

Human Umbilical Cord Tissue Allografts in Chondromalacia of the Shoulder: Data from an Observational Repository

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Abstract

Background

Chondromalacia is the cartilage erosion on the articulating surfaces of the shoulder. Conventional care encompasses activity modification, physical therapy, medication, and the consideration of surgical methods. This study evaluates umbilical cord tissue allografts (UCTa) as an alternative intervention for chondromalacia in the glenohumeral joint, utilizing structural and functional properties to provide support and cushioning when standard care fails.

Methods

From an observational repository, 115 patients with treatment-resistant chondromalacia of the shoulder were identified who received one to three applications of UCTa based on the severity of degeneration and reported pain. The data included patient-reported scales, the Numeric Pain Rating Scale, the Western Ontario and McMaster University Arthritis Index, and the Quality of Life Scale. The data were tested using the Wilcoxon signed rank (WSRT), Kruskal-Wallis H, Mann-Whitney U, and Jonckheere-Terpstra tests.

Results

The cohort showed improvements on average in all categories, irrespective of the number of applications, reaching significant p-values ($p < 0.05$) in the WSRT comparison of initial to final visits. No adverse events were reported.

Conclusions

Limitations included a small sample size, no control group, recall bias, and the use of a non-specific scale. The results of this study expand the current literature of alternative noninvasive care for chondromalacia of the shoulder. The application of UCTa correlates with beneficial patient outcomes, and further studies with randomized controlled trials are merited in validating efficacy and defining dosage and best practice procedures.

Introduction

Chondromalacia, the erosion of the cartilage on the articulating surfaces of the bone, results in the softening and subsequent tearing of the joint, specifically in joints with a high range of motion [1]. Due to its extensive range of motion, the glenohumeral (GH) joint in the shoulder is inherently unstable, leading to frequent injury and quicker degeneration [2]. Symptoms of cartilage defects in the glenohumeral joint of the shoulder include pain during and after sports activities, limited range of motion, and painful crepitation [3]. Often, symptoms do not develop in the early stages of shoulder chondral defects, causing difficulty in prompt detection [4]. Degeneration of the GH joint is often associated with shoulder osteoarthritis (OA), a progressive narrowing of the GH joint that causes significant pain and functional disability [5]. Osteoarthritis is often characterized by the level of chondromalacia, with stage 1 encompassing early softening of the cartilage and stage 4 encompassing severe loss of joint space and osteophyte formation [6, 8]. Chondromalacia solely describes the cartilage degeneration in a joint, while OA can stem from various factors, including metabolic dysfunction, chronic inflammation, and neurological complications [7]. Degeneration of the GH joint without systemic factors is more likely found in older individuals and those in occupations that involve collision sports or manual labor [8]. Chondromalacia related to shoulder OA is commonly found in women due to their differences in joint anatomy, alignment, muscle strength, hormonal influences, obesity, and genetics. Additionally, degenerative changes in the GH joint are found in up to 17% of patients with shoulder pain [9]. Shoulder OA is the third most common site for musculoskeletal pain, following only the low back and knee [10]. However, GH joint degeneration symptoms are still severe enough to have functional limitations and a decreased quality of life [9]. Current standard-of-care options for patients suffering from glenohumeral joint defects include invasive and noninvasive interventions.

Operative approaches to glenohumeral joint defects depend on the condition of the patient's defect location, size, depth, and containment. Standard surgical options include palliative, reparative, restorative, and reconstructive surgeries [8]. Joint-preserving procedures such as arthroscopic debridement, chondrocyte transplantation, and osteochondral transplantation have shown clinical

success but come with the risk of no pain improvement compared to non-operative methods and the risk of reoperation [11]. Surgical management of shoulder maladies carries significant financial stress, as economic analyses of both arthroscopic shoulder replacement and rotator cuff repair demonstrate that procedural costs, downstream revision rates, and postoperative complications collectively impose economic impracticalities on patients and healthcare systems [12, 13]. Noninvasive interventions for articular cartilage degeneration are commonly prescribed before surgical approaches are recommended, depending on the severity of injury. Standard-of-care practices aim to relieve symptoms through trials of activity modification, physical therapy, oral nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroid injections [8]. While temporary relief can be achieved, the noninvasive practices target symptomatic relief and not the source of the issue. Many patients desire to avoid surgery but are left without options after exhausting current conservative measures. The need to develop alternative medicine to target the root cause of patient pain, shoulder articular cartilage degeneration, could revolutionize the standard of conservative interventions for patients.

