Synergistic Coupling of PTH with Cold Therapy to Enhance Fracture Healing

Matthew Zakaria, MSc*; Michael Grant, PhD; Laura M. Epure; Fackson Mwale; Geraldine Merle, PhD; Edward J. Harvey, MD, FIOTA*

Purpose: Although high-dosage parathyroid hormone (PTH) therapy effectively promotes bone healing by increasing callus bone mineral density. Potential side effects, including hypercalcemia, have led to FDA approval only for intermittent low-dosage administration, necessitating optimization to minimize adverse effects. Cold exposure, known to influence bone mineralization and facilitate bone repair, has emerged as a promising method, with short-duration stimuli activating extracellular calcium sensing receptors in osteoblasts. Combining intermittent high-dosage PTH therapy with cold exposure offers a potential synergistic solution to optimize PTH therapeutic regimens.

Methods: 18 C57BL/6 mice underwent bilateral femoral fracture stabilization with retrograde nailing. Six mice received daily intermittent high-dosage PTH supplementation (40 ug/kg) along with cold immersion of the experimental leg (19°C, 15 min/day), 6 received only PTH, and 6 served as controls. Core-body and control leg temperatures were maintained. Calcium blood levels were assessed at days 7 and 14, and bone parameters (BMD [bone mineral density], Tb.Th., Tb.Sp., BV/TV) were evaluated at day 14.

Results: At day 7, the PTH-only group had higher calcium levels (10.95 mg/dL ± 0.1) than PTH/cold (10.63 mg/dL ± 0.10; P = 0.0008); by day 14, the PTH-only group increased to 11.43 mg/dL± 0.16, surpassing PTH/cold's rise to 11.04 mg/dL ± 0.07 (P = 0.00014), suggesting hypercalcemia mitigation by cold therapy. Morphological observations revealed larger fracture calluses in the PTH-only group. Furthermore, the PTH/cold group exhibited higher BMD (1016.33 HA/cm3 ± 29.69 vs 947.33 HA/cm3 ± 27.54), lower trabecular separation (169.20 um ± 9.92 vs 335.36 um ± 29.12, P = 0.0056), and greater bone volume percentage (39.11% ± 2.50 vs 28.38% ± 3.38; P = 0.014), indicating superior mineralization.

Conclusion: Findings confirm that cold exposure mitigates PTH-induced hypercalcemia, emphasizing its protective effect against elevated calcium levels in mice. The size difference and reduced mineralization in fracture calluses of the PTH-only group compared to PTH/cold imply intriguing differences in callus composition, further reflected in higher BMD and enhanced trabeculae architecture highlighting the influence of cold on bone mineralization. These findings contribute to optimizing PTH therapy regimens and advancing strategies for bone healing.