THE EFFECT OF COMBINED BONE MARROW ASPIRATE, LIPOASPIRATE, AND PLATELET-RICH PLASMA INJECTIONS ON PAIN, FUNCTION, AND PERCEIVED CHANGE AMONGST INDIVIDUALS WITH GLENOHUMERAL OSTEOARTHRITIS: A PILOT STUDY

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Submitted: 21 July 2022. Accepted: 12 November 2022. Published: 30 November 2022

Abstract

Purpose: This study was conducted to investigate the efficacy of a combined minimally processed bone marrow aspirate (BMA), adipose graft, and leukocyte-rich platelet-rich plasma (PRP) intra-articular injection series on pain, function, and global rating of change (GROC) among patients with glenohumeral osteoarthritis (GHOA) and record any complications or adverse events associated with the protocol.

Methods: Ten adults (mean age 65 years) previously recalcitrant to conservative care with clinical and radiographic evidence of GHOA were included. At the initial visit, patients were assessed for eligibility of treatment. All patients were assessed pre- and post-treatment with numerical pain rating and patient-specific functional scales (PSFS). All study participants were treated with 4–6 ml of PRP, 6 ml adipose graft, and 12 ml of BMA, which were administered via a landmark-based anterior intra-articular injection. Patients were requested to return twice over 4-week intervals for booster PRP injections. At each follow-up, the GROC and prior outcome measures were completed.

Results: Patients returned after an average of 27 days for first (F1) and 68 days for the second (F2) PRP injection. Friedman Chi Square analysis indicated significant improvements in best and worse pain and PSFS from baseline initial visit to F1 and F2 ($P \leq .002$). Post-hoc Wilcoxon signed-rank testing with Bonferroni correction ($\alpha = 0.017$) identified significant improvements from baseline to F1 and F2 for the PSFS ($P \leq 0.012$). Improvements in best and worse pain were significant at F2 ($P \leq 0.016$), not F1 ($P \geq 0.02$), compared to baseline. Effect sizes were large, ranging from $r = 0.57$ to 0.84 for pain and function. Improvements in pain, GROC, and PSFS met minimum clinically important differences at F2 based on previously validated clinimetrics. The only adverse events reported are related to administration of injectate that was temporary and managed in all cases with over-the-counter analgescics.

Conclusion: A minimally processed adipose graft with BMA and three PRP injections improved pain and function among individuals with GHOA who were recalcitrant to conservative care. Although significant functional improvement at both follow-up points occurred, clinically important and significant changes in pain did not occur until F2. A one-group design and multimodal approach limit generalization of results.

Level of Evidence: IV

Keywords: shoulder osteoarthritis; joint diseases; knee; platelet-rich plasma; stem cells

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INTRODUCTION

Glenohumeral osteoarthritis (GHOA) affects up to 17% of the population with shoulder pain and is associated with impairments, functional decline, and a considerable socioeconomic burden.\(^1\)\(^-\)\(^3\) Although efficacious interventions have been identified for the treatment of GHOA, a subgroup of individuals are recalcitrant to conservative care and may be steered toward pharmacological therapies with undesirable effects (e.g., opioids) or surgical care such as joint replacement.\(^2\)\(^-\)\(^3\) Although patients generally experience improved physical activity following joint replacement, surgery is costly and some patients may experience chronic post-operative pain and complications.\(^2\)\(^,\)\(^4\) When considering surgical costs and potential post-operative complications, nonsurgical interventions that have the potential to decelerate the disease process and improve function are of interest.\(^2\)\(^-\)\(^4\)\(^,\)\(^7\)

Novel regenerative medicine products (e.g., orthobiologics) have gained considerable attention in the musculoskeletal specialties, owing to the promise of decelerating the disease process and potentially offering a superior long-term solution to existing conservative treatments. Autologous orthobiological interventions such as bone marrow aspirate (BMA), bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), and adipose tissue derivatives may be some viable options for individuals with GHOA whose symptoms are recalcitrant to conservative care. These interventions require minimal post-procedural downtime, which allow individuals to pursue a timely resumption of physical activity.\(^8\)\(^-\)\(^10\) Furthermore, failure to respond to orthobiologics does not preclude future treatments.