Regenerative medicine has gained traction in recent musculoskeletal research, highlighting platelet-rich plasma (PRP), hyaluronic acid (HA), and mesenchymal stem cells as viable conservative approaches to cartilage repair. This study presents umbilical cord tissue allografts as an alternative method for addressing missing and damaged cartilage. Umbilical cord tissue (UCT), containing collagen fiber types I, II, III, and V, cytokines, proteoglycans, hyaluronic acid, and various growth factors, is an additional noninvasive measure after failure to progress with current standard of care practices for shoulder articular cartilage degeneration [14–17]. UCT functions as a support and cushioning against external forces that, when minimally manipulated into an allograft, can replace the connective tissue in the articular cartilage of the glenohumeral joint that has the same function. A study done by Lai (2024) achieved favorable results in applying UCT allografts (UCTa) to articular cartilage defects associated with hip osteoarthritis (OA), by supplementing missing cartilage and providing extra cushioning to the joint [18]. Results showed an increase in range of motion and overall function, with a reduction in pain. Given its structural properties and its similarity to the composition of the articular cartilage, UCTa can be used homologously in various sites to replace degenerating articular cartilage [3, 14, 16]. In this observational case study, UCTa were applied to patients with glenohumeral joint cartilage degeneration to evaluate the safety and preliminary effectiveness of umbilical cord tissue as an alternative intervention when the current conservative standard of care fails.

Materials and Methods

Study Design

The observational repository data have been collected following the guidelines of the Declaration of Helsinki, with approval from the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2022-311) since January 2022. Prior to application, all patients provided informed consent. The details of the repository design and UCTa processing can be found in other published works derived from the database [18, 20, 21]. All allografts used on included participants were the 150mg cryopreserved tissue in 2mL saline product from Regenative Labs (Pensacola, FL), manufactured following the FDA's 361 guidelines for minimally manipulated human cell and tissue products. Observer bias was minimized by having multiple observers at multiple clinical sites across the country. Inclusion criteria for intra-articular applications mirrored the Centers for Medicare & Medicaid Services (CMS) requirement for arthroplasty: documented radiographic evidence of the diagnosis (joint degeneration), documentation of moderate to severe pain or functional disability for 12 weeks, and documentation of at least 12 weeks of unsuccessful conservative therapy [22]. All reapplication determinations were at the discretion of individual providers and their assessment of each patient's progress. The cohort for this paper was selected by identifying completed data sets for intra-articular shoulder applications only, excluding patients who also had rotator cuff-related defects or more than three applications. Participants were also excluded if they were lost to follow-up or if the data were outside the respective time range (± 15 days for 30-day follow-up, ± 30 days for 90-day, 120-day, 150-day, and 180-day follow-ups). There were 6274 unique patients in the repository with over 180 different use sites. 616 of those patients had shoulder-related applications, 423 of those had intraarticular defects without rotator cuff or tendon involvement, and 114 of those patients, or 27%, had complete data sets. The final group sizes for patients who met the criteria with one, two, and three applications were 48, 31, and 35, respectively. No exclusions were made based on gender, age, body mass index (BMI), or level or initial score.

Study Population

A total of 115 patients were included in the post-observational analysis group, consisting of 55 (48%) males, 58 (50%) females, and 2 (2%) patients with unreported sex. Based on the severity of the defect and the physician’s discretion, 48 patients (25 males and 23 females) received a single application, 31 patients (12 males, 18 females, and 1 unreported) received two applications, and 35 patients (18 males, 16 females, and 1 unreported) received three applications. Throughout the analysis, the cohort was divided based on dosage. All patients receiving one application reported their final scores at the 90-day mark. In multi-application groups, final outcome date varied depending on when they received their second or third application, and data sets were defined as complete with one additional follow-up following their last UCTa application. In double application patients, 26 out of 31 patients reported final scores at the 120-day mark, and 5 patients reported final scores at the 90-day visit. In the triple application group, 22 out of 35 patients reported final scores at the 180-day mark, 7 reported scores at the 150-day mark, and 6 reported last scores at the 120-day visit. To account for the time variation, percentage improvement and total score difference were determined by utilizing the last data set provided, irrespective of the timeline. Several demographic factors were identified as potential confounders, including age, gender, and BMI, which may influence application response and reported outcomes. The mean age in the single, double, and triple application groups was 72, 73, and 72, respectively. The mean BMI in the single, double, and triple application groups was 29.15, 27.96, and 27.43, respectively. The patient demographics for each group are listed below (Table 1).

