Therapeutic Effect of Pulsed Electromagnetic Fields in a Mouse Model of Meniscal Degeneration

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INTRODUCTION: Meniscal pathology is clinically categorized as either traumatic or degenerative. While arthroscopic surgery is often effective for traumatic tears, its efficacy for degenerative meniscus is limited, showing no superior outcomes compared to conservative therapies. This highlights a critical need for effective interventions that alleviate pain and preserve knee function in patients with degenerative meniscus. Biomechanical studies indicate that the altered mechanical properties of degenerative meniscus disrupt joint homeostasis and are closely associated with early-onset post-traumatic osteoarthritis (OA). Based on our previous findings that pulsed electromagnetic fields (PEMF) enhanced meniscal healing and delayed OA progression after acute injury, this study aimed to evaluate the therapeutic effect of PEMF on meniscal degeneration and associated knee pain.

METHODS: Meniscal degeneration was induced in 12-week-old C57 mice by transection of the mensicotibial/coronary ligament of the medial meniscus. (In this study, we only applied male animals because our prior studies in meniscal research have exclusively used male rats. Continuing with male animals ensures the comparability and continuity of data across studies.) Following surgery, animals were randomized into four groups: Sham, Negative Control (NC), PEMF, and Celecoxib (CCB). To replicate the chronic nature of meniscal degeneration, interventions began at week 4 post-surgery. The degenerative changes in menisci were confirmed by pilot study via histology and pain behavior. The PEMF group received daily treatment according to our established protocol from weeks 4 to weeks 12. In contrast, the CCB group received daily oral celecoxib (10 mg/kg), serving as a positive control due to its clinical use in alleviating joint pain for OA patients. Therapeutic outcomes were assessed in two domains. **Behavioral evaluation** (n=10/group**)** included weekly Von Frey testing (0–12 weeks), weekly gait analysis (excluding week 1), and open-field testing at week 12 to assess pain and knee function. **Structural evaluation** (n=8/group/time point) focused on meniscal degeneration: radiographs at 8 and 12 weeks were graded using the Kellgren–Lawrence (KL) scale; micro-CT at 12 weeks quantified meniscal destruction by calculating total volume (TV) and bone volume fraction (BV/TV); and histological analysis of meniscal sections stained with Safranin O/Fast Green was performed at 4, 8, and 12 weeks. All procedures were approved by IACUC.

RESULTS: Body weight remained similar across all groups throughout the 12-week study period. Following intervention from week 4, Von Frey tests showed that both PEMF and CCB groups demonstrated significant pain relief compared to NC. Gait analysis revealed that PEMF and CCB improved symmetry of key gait parameters, including paw intensity, single stance, and swing speed, compared to NC, aligning with Von Frey findings and indicating limb functional recovery and pain relief. In open-field tests at 12 weeks, PEMF-treated mice traveled significantly farther (22.9 m, $p < 0.001$) than NC (15.2 m), comparable to CCB (21.5 m) and Sham (29.8 m), with representative tracks confirming enhanced mobility. Radiographic analysis (**Figure A**) at 8 weeks showed that the NC and CCB groups displayed joint space narrowing, patellar morphology changes, osteophytes, and greater meniscal ossification. By 12 weeks, these groups exhibited severe OA features, including calcification in the infrapatellar fat pad tissue and pronounced subchondral sclerosis, while PEMF-treated knees showed only mild-to-moderate degenerative changes. KL grading at 12 weeks demonstrated significantly lower scores for PEMF than NC ($p = 0.047$), indicating less severe knee joint degeneration. Micro-CT analysis (**Figure B**) revealed that NC and CCB groups had significantly larger and irregular meniscal ossification volumes compared to Sham, while PEMF reduced ossification volume compared to NC and CCB ($p = 0.001$ and $p = 0.01$, respectively). Total volume (TV) for PEMF (0.26) was higher than Sham (0.14) but significantly lower than NC (0.39), and bone volume fraction (BV/TV) for PEMF (0.67) preserved a higher bone fraction than NC (0.51) or CCB (0.54), though lower than Sham (0.79). Histological evaluation (**Figure C**) at 8 weeks showed that Sham menisci maintained normal wedge-shaped morphology, smooth surfaces, and intact extracellular matrix (ECM), while NC and CCB exhibited fibrillation, cyst-like regions, and bone marrow-like infiltration. PEMF showed relatively preserved morphology with only minor surface deformation and ECM loss. At 12 weeks, NC and CCB displayed extensive cysts, fibrochondrocyte hypertrophy, and horizontal tears, while PEMF demonstrated delayed progression of meniscal degeneration, with smaller lesions and less ECM destruction. Meniscus scores for NC and CCB were significantly worse than Sham ($p < 0.001$), and PEMF showed lower degeneration scores than NC ($p = 0.028$).