Of the injectable orthobiologics, PRP is most performed, due to ease of procurement and reduced cost. Evidence suggests that PRP products contain a supra-physiological concentration of cells, namely platelets, as well as a reservoir of growth factors (e.g., insulin-derived growth factor [IGF-1]), proangiogenic factors (e.g., platelet-derived growth factor), and anti-inflammatory cytokines (e.g., interleukin 1 receptor agonist [IL-1RA] and interleukin-10). The interest in BMA and adipose-derived products resides in the multipotent regenerative capacity of their mesenchymal stem cells (MSCs). Evidence suggests that MSCs have the ability to differentiate along their mesodermal lineage, indicating the potential for promoting tissue repair and regeneration.\(^11\)\(^,\)\(^12\) The benefits of these procedures extend beyond cellular plasticity, as MSCs can manipulate the microenvironment through immunomodulation and anti-inflammatory influences.\(^13\)\(^-\)\(^19\) Furthermore, in addition to cellular content, adipose and BMA possess bioactive molecules such as cytokines, proangiogenic and antiapoptotic substances, as well as trophic factors.\(^10\)\(^,\)\(^18\)\(^-\)\(^21\) Although BMA is rich in hematopoietic stem cells, a decline in MSC numbers occurs with aging.\(^22\) Thus, procuring a fat graft via lipoaspirate may provide the required MSCs that are deficient in BMA when culture expansion is not an option.\(^22\)\(^,\)\(^23\)

An interventional approach that concurrently utilizes a minimally processed lipoaspirate (fat graft) and BMA, with leukocyte-rich PRP among individuals with GHOA has not been previously investigated. Thus, the purpose of this study was to investigate the short- and medium-term efficacy of a combined minimally processed BMA and adipose graft with a leukocyte-rich PRP intra-articular injection series on pain, function, and global rating of change (GROC) among individuals with GHOA who were recalcitrant to conservative care. Additionally, recording any adverse events associated with treatment was important to demonstrate safety with this treatment protocol. We hypothesized that, although the patients were recalcitrant to conservative care, significant improvements in pain, function, and perceived change would be identified at both the initial (~1 month) and subsequent (2+ months) follow-up periods.

METHODS

The study was approved by the Institutional Review Board at Nova Southeastern University (# 2018-496). We retrospectively reviewed the records of patients with shoulder pain who completed orthobiologic treatments for unilateral GHOA
between February 2018 and January 2019 at a medical facility that specialized in regenerative medicine. Specifically, 10 patients seeking care at an outpatient regenerative medicine facility for unilateral GHOA who received minimally processed BMA, a lipoaspirate adipose graft, and series of 3 leukocyte-rich PRP injections were included in the study. Eligibility criteria included fulfillment of radiological findings Kellgren–Lawrence Grade 2 minimum (osteofytes with definite joint space narrowing) and clinical criteria, which included shoulder pain plus a loss of mobility and clearly identified functional impairments at the shoulder. Additionally, patients were required to have been recalcitrant to conservative care including physiotherapy and corticosteroid injections. Patients were excluded if they did not complete the three-series PRP protocol, refused to complete outcome measures, or had a corticosteroid injection within the past week of the initial visit or during the post-treatment follow-up points.

Assessment Procedures

On the initial visit, patients were evaluated by a single board-certified orthopedic surgeon (JP) with a subspecialty in regenerative medicine. Both radiological and clinical examinations were completed by the orthopedic surgeon. Kellgren–Lawrence grading was based on radiograph interpretation from the orthopedic surgeon. Once diagnosis was confirmed by the treating orthopedic surgeon, a medical assistant trained in educating patients, who was not part of the team delivering the interventions, provided patients with the self-reported outcome measures which included a numerical pain scale, rating pain (circling on a paper diagram) at best and worse ranging from a 0 = no pain to 10 = worse pain. Numerical pain scales have a reported intraclass correlation coefficient (ICC) = 0.74 for patients with shoulder disorders. For patients with shoulder pain, the numerical pain scale has been reported to have a minimum clinically important difference (MCID) of 1.1 points, which indicates that a change of 1.1 points or more is needed to be clinically meaningful. Patients also completed the patient-specific functional scale (PSFS), which is a self-reported outcome measure documenting and quantifying key activity impairments with a ranked level of difficulty. The PSFS has been reported to have excellent reliability (0.87) for patients with shoulder dysfunction, and the MCID has been reported at ≥1.29 raw points on a scale of 0–10, with larger changes correlating to greater improvements when multiple items are averaged.