Table 1
Patient age, BMI, and gender by application amount.

Age Range	1 app	2 app	3 app	Total	BMI Range	1 app	2 app	3 app	Total
20–29	0	0	0	0	Underweight (< 18.5)	1	0	2	3
30–39	0	0	1	1	Healthy weight (18.5–24.9)	5	1	3	9
40–49	1	0	0	1	Overweight (25.0-29.9)	12	3	15	30
50–59	0	0	0	0	Obese (> 30.0)	13	3	7	23
60–69	14	6	10	30	NA	17	24	9	50
70–79	27	20	20	67	Mean BMI	29.15	27.96	27.43	
80–89	4	4	3	11	Gender	1 app	2 app	3 app	total
90–99	1	0	1	2	Male	25	12	18	55
NA	1	1	1	3	Female	23	18	17	58
Mean Age	72	73	72		NA	0	1	1	2

Intervention and Patient Care Procedures

Patients in this study presented visible cartilage degradation in the intra-articular space of the shoulder at Kellgren and Lawrence grade levels 3–4, limited range of motion, and shoulder instability. Patients had undergone at least 3 months of conservative care, including measures such as physical therapy, topical medication, NSAIDs, and activity modification. All patients in this group were eligible for surgery before umbilical cord tissue intervention based on the advanced grading of tissue deterioration and failed conservative care. X-ray and MRI imaging were used to determine the location and severity of structural tissue degeneration and damage to the surrounding tendons and ligaments. After failed standard conservative methods, the patients in this repository opted to receive umbilical cord allografts to evade or delay surgical intervention. Patients were instructed to avoid the use of NSAIDs and oral steroid treatments for two weeks before application. Intra-articular applications of the allografts were administered to patients with tissue defects aligned with osteoarthritic degeneration. Sterile technique was used to prepare the application site, and a topical anesthetic spray was used at the site of needle entry. Following sterile technique, 2.0 ml of the 150mg Wharton’s Jelly Allograft was drawn up into a 3 ml syringe and administered using anatomical landmarks and ultrasound to guide directly to the posterior side of the shoulder using a 25-gauge 1.5-inch needle. Following administration, the shoulder was passively moved through the full range of motion, and a sterile dressing was applied. Patients were instructed to minimize movement and strenuous activity, use ice packs in 15–20 minute intervals every 3–4 hours, support the arm with a pillow while resting, and remain hydrated while eating nutrient-rich foods for 72 hours following the procedure. Aftercare instructions were also to avoid the use of NSAIDs for at least 4 weeks following the procedure. Patients were instructed to gradually ease into using the shoulder by starting with mobility exercises like

pendulum swings and shoulder rolls and working up to shoulder circles, resistance bands, and weights. At 3 months, patients were expected to resume regular activity. Follow-up appointments took place at the 30 and 90-day post-UCTa application mark, during which some patients received additional applications based on the severity of degeneration and the evaluation from their provider, duplicating the same sterile administration technique, and filled out the NPRS, WOMAC, and QOLS scales.

Data Analysis

The NPRS, WOMAC (Pain, Stiffness, Physical Function, and Total), and QOLS were used to measure patient-reported outcomes at initial and follow-up visits across all application groups. Although the WOMAC is not site-specific, clinical sites offering multiple musculoskeletal site applications used the WOMAC scale for all use sites for homogeneity of data entry. Descriptive statistics presented baseline characteristics (mean, standard deviation, median, and interquartile range [IQR]) in single, double, and triple application groups. No imputation was performed in statistical analyses, and all missing data sets were excluded. The threshold of significance was set to $p < 0.05$ in all statistical tests. All statistical analyses were conducted using SPSS Statistics (Version 31, IBM Corp., Armonk, NY) and verified in Python (Version 3.11) using SciPy and Stats models, and RStudio (Version 312026.1.1.403, Posit Software, Boston, MA). The R analysis script used was drafted with assistance from Claude (Anthropic, claude.sonnet-4-6, 2026). All code was reviewed, verified, and executed by the authors, who take full responsibility for the analytical outputs. Given the non-normal distribution of outcomes confirmed by descriptive inspection, all primary analyses employed nonparametric methods.

