method/duration of follow up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen OT. et al., (1995)(37) Four dogs Mandible</td>
<td>e-PTFE Autogenous, Iliac bone/Allogene/DFDB</td>
<td>Histology 6 months</td>
<td>Maintained bone graft volume was 75-125% in the test and 20-50% in the control group.</td>
<td></td>
</tr>
<tr>
<td>Von Arx T. Three dogs</td>
<td>e-PTFE</td>
<td>Histology</td>
<td>Increase in crestal bone width was 1.5±1.6</td>
<td></td>
</tr>
</tbody>
</table>
### Discussion:

The present study aimed at collecting data on the effect of membrane on bone graft/bone substitute materials. As observed in Tables 1-5, many studies have demonstrated that the combination of membrane and bone graft is effective (6, 10, 11, 14, 16-18, 22, 24, 26-30, 32-38, 42); whereas, other studies could not confirm the efficacy of membranes for bone regeneration (7, 8, 9, 13, 15, 19, 23, 25, 31, 39, 40, 41). Donos in his study on rats showed that exposure of e-PTFE membrane compromises wound healing and thus, has a negative influence on bone regeneration success (18). Gielken in his review study concluded that in situations where membrane is going to be used, membrane exposure should be prevented in order to obtain more predictable results (1). Several systematic reviews have so far been
conducted on the effect of membrane on bone regeneration. Nevins et al, in their review study in 1997 reported membranes to be a valuable tool for decreasing resorption in large bone grafts. However, due to the small number of studies by that time and also inclusion of uncontrolled studies in their review study, the obtained evidence are not much reliable (43). A review study by Gielkens et al. was conducted on human and animal experiments to obtain evidence regarding the protective effect of membranes on bone resorption. Although the majority of studies reviewed by them confirmed the inhibitory effect of membrane on bone resorption, the authors believe that the available data are not conclusive enough to prove this claim (1). The mentioned review article did not state whether the bone regeneration was vertical or horizontal. The results of Gielkens’ study are almost in accord with the present study findings. However, the mentioned study, similar to ours, has mainly focused on animal studies. In a systematic review by Sculean et al, simultaneous use of membrane and graft materials has been evaluated for periodontal tissue regeneration (12). In their study, animal experiments were used to obtain histological evidence. According to them, histological evidence of bone regeneration was observed in suprabony and two-wall intrabony defects due to the combined use of membrane and graft materials. Due to the use of different parameters, their results cannot be compared with ours. Available evidence mostly indicates that coverage of graft materials with a membrane is effective for bone regeneration. However, several biological differences exist between animal and human models such as bone density, blood supply, immune system, soft tissue tension and etc that along with the controllability of confounding factors i.e. microbial contamination, poor oral hygiene and etc. in animal models, compromise the extrapolation of results to human models. This issue further illuminates the lack of adequate evidence-based results in this respect and highlights the need for controlled human studies.

**Conclusion:**

Available evidence suggests that membranes can be effective in bone regeneration. However, differences in factors such as surgical technique, type of bone defect, maintenance phase and follow up period do not allow for reaching a definite conclusion. Number of randomized clinical trials with an appropriate design on this subject is limited. Therefore, greater number of randomized clinical trials is required to answer the question whether the use of membranes is superior to the conventional methods of bone regeneration.

**References:**