Intervention Procedures

Following the clinical examination and completion of outcome measures, patients underwent an antecubital venipuncture to obtain approximately 40 ml of blood using a 21-gauge needle. The blood was collected in four tubes, each containing 1 ml of 3.8% sodium citrate to prevent clotting. The blood was then manually processed using a double-spin centrifugation technique per the standard procedure for the facility. Specifically, the blood tubes were placed in the centrifuge (Executive Series Centrifuge II, GS-022624340-AC, Accellerated Biologics, Florida, USA) for 10-min of slow spinning at a rate of 1600 rpm, which converts to a relative centrifugal force of 229 g. The tubes were then processed in a laminar flow biological safety cabinet (LABGARD, NuAire Inc., MN, USA) to remove the top layer of clear plasma. The tubes were then placed in the centrifuge once again for the second centrifugation at 3800 rpm (1294 g) for 10 min and processed again under the laminar flow biological safety cabinet to retain buffy coat; however, given manual processing, some of the bottom layer of erythrocytes and platelets were captured. The retained samples were then resuspended yielding 4–6 ml of leukocyte-rich PRP for injection. Following the PRP blood draw, a manual liposuction (adipose tissue harvest) was performed at the flank region based on the physician's standard procedure. The flank region was used based on the availability and accessibility of adipose tissue. For this procedure, patients assumed the lateral decubitus position, and the donor site was first anesthetized with 3 ml of 1% lidocaine (Hospira, Inc. Illinois, USA) without epinephrine. After the initial anesthetic injection, a tumescent solution (amount based on patient morphology) containing 1 mg epinephrine, Ringer’s lactate, and 2% lidocaine (Hospira Inc., IL, USA) was injected into the adipose region. A 2.4 mm × 15 cm
lipoaspirate-procured fat graft was then exposed to gravity to allow migration of the infranatant in the collection tube, which was then discarded. The remaining adipose (6 ml) was passed between two syringes with normal saline twice in a manner that would irrigate the fat and allow intra-articular injection using an 18-gauge needle as per the orthopedic surgeons standard practice. The final volume of adipose tissue was separated into two 3 ml syringes for injection. In keeping with the guidelines for minimal processing, the fat graft was subjected to neither enzymatic degradation nor centrifugation.

The BMA was performed at the posterior ilium with patients positioned prone and fluoroscopic guidance. Once positioned, the soft tissue and harvest site periosteum was first anesthetized (peppered) with both 5–10 ml (depending upon patient morphology) of 1% lidocaine ( Hospira Inc., IL, USA) and 3 ml of 0.5% bupivacaine ( Hospira Inc., IL, USA). A 11 gauge J-style bone marrow aspiration needle ( Busse Hospital Disposables, NY, USA) was then advanced to collect the BMA. A metal mallet was used to advance aspiration needle to progressive depths, yielding a total of 12 ml of non-centrifuged BMA for injection per the standard practice of the orthopedic surgeon. Specifically, four 10 ml collection syringes were used, each yielding 3 ml of BMA plus 1 ml of heparin ( SAGENT Pharmaceuticals, IL, USA) to prevent clotting. Heparin was used, as evidence suggests that heparinized BMA products showed an increase in colony-forming units with a fibroblast morphology (CFU-F) compared to sodium citrate, and CFU-F counts may represent potential stem cell counts. Following the procedure, the harvest site was cleansed, and steri-strips applied. Patients were then transferred to a treatment recovery room to monitor harvest sites for hemostasis.

The PRP vials underwent photoactivation for 10 min using low-level integrated LED light ( AdiLight-2, AdiStem Ltd. Carnegie, VIC, Australia), whereas the fat graft and BMA underwent 20-min of photoactivation per the orthopedic surgeons standard practice. No additional activation methods were used.