Within-group changes over time were evaluated using the Wilcoxon Signed-Rank Test (WSRT), comparing baseline to 30-day, baseline to 90-day, and baseline to final endpoint scores within each dosage group. To control for Type I error within each outcome, Bonferroni correction was applied within each dosage group to control the family-wise error rate across the number of time-point comparisons made per group ($\alpha = 0.05/2 = 0.025$ for the single application group; $\alpha = 0.05/3 = 0.0167$ for the double and triple application groups). Effect size was calculated as $r = |z| / \sqrt{n}$, where $r \geq 0.10$ indicates a small effect, $r \geq 0.30$ a medium effect, and $r \geq 0.50$ a large effect. Between-group differences in baseline scores, final scores, and change scores were assessed using the Mann-Whitney U test across all three pairwise dosage comparisons (1 App vs. 2 App; 1 App vs. 3 App; 2 App vs. 3 App), with Bonferroni correction applied for three comparisons ($\alpha = 0.0167$). Group medians determined the direction of significant differences. To address the potential confounding influence of baseline demographic variables, two complementary analyses were conducted. First, Spearman rank correlations were computed between age or BMI and Δ change scores within each dosage group, and Mann-Whitney U tests compared Δ change scores between female and male patients, with Bonferroni correction for 18 tests per group ($\alpha = 0.0028$). Second, rank-based multiple regression was conducted on the combined sample, converting all variables to ranks prior to analysis to preserve the nonparametric framework. The outcome variable was the ranked Δ change score; predictors entered simultaneously were ranked baseline severity, age, gender (female = 0, male = 1), and dosage group (dummy-coded: 2 Applications vs. 1 Application reference; 3 Applications vs. 1 Application reference). BMI was excluded from the combined regression model due to 77% missing data in the double application group, though BMI was examined in separate within-group Spearman correlations where available. Individual predictor coefficients (B), standard errors, t-statistics, and p-values are reported to evaluate the independent contribution of each variable to treatment outcomes.

Results

The cohort of 115 patients was divided into categories based on dosage frequency. A decrease in NPRS and WOMAC scores equates to improvement; inversely, an increase in QOLS scores equates to improvement. Table 2 presents the average percent improvement for all application categories. WOMAC scores in the multi-application groups fluctuated from visit to visit. Despite the variation, they displayed a total decline in scores from the initial date to the final follow-up. Variability in multi-application use was common, often driven by slight increases in pain experienced by patients, which subsequently necessitated reapplication. Figure 1(A-C) presents a visual analysis of the average scores for each scale.

Table 2
Percent improvement in each scale by number of applications from the initial to the final visit.

Scale	1 application	2 applications	3 applications
NPRS	50.77%	43.59%	57.10%
WOMAC Total	41.95%	49.80%	47.53%
Pain	40.97%	50.00%	47.69%
Stiffness	45.32%	49.58%	52.54%
Functionality	41.70%	49.78%	46.59%
QOLS	12.00%	3.50%	6.31%

To assess within-group changes over time, the Wilcoxon Signed-rank test (WSRT) was employed as a non-parametric alternative for the data. Parametric testing was not considered for this study due to the skewness of the data, as shown in the descriptive statistics in Appendix A. The WSRT was utilized on each application group to compare outcomes between the initial and follow-up visits (Table 3). In the multi-application groups where the endpoint was variable due to non-standardized reapplication schedules, the last available dataset was used regardless of date. Significant differences between initial and follow-up visits were identified in all application groups, across multiple scales, after applying Bonferroni's correction. All application groups observed significance in the initial to final scores in various scales. A summary of the NPRS, WOMAC, and QOLS scores from initial to last available visit is presented in Fig. 2.

Table 3

Wilcoxon Signed-Rank Test Statistics in all application groups from initial to follow-up visits (single application adjustment $\alpha = 0.05/2 = 0.025$; double and triple application adjustment $\alpha = 0.05/3 = 0.017$).