Discussion: This study demonstrates that PEMF therapy offers therapeutic effects in a mouse model of degenerative meniscus: (1) alleviation of pain comparable to Celecoxib, and (2) structural protection against meniscal degeneration and ossification, which Celecoxib failed to achieve. However, several limitations should be acknowledged. First, due to the constraints of current PEMF devices, the entire body of the animals was exposed to PEMF rather than targeting the knee joint specifically. Future studies should aim to refine exposure methods to better localize PEMF treatment and clarify its specific biological effects on meniscal tissue and cells. Second, while the present and previous studies have established the therapeutic potential of PEMF therapy, the underlying cellular and molecular mechanisms remain largely undefined. Understanding these mechanisms is essential for optimizing both the safety and efficacy of PEMF treatment. Prior research has demonstrated anti-inflammatory effects of PEMF, and our previous work also observed reduced synovial inflammation following PEMF therapy. Based on these findings, we hypothesize that the effects of PEMF on meniscal degeneration and pain may be mediated through modulation of joint inflammation. Future investigations will focus on elucidating the precise mechanisms by which PEMF influences meniscal pathology and inflammatory processes within the knee joint.

Significance: PEMF therapy may offer a new approach for the treatment of meniscal degeneration by mitigating knee pain and preserving meniscal tissue.

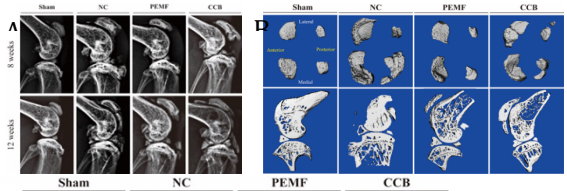

Figure A. The radiologic and morphological changes observed in knee joints in radiographs taken at 8 and 12 weeks after surgery. **Figure B**. The results of micro-CT scanning of the meniscus from a top and lateral view at 12 weeks after surgery. The results show that the NC and CCB groups exhibited significantly larger ossification in the meniscus compared with the Sham and PEMF groups. NC, Negative control; PEMF, Pulsed Electromagnetic Field; CCB, Celecoxib group.

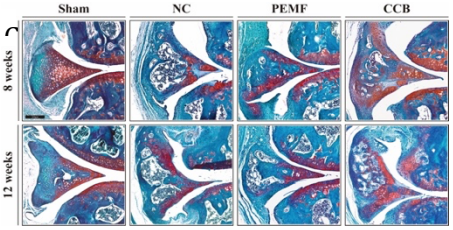

Figure C. The results of Safranin O/Fast green staining of the anterior horn of the medial meniscus at 8 and 12 weeks after surgery. The results show significant meniscal tissue destruction in the NC and CCB groups compared to the Sham group, with larger bone marrow-like regions, diffused hypertrophy of fibrochondrocytes, and worse destruction of the meniscal tissue. In contrast, the PEMF group exhibited fewer abnormal morphological and histological changes in the meniscus, with less bone marrow-like regions and less surface undulation. These findings suggest that PEMF therapy may have a protective effect on meniscal health. NC, Negative control; PEMF, Pulsed Electromagnetic Field; CCB, Celecoxib group.