Prior to receiving the injections of PRP, BMA, and adipose graft, patients received a radial shockwave ( CuraMedix D-ACTOR 100, STORZ MEDICAL, Switzerland) treatment to the shoulder. Shockwave parameters included a 15 mm head, with a frequency of 15 Hz, 2-bars power (air-compressed unit), at 2000–4000 shocks based on patient tolerance. Radial shockwave therapy has been shown to improve function and pain among patients with chronic shoulder conditions and has shown a positive effect on chondrogenesis, neovascularization, and tissue regeneration. Furthermore, in a previous study, shockwave therapy has been shown to have a benefit on the metabolism of MSCs. Thus, we included shockwave as a part of our multimodal regenerative rehabilitation approach.

Following the shockwave treatment, glenohumeral injections were performed with an anterior intracapsular approach using fluoroscopy ( Brivo OEC, General Electric, WI, USA). Once injections were completed, steri-strips were applied to the injection site with ice application for 10 min. Patients were sent home with instructions for icing, and physical activity was encouraged as tolerated to begin the next day. All patients were referred to physiotherapy for therapeutic exercise and manual therapy. Table 1 provides a summary of the post-procedural care. Patients were advised to return twice over 4-week intervals for additional PRP injections using the same processing methods. Shockwave treatments were performed in addition 1 week later and prior to receiving the two booster PRP injections at follow-up visits for a total of four shockwave treatments over the course of care.

Post-procedural Follow-up Assessments

The outcome measures completed at baseline were reissued at each follow-up visit along with GROC questionnaire by a trained medical assistant not involved in delivering the interventions. The GROC is a self-report outcome measure that documents the patients’ perceived change in condition compared to baseline and is rated on a 15-point ordinal scale from −7 (much worse) to +7 (much better),
Evidence suggests that the GROC has a reliability of ICC = 0.62 for patients with shoulder pain, and has an MCID of ±3 points for patients, with recommendations for a change of 3 points being small, 4–5 points being moderate, and 6–7 points being large amounts of perceived improvement.

**Statistical Analysis**

Data were entered into SPSS version 27 for Windows software program (IBM SPSS, Armonk, NY, USA) for analysis. Descriptive data and outcome measure scores were calculated as appropriate using frequency counts and means ± standard deviation (SD). For the outcome measures, averages were reported as mean values, as opposed to median values, based on standard clinical application for scoring and interpreting change scores using the MCID. Outcome measure comparison points were analyzed as nonparametric data utilizing a Friedman Chi Square analysis with \( \alpha = 0.05 \). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at \( P < 0.017 \). Effect sizes were calculated using Z scores from the Wilcoxon signed-rank test using the formula \( r = Z/\sqrt{N} \), where \( N \) = number of observations for which Z is based. Interpretation of effect sizes were based on recommendations for nonparametric tests such that a large effect is 0.5 or greater, a medium is 0.3, and a small is 0.1.

**RESULTS**

Ten patients, including six females and four males (mean age ± SD = 65 ± 9.4 years), met inclusion criteria and were included in the analysis. Right dominance was reported in 6 of the 10 participants. No adverse events were reported beyond increased pain and swelling for the first few days lasting up to 1 week following the first procedure in approximately 30% of the patients, based on telephone follow-up contact and upon reporting at the first post-procedural follow-up visit 1 week later. Patients returned after an average of 27 days (SD ± 4) after initial injection for the second PRP injection (Follow-up 1 [F1]) and 68 days (SD ± 13) from the initial visit for the third PRP injection (Follow-up 2 [F2]). Results from the outcome measures including mean ± SD and P-values are illustrated in Table 2. Friedman Chi Square analysis indicated statistically significant differences in pain at best and worse, and patient-perceived function (based on PSFS) from baseline to both outcome points as well as between the first and second follow-up points (\( P \leq 0.002 \)). Post-hoc analysis with Wilcoxon signed-rank test with a Bonferroni correction applied compared change

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**Table 1. Post- and Peri-procedural Care**

