Randomized, Placebo-Controlled Clinical Trial Evaluating Ketotifen Fumarate in Reduction of Posttraumatic Elbow Joint Contracture

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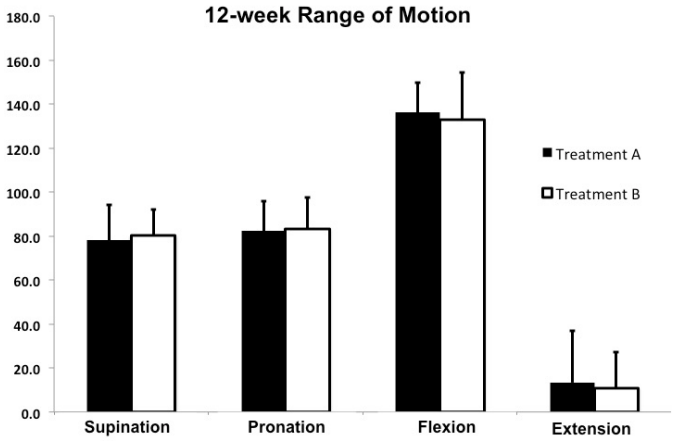
Purpose: Our research has established that a myofibroblast-mast cell-neuropeptide axis underlies the joint capsule fibrosis associated with posttraumatic joint contractures (PTJCs). In our rabbit model, ketotifen fumarate (KF), a mast cell stabilizer, decreased PTJCs by 50%, concomitant with decreased measures of fibrosis. This Phase II trial was designed to determine safety and feasibility of a Phase III trial for further clinical study of KF.

Method: A randomized, placebo-controlled clinical trial (RCT) comparing 6 weeks of oral KF 5 mg twice daily to a lactose placebo for distal humerus and proximal radius ± ulna fractures and/or dislocations. The primary outcome measure was flexion-extension range of motion (ROM) at 12 weeks post-injury. Secondary outcomes included DASH score, complications, and fracture healing. Subgroup analysis compared operative with nonoperative treatment. Statistical analysis consisted of chi-square for categorical variables and ANOVA for continuous variables. Multiple linear regression was used to assess the adjusted effect of KF.

Results: 145 patients were randomized (76 KF, 69 placebo). More patients were treated nonoperatively (n = 80), at the discretion of treating surgeons. There was no difference between the mean age (46.7 ± 18.3 years for KF vs. 44.4 ± 13 years for placebo), sex (54% female for KF vs. 42% for placebo), side of injury, hand dominance, pre-injury work status, time from injury to randomization (mean 3.7 days), injury classification, and surgical treatment (45% in each group); all $p > 0.05$. 12-week follow-up rate was 88% in the KF group and 89% in the placebo group. There was no significant difference between treatment groups for 12-week ROM, DASH, adverse events, or reoperation rate; all $p > 0.05$. There was a significant decrease in ROM in the operative subgroup ($p = 0.03$). Fracture union was 48% in each group at the time of analysis.

Conclusion: This Phase II RCT was completed successfully with adequate follow-up and several measures confirmed the safety of KF. Patients requiring surgical treatment demonstrated increased PTJC. There were more patients treated nonoperatively; therefore, it is possible that a lower likelihood of developing PTJC (due to lower injury severity) may have masked the full treatment effect of KF. The greater loss of motion at 12 weeks in the operative subgroup will inform the Phase III multicenter injury inclusion criteria to elbow fractures or dislocations requiring surgery.



See pages 401 - 442 for financial disclosure information.