Osteoinductivity of Medtronic Progenix®
in the Athymic Mouse Model

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The objective of this study was to characterize the osteoinductive properties of two commercially available products containing demineralized bone matrix: Progenix DBM Putty and Progenix Plus (both Medtronic). Osteoinductivity (OI), the ability to produce *de novo* heterotopic bone, was assessed histologically (OI ranked on a scale of 0-4) following intramuscular implantation of multiple samples for each test group in an athymic mouse model. Results of this study suggest that:

- **Progenix DBM Putty was marginally osteoinductive** in this model; only 21% of the samples were osteoinductive, with an average osteoinduction score of $0.21 \pm 0.41$.

- **Progenix Plus was marginally osteoinductive** in this model: only 29% of the samples were osteoinductive, with an average osteoinduction score of $0.29 \pm 0.46$.

**INTRODUCTION AND BACKGROUND**

Demineralized bone matrix (DBM) is used for treating bony defects as a bone void filler. The purpose of this study was to characterize the osteoinductivity of Progenix DBM Putty and Progenix Plus, which are commercially-available products containing DBM, both from Medtronic.

When implanted into normal animals, human DBM is xenogeneic, and is expected to provoke an immune response that may compromise the analysis of osteoinduction. To avoid this, the athymic mouse model was used. The athymic mouse lacks a thymus gland and therefore cannot mount a humoral immune response to the human DBM implants. Precedence of the use of
an athymic mouse (Nu/Nu) model for studying the osteoinductive potential of
demineralized bone allograft was noted in Schwartz et al.\(^1\)

Samples of the test groups were implanted bilaterally into the mouse hamstring
muscle. Intramuscular implantation of active DBM is expected to induce cartilage
and then bone formation within the implants, a process termed osteoinduction.
The hamstring muscle group (biceps femoris muscle) is a large, easily accessible
muscle, which is commonly used as an implant site to evaluate heterotopic bone
formation. Histological evaluation of the test articles was conducted 28 days after
implantation to assess osteoinduction.

**METHODS AND MATERIALS**

This study utilized two test groups: Medtronic Progenix DBM Putty (3 lots;
*Table 2*) and Medtronic Progenix Plus (1 lot; *Table 2*). For comparisons, this
study references osteoinductivity data on Enhance™ Demineralized Cortical
Fibers collected by the same investigator using techniques identical to those
described in this study.\(^2\) In some cases, the reference data was obtained
contemporaneously with test samples in this study.

Eight samples (weighing 25 mg each) from each lot of material were prepared
for implantation. The samples were randomized and implanted bilaterally in the
hamstring muscles of athymic nude mice. Animals were sacrificed at 4 weeks
post-implantation. Decalcified histology was then performed on the explanted
samples; 5 histological slides with 3 sections per slide were prepared for each
sample (15 sections total per sample). Slides were stained with hematoxylin
and eosin, and samples were evaluated for osteoinductivity. A semi-quantitative
scoring system was utilized to assess osteoinduction.
The relative amount of osteoinduction was evaluated semi-quantitatively by the study investigator using the scoring system described below; the observer was blinded to the identification of the implant. Osteoinductive scores were based on the degree to which new bone, bone cells, osteoid, calcified cartilage remnants, and marrow elements were present. To be consistent with proposed standards in the industry\textsuperscript{3}, the scoring system in Table 1 was utilized.

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of new bone formation</td>
</tr>
<tr>
<td>1</td>
<td>1-25% of the section is covered by new bone</td>
</tr>
<tr>
<td>2</td>
<td>26%-50% of the section is covered by new bone</td>
</tr>
<tr>
<td>3</td>
<td>51%-75% of the section is covered by new bone</td>
</tr>
<tr>
<td>4</td>
<td>&gt;75% of the section is covered by new bone</td>
</tr>
</tbody>
</table>

Table 1: Osteoinductivity Scoring Scale and Criteria

The overall score for each sample was obtained by averaging the highest 5 scores from the histological slides; scores for each experimental group were determined by pooling the overall scores of the individual samples. The results of semi-quantitative scoring are presented as a mean ± standard deviation.

Images of histological slides from each test group were also captured and stored using a digital camera and computer system (Image-Pro Plus\textsuperscript{TM} imaging software).
RESULTS & CONCLUSIONS

Progenix DBM Putty was marginally osteoinductive in this model; only 21% of the samples were osteoinductive, with an average osteoinduction score of 0.21 ± 0.41 (Tables 2 & 3).

Progenix Plus was marginally osteoinductive in this model as well: 29% of the samples were osteoinductive, with an average osteoinduction score of 0.29 ± 0.46 (Tables 2 & 3).

Figures 1 and 2 show the most representative histological response to the Progenix Putty and Plus implants, respectively, with primarily a fibrous tissue/inflammatory response, and no new bone formation. There were a few small regions with calcified cartilage formation.

The osteoinductivity scores for Progenix (both Putty and Plus compositions) are significantly lower than the osteoinductivity scores for Enhance™ Demineralized Cortical Fibers. In all cases, 100% of Enhance™ Demineralized Cortical Fibers samples are osteoinductive when assessed using this model.²

In conclusion, these results suggest that under the conditions of this study, and for the batches (donors) tested, the osteoinductivity for both the Putty and Plus compositions of Medtronic Progenix DBM is significantly less than that of MTF Enhance™ Demineralized Cortical Fibers.

It is unknown how the osteoinductive potential, measured in the athymic mouse model, will correlate with clinical performance in humans.
**Table 2: Progenix osteoinduction scores**

<table>
<thead>
<tr>
<th>Article</th>
<th>Lot</th>
<th>Average Osteoinductive Score</th>
<th>Group Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progenix DBM Putty</td>
<td>1193280035</td>
<td>0.13</td>
<td>0.33</td>
</tr>
<tr>
<td>Progenix DBM Putty</td>
<td>1340040014</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Progenix DBM Putty</td>
<td>1347670067</td>
<td>0.50</td>
<td>0.51</td>
</tr>
<tr>
<td>Progenix Plus</td>
<td>1413960100</td>
<td>0.29</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Table 3: Summary statistics, number of samples that could be histologically evaluated, and number of osteoinductive samples for each group. Number of osteoinductive samples is divided by the number of evaluated samples to give the % of osteoinductive samples for each group.**
REFERENCES:


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