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Treatment</th>
<th>Ice Guidelines</th>
<th>NSAIDs</th>
<th>Activity</th>
<th>Physiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-procedural</td>
<td>Ice application to shoulder Shockwave prior to injections</td>
<td>Advised to ice as needed multiple times per day</td>
<td>Advised may take OTC NSAIDS as needed until follow-up</td>
<td>Advice to stay active</td>
<td>Physiotherapy referral for therapeutic exercise and manual therapy</td>
</tr>
<tr>
<td>Telephone contact 2–3 days later</td>
<td>Interviewed for post-procedural symptoms</td>
<td>Reinforced instructions</td>
<td>Reinforced instructions</td>
<td>Reinforced instructions</td>
<td>Reinforced instructions</td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>Shockwave</td>
<td>Advised to ice as needed</td>
<td>May take OTC NSAIDS as needed</td>
<td>Advice to stay active</td>
<td>Physiotherapy referral for therapeutic exercise and manual therapy</td>
</tr>
<tr>
<td>4-week follow-up</td>
<td>Shockwave Booster PRP</td>
<td>Advised to ice as needed</td>
<td>May take OTC NSAIDS as needed</td>
<td>Advice to stay active</td>
<td>Physiotherapy optional</td>
</tr>
<tr>
<td>8–10 week follow-up</td>
<td>Shockwave Booster PRP</td>
<td>Advised to ice as needed</td>
<td>May take OTC NSAIDS as needed</td>
<td>Advice to stay active</td>
<td>Physiotherapy optional</td>
</tr>
</tbody>
</table>

NSAIDS: nonsteroidal anti-inflammatory drugs; OTC: over-the-counter (nonprescription); PRP: platelet-rich plasma.

with a 0 = no change. Evidence suggests that the GROC has a reliability of ICC = 0.62 for patients with shoulder pain, and has an MCID of ±3 points for patients, with recommendations for a change of 3 points being small, 4–5 points being moderate, and 6–7 points being large amounts of perceived improvement.

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between individual time points with an adjusted \(\alpha = 0.017\). A statistically significant difference indicating improvement from baseline to F1, as well as baseline to F2, for patient-perceived function using the PSFS was present \((P \leq 0.012)\). Significant improvements between F1 to F2 were not present for the PSFS \((P = 0.021)\). Significant improvements in pain at best and worse were present between baseline and F2 \((P \leq 0.016)\). Significant improvements between baseline and F1 were not present for pain at best and worse \((P \geq 0.02)\). When comparing change between F1 and F2, worse pain was significantly improved \((P = 0.005)\), however, significant change for best pain was not present \((P = 0.026)\). Although statistical significance was present for pain and function when comparing baseline to F2, effect size estimates were calculated to determine change magnitude. Effect size calculations (Table 3) indicated a large effect from baseline to the terminal follow-up point F2 for all dependent variables \((r \geq 0.57)\).

In addition to the magnitude of change, outcome measure improvements were compared to previously validated clinimetric thresholds using MCID values. The MCID values provided an interpretation of clinical improvement based on change scores. For shoulder pain, the MCID was reported at 1.1 points on a 0–10 scale, whereas the PSFS was reported with variable results ranging from 1.3 to 2.7, with larger values indicating greater clinically important improvements\(^{25-27}\). Improvements in pain at best did not satisfy the MCID of 1.1 points between baseline and F1, however, exceeded thresholds at F2 when compared to baseline (change of 2 points) pain improvements at worse satisfied the MCID of 1.1 points between baseline and F1 (change of 1.4 points), baseline and F2 (change of 3.7 points), and between F1 and F2 (2.3 points; see Figure 1).

Improvements in patient-perceived function (using PSFS) exceeded MCID threshold of 1.3 points at F1 and F2, as well as between F1 and F2.

With regard to the GROC, F1 and F2 indicated an average report of +3.0 and +4.7, respectively, which indicate patient-perceived overall improvement based on the lower threshold MCID of +3.0. Wilcoxon signed-ranks testing indicated statistically significant improvements in the GROC from F1 to F2 \((P = 0.035)\).

### Adverse Event and Safety Assessments
There were no adverse events or complications experienced by any patients except for pain related...
to the injection procedure that was resolved immediately, or shortly thereafter with over-the-counter (OTC) analgesics. No study participants had any minor or major complications related to blood draw for PRP, adipose tissue harvest, or bone marrow aspiration.

