Do intra-articular corticosteroid and platelet-rich plasma injections differentially regulate clinical and biochemical responses in osteoarthritic knees?

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Introduction: Osteoarthritis (OA) is a leading cause of pain and disability worldwide. Intra-articular corticosteroid injections have been considered to be the "gold standard" for joint-specific non-surgical management of OA-related symptoms. While corticosteroid injections (CSI) are most widely used for this purpose, platelet-rich plasma (PRP) has emerged as viable alternative for joint injections to manage OA. While clinical outcomes associated with CSI and PRP injections have been reported, there is significant interpatient and interstudy variability in the magnitude and duration of effects for each such that decision making algorithms for selection of injectate have not been established. Therefore, there is a need to develop improved patient screening methods to optimize injectate selection and treatment outcomes for patients receiving intra-articular injections for non-surgical management of symptomatic OA. Synovial fluid, serum and/or urine biomarkers for catabolic, anabolic, and inflammatory processes involved in OA may provide a valid method for determining patients' responses to CSI and PRP injections. Therefore, this prospective, randomized, double-blind clinical trial was designed to characterize body fluid biomarker concentrations from patients with mild-to-moderate knee OA and the related patient reported outcome measures (PROM) following treatment with CSI or PRP. It was hypothesized that statistically significant differences in baseline versus four-week follow-up biomarker concentrations and PROMs would be observed within each treatment cohort. Additionally, it was hypothesized that four-week change in biomarker concentrations and two-, four-, eight-, and twelve-week changes in PROMs would be significantly different between treatment cohorts.

Methods: ***Patients:*** With IRB approval (IRB#2092036) and informed patient consent, knee OA patients (n=15 patients/16 knees, 5 F, mean age = 67.18 y, mean BMI = 32.3 kg/m^2) with KL grade 2 or 3 radiographic knee OA were enrolled and randomized into either the CSI or PRP treatment cohort. Patients with a BMI > 40 kg/m^2, age < 40 years, and history of meniscal injury or reconstructive knee surgery in the affected knee were excluded. Patients randomized to the CSI cohort received a single injection containing 40 mg triamcinolone acetonide. Patients randomized to the PRP cohort received a single injection of leukocyte-poor PRP prepared using a commercially available system. ***Biomarker Analysis:*** Serum (s) and urine (u) samples were collected from patients at the time of injection and 4 weeks post-treatment and stored at -80°C until used for assays. Fluid samples were assessed for concentrations of GRO-α, IFN-γ, IL-1RA, IL-1β, TNF-α, IL-4, IL-6, IL-8, IL-10, MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES, PDGF-AA, VEGF, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, TIMP-1, TIMP-2, TIMP-3, TIMP-4, OPG, OPN, OC, DKK-1, SOST, PTH, Leptin, Adiponectin, Resistin, Adipsin, and CRP using commercially available assays. All urine concentrations were standardized to creatinine content. ***PROMs:*** Visual analog scale (VAS) for pain, Knee Osteoarthritis Injury and Outcome Score for Joint Replacement (KOOS JR), and UCLA activity score were collected at the time of injection, and 2, 4, 8, and 12 weeks after treatment, using a secure electronic data capture system. Patients with minimal clinically important difference (MCID) values of 2 units for VAS pain and 15.0 units for KOOS JR were classified as "responders" to treatment. ***Statistical Analysis:*** Baseline characteristics of the two patient cohorts were compared utilizing a Student's *t*-test (with or without Welch's correction), Wilcoxon Rank Sum test, or Fisher's exact test, as appropriate. Significant ($p<0.05$) differences in PROMs were determined between time points within each treatment cohort using a generalized linear model or Kruskal-Wallis test and between treatment cohorts at each time point using a Student's t-test or Wilcoxon Rank Sum test. Biomarker concentrations were natural log transformed, and significant differences between time points within each treatment cohort, and between treatment cohorts using the change in biomarker concentration from baseline to four-week, were determined using a Student's *t*-test or Wilcoxon Rank Sum test.

Results: Baseline patient demographics and PROMs were not significantly different between the two cohorts. ***Patient-Reported Outcomes (Figure 1)*** In the CSI cohort, VAS pain decreased significantly from baseline to 2 ($p=0.001$), 4 ($p=0.002$), 8 ($p<0.001$), and 12 weeks ($p<0.001$), but not in the PRP cohort. Further, the decrease in VAS pain in the CSI cohort was significantly greater than the PRP cohort at 4 ($p=0.048$) and 12 weeks ($p=0.017$) after injection. Significant differences in the KOOS JR and UCLA activity score within and between the CSI and PRP treatment cohorts were not observed. ***Fluid Biomarkers (Figure 2)*** Within the PRP cohort, uPDGF-AA was significantly ($p=0.008$) higher 4 weeks post-injection. Within the CSI cohort, significantly higher sMMP-3 ($p=0.048$), uGRO-α ($p=0.016$), uPDGF-AA ($p=0.038$), uCRP ($p=0.037$), uOPG ($p=0.046$), and uDKK-1 ($p=0.028$) were observed 4 weeks post-injection. There was a significant decrease in the concentration of sMMP-2 ($p=0.026$), sMMP-7 ($p=0.048$), and sOC ($p=0.018$), and a significant increase in the concentration of sMMP-3 ($p=0.006$), sLeptin ($p=0.025$), and uAdipsin ($p=0.020$), from baseline to 4 weeks in CSI cohort compared to the PRP cohort. ***Responders to treatment (Table 1)*** In the CSI cohort, 38% (2 WK), 25% (4 WK), 38% (8WK), and 57% (12WK) were classified as responders based on the KOOS JR score, and 50% (2 WK), 38% (4 WK), 75% (8WK), and 71% (12WK) were classified as responders based on the VAS pain. In the PRP cohort, 0% (2 WK), 43% (4 WK), 0% (8WK), and 0% (12WK), were classified as responders based on the KOOS JR score, and 0% (2 WK), 0% (4 WK), 29% (8WK), and 20% (12WK) were classified as responders based on the VAS pain.

Discussion: The data from this study indicate that intra-articular CSI injection may provide more statistically significant and clinically meaningful improvements in OA-related pain versus PRP during the 12 weeks after injection. Further, the present study provides evidence of treatment-dependent regulation of systemic biomarker concentrations that may reflect unique biochemical impacts for each of the two injection types. The intra-articular injection of CSI appears to have significant effects on bone metabolism in knee OA compared to PRP based on diffferences observed in uOPG, uDKK-1, and sOC. Further, intra-articular CSI and PRP injections appear to have a differential effects on the production of MMP, with CSI increasing MMP-3 and decreasing MMP-2 and MMP-7 relative to PRP, which may indicate pathways of catabolic modulation stimulated by each injectate. However, further study is required to establish a causative relationship for the changes in serum and urine biomarker concentrations observed, and to determine if these changes in biomarker concentrations are related to changes in PROMs after injection. Further research is needed to determine the potential for body fluid biomarkers to provide a valid method for determining patients' responses to CSI and PRP injections.

Significance: The data from this study indicate that intra-articular corticosteroid injections may provide more improvement in patient-reported knee pain during the first 12 weeks post-injection when compared to PRP injections for non-surgical treatment of knee OA. Assessment of OA-related serum, urine, and synovial fluid biomarkers revealed significant differences in mechanistic effects for each of the two injectates. Ongoing research in our lab is expanding the number of patients enrolled in this clinical trial and including longer-term ffollow-up to develop a valid decision-making algorithm for selection of injectate to optimize outcomes after intra-articular injection therapy for non-surgical management of OA-related symptoms.