Effects of Local Infusion of Osteogenic Protein-1 on NSAID-Mediated Bone Formation in vivo

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Introduction:

NSAIDs are commonly prescribed medications to treat osteoarthritis and other painful conditions. Administration of NSAIDs is associated with delayed fracture healing and bone formation. Osteogenic protein-1 (OP-1) improved the healing of bone defects in several animal models as well as in some clinical studies. OP-1 also induced osteoblast commitment from mesenchymal stem cells in vitro. In this study, we examine the effects of continuous local infusion of OP-1 on localized bone formation in the presence of an oral NSAID administration, using a well-established rabbit model. We hypothesize that the infusion of OP-1 can reverse the inhibition of bone formation by NSAIDs.

Methods:

Institutional guidelines for the care and use of laboratory animals were strictly followed. The bone ingrowth chamber was implanted in the proximal tibia of 11 mature NZW rabbits unilaterally (**Fig1**). The chamber provides a continuous 1x1x5 mm canal for bone ingrowth. After an initial osseointegration period, the chambers were emptied of tissue and the treatments in **Table 1** were given for 6 weeks each, followed by a harvest in each case. The NSAID, naproxen sodium, was given orally in drinking water at a dose of 110 mg/kg/day. The OP-1 solution and its carrier (Stryker Biotech) were infused to the chamber by an Alzet osmotic pump (model 2004) at 110ng/day. Tissue samples were snap-frozen and examined by histology. Hematoxylin and Eosin staining was used for bone morphometry. Alkaline Phosphatase was used as a marker for osteoblast like cells. Bone areas and positive staining areas of Alkaline Phosphatase were quantified by NIH image program.

Data from animals that completed all the treatments were analyzed (N=8). Kruskal-Wallis nonparametric test and Wilcoxon Signed Rank test were performed. A p value less than .05 was considered significant.

Table 1: Experimental protocol

Week	Treatment
0	osseointegration
6	no NSAIDs, infuse the carrier of OP-1
12	systemic NSAIDs, infuse the carrier of OP-1
18	systemic NSAIDs, infuse OP-1
24	euthanasia

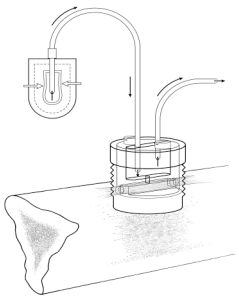

Figure 1. Drug Test Chamber

Results/Discussion:

Oral administration of NSAID reduced local bone formation dramatically ($p<0.05$). When OP-1 was infused in the presence of the NSAID, the suppressive effect was completely reversed ($p < 0.05$) in this model (**Fig 2**). The levels of bone formation in the presence of OP-1 and the NSAID were not different from the normal control condition when neither of the two treatments was given (**Fig 2**). NSAID reduced the positive staining area of alkaline phosphotase in tissue sections ($p<0.05$) (**Fig 3**). The infusion of OP-1 brought the levels of alkaline phosphotase back to the control level (**Fig 3**). The staining of Alkaline Phosphotase for osteoblast-like cells closely correlated with the levels of bone formation observed, suggesting that OP-1 exerts it's effect via stimulating osteogenesis.

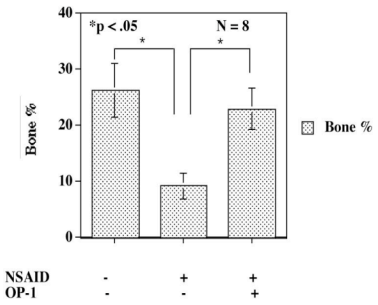

Figure 2. Percentage of Bone Area in Tissue Section

Bone% was defined as total bone area divided by entire tissue section area and expressed as percentag

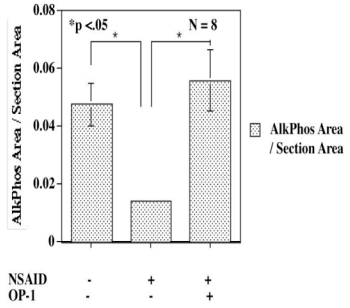

Figure 3. Alk. Phos. Positve Area in Unit Tissue Area

Conclusions:

In the current experiments, administration of OP-1 significantly reversed the adverse effect of naproxen on local bone formation, which was accompanied by increased expression of Alkaline Phosphatase. These findings underline a role for local treatment with OP-1 to increase bone formation in the presence of potentially adverse stimuli such as NSAID use.

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