**DISCUSSION**

Evidence for the treatment of GHOA with orthobiologics is promising, however, a lack of clinical trials, absence of studies to determine efficacy of combined procedures, variability in processing procedures, and processing restrictions challenge generalization.\(^{18,38,39}\) Evidences, albeit limited, from published studies support the use of autologous injectable procedures such as PRP, lipoaspirate, BMA, and BMAC for treatment of GHOA.\(^{8,23,40–44}\) With regard to the use of PRP for GHOA, the evidence is limited albeit promising.\(^{8,42,44}\) In one study, the effect of single injection of leukocyte-poor PRP was compared to hyaluronic acid in the treatment of GHOA with improvements in pain and function identified 1–2 months following the injection.\(^{44}\) Of interest in the aforementioned study was that no differences in outcomes or side effects were present between groups.\(^{44}\) In a retrospective study, individuals with GHOA under the age of 51 who received a series of three leukocyte-poor PRP injections were able to postpone shoulder arthroplasty by 3.5 years.\(^{42}\) While these results are promising, patients in the aforementioned study receiving hyaluronic acid had comparable outcomes.\(^{42}\)

PRP is not a stem cell product, and current options for obtaining autologous MSCs include both BMA and adipose derivatives. Evidence underpinning the efficacy of BMA for GHOA is limited to three studies, whereas evidence for adipose tissue is limited to studies using processing systems or procedures. In one cohort study, the use of BMA was compared to BMAC in patients with GHOA.\(^{43}\) Additionally, the authors evaluated differences in outcomes between one and two injections for both groups. Results of the aforementioned study suggested a greater improvement in pain for the groups receiving two injections, with both the BMA and BMAC groups having comparable improvements in pain and function.\(^{43}\) In another study of registry data, patients with GHOA with or without rotator cuff tears underwent

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**Figure 1. Pain Score Comparison**

Pain scores based on a numeric pain scale rating pain from 0 (no pain) to 10 (worse possible pain). F1: Follow-up 1; F2: Follow-up 2.
treatment with platelet lysate, PRP, and BMAC. Results indicated improvements in pain and function at the 1-month follow-up that lasted into 2 years, which was the terminal follow-up point. In a pilot clinical trial, individuals with GHOA received either a corticosteroid or an injection of BMA. Results indicated that at the 12-month follow-up, individuals treated with BMA had greater improvements in function and pain, suggesting a superiority of BMA compared to a corticosteroid injection.

With regard to adipose-derived orthobiologics, autologous non-digested microfragmented adipose was used to treat patients with GHOA in two cohort studies. In one study, patients with mild to moderate GHOA received one injection of microfragmented adipose. At the 6-week follow-up point, significant improvements in pain and function were present that sustained at 1-year follow-up. Furthermore, at the 6-week follow-up through 18-weeks and lasting into the 1-year follow-up, an increase in joint space was present when compared to baseline. In another study, patients with mild to severe GHOA and secondary soft tissue pathology (e.g., rotator cuff, biceps, labral pathology) received one injection of microfragmented adipose. Results indicated significant improvements in pain and function at the early follow-up point persisting into the terminal follow-up period of 1 year.

Although a growing body of evidence supports autologous orthobiologics for GHOA, regulatory requirements and cost may present as barriers for use. For example, geographic restrictions limit physicians’ ability to perform procedures requiring more than minimal manipulation. The United States Food and Drug Administration, under Title 21 of the Code of Federal Regulations Part 1271.10 (a & b) and Part 1271.3 (c & f), provide a criterion for minimal manipulation of orthobiologics. In their documents, minimal manipulation is defined as a processing that does not alter original relevant characteristics of the cells or tissues. As such, processing adipose tissue to isolate cellular components and produce a stromal vascular fraction or using methods to enzymatically digest the tissue would be considered more than minimal manipulation. Thus, techniques using a lipoaspirate fat transfer without enzymatic degradation must be performed. Furthermore, using BMA or fat to produce terminally differentiated cells by culturing would exceed minimal manipulation thresholds. The clinical application of orthobiologics that are more than minimally manipulated results in the need to satisfy regulatory requirements such as an approved research trial or an Investigational New Drug application prior to patient care. Treatments based on expanded cell cultures and expensive processing kits or enzymes also involve a higher cost of care which may limit general population access. This may present a barrier for advancing knowledge in the area of GHOA. As a result, such regulations have incentivized physicians to develop treatment strategies for delivering orthobiologic agents with minimal manipulation.

