The short term effect of a single Parathyroid Hormone (PTH) injection on the healing of stress fractures.

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INTRODUCTION

Stress fractures (SFx), or fatigue fractures, occur as a result of repetitive non-traumatic cyclic loading [1]. They are common in professional athletes, soldiers and dancers [2, 3]. Common analgesic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) can retard SFx healing [4], but there is little evidence for therapies that might accelerate it. Parathyroid hormone (PTH) has an anabolic effect that can accelerate bone remodeling [5]. Therefore, our aim was to investigate the short term effect of a single PTH injection (24 hours post SFx) on SFx healing within the first two weeks.

Hypothesis: A single injection of PTH will be sufficient to accelerate morphometric indices of SFx healing

MATERIALS AND METHODS:

Sixteen female wistar rats 300 g were allocated to PTH and vehicle (VEH) groups. Both groups had uNAR injected in a single session (Fig 1). 24 hours after SFx, PTH group received a single dose of hPTH-1(3-4) peptide (Sigma-Aldrich) (8 µg/100g) dissolved in 0.9% saline with 1% rat heat-inactivated serum. Ulnae were harvested two weeks after loading, dissected, processed for paraffin histology and stained with Toluidine blue and for TRAP. Histomorphometry was conducted using Osteomeasure™.

RESULTS:

There were no significant differences between groups with regards to standard bone parameters such as cortical area (Ct.Ar, mm2) or length of fracture (Sx.Le, µm), but woven bone area (Wb.B.Ar, mm2) was marginally greater in the PTH group (P = 0.07) (Table 1). Following treatment, there were no significant differences between groups for Sx porosity (resorption) (Sx.Po.Ar, µm2), Sx erosion (unhealed) area (Sx.E.Ar, µm2), new bone formation (Sx.He.Ar, µm2), or osteoclast surface (Oc.Pm, µm). However the PTH group had a significantly greater number of Osteoclasts when compared to VEH (P<0.01) as shown in Fig 2.

Table 1: Mean (SEM) morphometric values for for VEH and PTH groups.

<table>
<thead>
<tr>
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<th>VEH</th>
<th>PTH</th>
<th>Significance (P)</th>
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</thead>
<tbody>
<tr>
<td>Cortical area (Ct.Ar, mm²)</td>
<td>1.39 (0.05)</td>
<td>1.31 (0.04)</td>
<td>0.290</td>
</tr>
<tr>
<td>Woven bone area (Wb.B.Ar, mm²)</td>
<td>0.67 (0.08)</td>
<td>0.85 (0.05)</td>
<td>0.074</td>
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<tr>
<td>Length of fracture (Sx.Le, µm)</td>
<td>1.48 (0.10)</td>
<td>1.40 (0.09)</td>
<td>0.618</td>
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<td>Sx porosity (Sx.Po.Ar, µm²)</td>
<td>0.010 (0.003)</td>
<td>0.015 (0.003)</td>
<td>0.198</td>
</tr>
<tr>
<td>Sx erosion (unhealed) area (Sx.E.Ar, µm²)</td>
<td>0.334 (0.085)</td>
<td>0.491 (0.066)</td>
<td>0.157</td>
</tr>
<tr>
<td>Healed new bone formation (Sx.He.Ar, µm²)</td>
<td>0.0019 (0.001)</td>
<td>0.002 (0.001)</td>
<td>0.824</td>
</tr>
<tr>
<td>Number of Osteoclasts (N.Oc)</td>
<td>8.1 (1.8)</td>
<td>17.7 (1.6)</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Osteoclast Surface (Oc.Pm, µm)</td>
<td>0.298 (0.072)</td>
<td>0.450 (0.054)</td>
<td>0.267</td>
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a = marginally significant (mean difference > 2 x SEM)

DISCUSSION:

Stress fractures heal by direct remodelling through the fracture line (Fig 1C) [6,7]. During the initiation of remodelling, bone resorption by osteoclasts plays a significant role in repair. We showed a highly significant increase in the number of osteoclasts along the SFx in the PTH group. This can be explained by PTH induction of monocyte chemotactic protein-1 (MCP-1) which is responsible for differentiation and recruitment of osteoclasts precursors in early remodeling phases [8,9]. We believe that the amount of healed bone along the SFx line could also be greater as the formation period progresses from 2 weeks. A significant amount of new bone formation needs about 4-6 weeks post SFx.

CONCLUSION:

Our study provides evidence that a single PTH injection 24 hours after SFx results in active changes in the dynamics of bone remodeling after 2 weeks. Further research is necessary to investigate the longer term effect of PTH injections on the healing phase of SFx.

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Reference:
5. Sham AF, Martin JB, Li S, Li L. Parathyroid hormone and biphasic forces have opposite effects on stress fracture repair. Bone. 2015; 75:135-141.

Fig 2: (A) PTH treatment increased the number of osteoclasts (Oc) associated with BMU of healing SFx. (B) Staining for TRAP clearly demonstrated Oc recruitment and activity of Oc (red areas) in the BMU and along the SFx. * p < 0.01