The novel aspect of the study is based on procedures, whereby both BMA and adipose where minimally processed and processing kits were not used. Furthermore, all patients received an injection series of three leukocyte-rich PRP injections, and all vials underwent photoactivation.

The study results indicate that despite being recalcitrant to prior conservative measures, patients derived a statistically significant benefit with regard to reduced pain, improved function, and perceived change at the second follow-up period. While statistical probability is a means of interpreting change, statistical significance does not offer an interpretation of the clinical importance or magnitude of change. Magnitude may be determined through effect sizes, whereas a comparison of change scores and their ability to meet published MCID thresholds helps to determine clinical importance. As a result, effect sizes were calculated, and a large effect at the second follow-up suggested an appreciable magnitude of change. Furthermore, clinical application was a priority in this study. Thus, change scores were compared to previously established MCID values. While the differences were statistically different implying improvement from baseline to F2 for all outcome measures, actual change scores did not meet the threshold for clinically important change until F2 for pain at best, which was on average 68 days from baseline. Thus, clinically important outcomes may be achieved on a more medium-term basis, which...
Orthobiologics for shoulder osteoarthritis

The study findings in this cohort are consistent with previous investigations of orthobiologics for GHOA. Though there are variations in preparation, one area of debate is the use of leukocytes in PRP. A concern over potential proinflammatory effects of leukocytes may steer practitioners toward leukocyte-poor products, despite evidence to the contrary. For example, in one study, subjects with knee OA received leukocyte-rich PRP using a protocol of three weekly injections. In the study, peripheral blood and synovial fluid were tested for proinflammatory cytokines and growth factors before and after the intervention with results indicating similar proinflammatory levels prior to and after treatment. From the perspective of clinical evidence, two studies have evaluated the use of PRP for GHOA, with both showing comparable outcomes to hyaluronic acid using a leukocyte-poor product. Although Centeno et al. reported efficacy with a PRP plus BMAC injection, the type of PRP was not reported. Thus, given evidence for the lack of increasing proinflammatory cytokines at the knee and the relative outcome comparability of PRP and hyaluronic acid using a leukocyte-poor PRP product, we were not compelled to use a similar procedure for the shoulder. Further to this point, a leukocyte-rich product may have contributed to our outcomes particularly as leukocytes are a key component of healing.

Reports of post-procedural pain and swelling were the only adverse events identified in this study. In a previously published multicenter study, the overall reported adverse events were 12.1% of the individuals, with 29% of the adverse events (3.9% of study population) the result of post-procedural pain. Of interest in the aforementioned study was that procedures combining different orthobiological treatments (injections) had higher adverse events, and many of the total adverse events were attributed to degenerative joint disease. Reports of post-procedural pain in our study was 30% and may be higher than published data as a result of the patients having degenerative changes based on a minimum Kellgren–Lawrence Grade 2 and having been recalcitrant to conservative care including corticosteroid injections and physical therapy. Furthermore, evidence suggests that combined procedures may increase post-procedural pain, which offers a reasonable explanation.

Another relevant area to consider is the number of injections, as there is currently no evidence to guide the number of PRP injections for GHOA. In studies using BMA and BMAC for GHOA, serial injections were of greater benefit than single injection. The published studies for PRP at the GHOA used a single injection; however, outcomes were comparable to hyaluronic acid, prompting us to deviate from the single-injection protocol and use a series of three leukocyte-rich PRP injections in our patients.

One area of discussion that should be noted is that we permitted our patients to take OTC anti-inflammatory medications as needed. Evidences suggest that certain antiplatelet medications may decrease growth factor release and platelet counts in PRP, however, the evidence for OTC anti-inflammatories is less compelling. In one study, it was determined that the use of cyclooxygenase-2 inhibitors had no effect on growth factor release from PRP, however, the study used dogs which may not be comparable to human participants. However, in a recent systematic review, evidence suggested that patients taking acetaminophen and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) had reductions in platelet aggregation. However, patients taking selective cyclooxygenase-2 NSAIDs showed no differences in platelet aggregation. Furthermore, the review suggested that NSAIDs did not lead to a significant decrease in platelet count. While we recognize that NSAIDS may affect platelet aggregation, the benefits of early mobilization for our patients superseded these concerns. In cases where there is a concern for platelet aggregation or attenuated growth factor release and NSAIDs are permitted, physicians may be prompted to prescribe a cyclooxygenase-2 inhibitor such as celecoxib or meloxicam. The novel aspect of our study is the concurrent use of minimally processed BMA, lipoparticle, and leukocyte-rich PRP. Despite minimal processing,
satisfactory outcomes were achieved, and utilization of best practice may have contributed to the results. For example, the posterior ilium was utilized for the BMA, which has been shown to possess 1.6 times greater cell yield than other regions.\textsuperscript{18,39,55,56} Moreover, use of a 10-ml syringe for BMA procedures has been shown to produce the best cell yields.\textsuperscript{39,57} Furthermore, aspirating bone marrow from the iliac crest using small volumes with a 10-ml syringe, as we did with our patients, has been proposed for harvesting adult mesenchymal cells as a standard technique to avoid blood dilution.\textsuperscript{57} Additionally, photoactivation of the vials may have had an effect on the outcomes. Although high quality studies with large sample sizes do not exist to support the efficacy of LED light exposure, evidence does exist to suggest an increase in interleukin-10 along with a reduction in proinflammatory cytokines (TNF-\(\alpha\) and IL-6).\textsuperscript{58} Our understanding of the potential benefits for using photoactivation comes from the data published by Zhevago et al.\textsuperscript{58} who exposed human peripheral blood to transcutaneous and in vitro irradiation with polychromatic visible and infrared polarized light. In the study, a decrease in the level of proinflammatory cytokines TNF-alpha and IL-6, as well as increases in IL-10, was reported. Lastly, all of our patients received a multimodal regenerative rehabilitation procedure that included radial shockwave therapy, activity guidelines, and a minimal course of physiotherapy, which most certainly would contribute to improved functional outcomes.

Study Limitations

A limitation resides in the utilization of a retrospective one-group design and average short and medium terminal follow-up points of 27 and 68 days, respectively. One aspect to consider when evaluating this limitation is the inclusion criteria of being recalcitrant to prior care. Essentially, patients served as their own controls having had prior physiotherapy and corticosteroid injections. Another limitation was the lack of magnetic resonance imaging (MRI) at baseline and lack of follow-up radiographs. Our reasoning for using standard radiographs at baseline for diagnosis was patient cost. While follow-up imaging may have been of value to determine structural changes, our priority was clinical change, particularly as imaging may be discordant to clinical findings.\textsuperscript{59} Nevertheless, we acknowledge this study limitation. Furthermore, cell counts were not obtained, thus limiting the precise understanding of the products used in the study. Lastly, the procedures (orthobiologics and both peri- and post-regenerative rehabilitation) used represent the approach used by a single medical facility, which may not be generalizable to other practices using a different approach. Furthermore, the use of a combined procedure in a single cohort limits the ability to identify causation, as it is not clear whether benefits were derived from the combined approach or a single component of care. Future studies should target 2–3 arm trials and determine the most efficacious orthobiological strategy with regard to combined versus individualized treatment approaches as it is not clear which specific treatment or combination had the greatest influence on results.

CONCLUSION

A minimally processed adipose graft with BMA and three PRP injections improved pain and function among individuals with GHOA who were recalcitrant to conservative care. The only adverse events reported are related to administration of injectate that were temporary and managed in all cases with OTC analgesics indicating safety of the protocol. Although significant functional improvement at both follow-up points occurred, clinically important and significant changes in pain did not occur until F2. A one-group design and multimodal approach limit the generalization of results.

AUTHORS’ CONTRIBUTIONS

All authors contributed to the concept and design, patient data, or study materials acquisition and provision, analysis, drafting, and final approval of the manuscript.

ACKNOWLEDGMENTS

There are no acknowledgments.

FUNDING

The authors have no funding sources to declare.
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REFERENCES


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