Comparison	NPRS	WOMAC Pain	WOMAC Stiffness	WOMAC Function	WOMAC Total	QOLS
1 Application (Bonferroni $\alpha = 0.0250$)						
Initial → 30-Day	p = < .0001 <i>r = 0.818</i>	p = 0.0024 <i>r = 0.662</i>	p = < .0001 <i>r = 0.802</i>	p = 0.0003 <i>r = 0.665</i>	p = < .0001 <i>r = 0.685</i>	p = 0.0006 <i>r = 0.702</i>
Initial → 90-Day (Final)	p = < .0001 <i>r = 0.847</i>	p = 0.0001 <i>r = 0.645</i>	p = < .0001 <i>r = 0.751</i>	p = < .0001 <i>r = 0.619</i>	p = < .0001 <i>r = 0.642</i>	p = 0.0004 <i>r = 0.640</i>
2 Applications (Bonferroni $\alpha = 0.0167$)						
Initial → 30-Day	p = 0.0001 <i>r = 0.874</i>	p = 0.0002 <i>r = 0.788</i>	p = 0.0009 <i>r = 0.817</i>	p = < .0001 <i>r = 0.864</i>	p = < .0001 <i>r = 0.873</i>	p = 0.0256
Initial → 90-Day	p = 0.0071 <i>r = 0.751</i>	p = 0.0002 <i>r = 0.748</i>	p = 0.0014 <i>r = 0.692</i>	p = < .0001 <i>r = 0.774</i>	p = < .0001 <i>r = 0.755</i>	p = 0.2269
Initial → Final (Endpoint)	p = 0.0004 <i>r = 0.794</i>	p = < .0001 <i>r = 0.873</i>	p = < .0001 <i>r = 0.813</i>	p = < .0001 <i>r = 0.822</i>	p = < .0001 <i>r = 0.841</i>	p = 0.1297
3 Applications (Bonferroni $\alpha = 0.0167$)						
Initial → 30-Day	p = 0.0005 <i>r = 0.706</i>	p = 0.0178	p = 0.0093 <i>r = 0.821</i>	p = 0.0128 <i>r = 0.793</i>	p = 0.0066 <i>r = 0.768</i>	p = 0.1569
Initial → 90-Day	p = < .0001 <i>r = 0.749</i>	p = 0.0505	p = 0.0007 <i>r = 0.807</i>	p = 0.0033 <i>r = 0.667</i>	p = 0.0021 <i>r = 0.595</i>	p = 0.1481
Initial → Final (Endpoint)	p = < .0001 <i>r = 0.827</i>	p = < .0001 <i>r = 0.822</i>	p = < .0001 <i>r = 0.842</i>	p = < .0001 <i>r = 0.771</i>	p = < .0001 <i>r = 0.784</i>	p = 0.0006 <i>r = 0.673</i>
Bold = statistically significant after Bonferroni correction. NPRS and WOMAC subscales: lower scores indicate improvement. QOLS: higher scores indicate improvement. Effect size r: small $\geq .10$, medium $\geq .30$, large $\geq .50$. r reported only where significant. 1 Application: $\alpha = 0.05/2 = 0.0250$. 2 and 3 Applications: $\alpha = 0.05/3 = 0.0167$. Endpoint: last available visit per patient. For the 2 Application group, 5 patients had endpoint at 90-Day (visit 3); remainder at 120-Day (visit 4). For the 3 Application group, endpoint is the last non-missing value across visits 4 (120-Day), 5 (150-Day), and 6 (180-Day). NPRS n varies: 1 App n = 35–44; 2 App n = 26–28; 3 App n = 32–33. All other scales: 1 App n = 48; 2 App n = 31; 3 App n = 35.						

To determine the difference in overall improvement between specific dosage groups, the Mann-Whitney U test was conducted on initial scores, final scores, and the difference in initial and final scores for each group. Prior to the assessment with the Mann-Whitney test, a Kruskal-Wallis test was utilized to determine if significance could be found across all dosage groups. Once significance was detected, the analysis with the Mann-Whitney test was considered appropriate. Data sets were completed with a 30-day follow-up after the last application in multi-application groups, which led to fluctuating final visit dates for patients, as the practicing physician determined the reapplication schedule. The final visit scores were the last follow-up submitted for each patient, regardless of timeline. Table 4 displays the test statistics for each comparison group (single vs. double application, single vs. triple application, and double vs. triple application). After adjustment with Bonferroni's correction ($\alpha = 0.05/3 = 0.017$), comparisons between the single and double application groups revealed that the double application group had lower baseline NPRS scores ($p < 0.001$, $r = 0.45$, and lower improvement in NPRS scores than the single application group, $p = 0.005$, with a moderate effect size ($r =$

0.35). When comparing double and triple application groups, notable significant differences in baseline scores were found in NPRS ($p = 0.002$, $r = 0.40$) and stiffness ($p = 0.012$, $r = 0.31$) scores, indicating that double application patients began with lower scores than the triple application group. Triple application patients also experienced significantly greater NPRS score improvement than the double application group, $p = 0.01$, with a moderate effect size, $r = 0.33$. No significant differences were found between the single and triple application groups.

Table 4

Significant differences (Bonferroni-adjusted $\alpha = 0.0167$) in initial scores, final (endpoint) scores, and overall change scores (Δ) between dosage groups across all outcome scales. Bold values indicate statistical significance; effect size r is shown where significant.

Comparison	NPRS	WOMAC Pain	WOMAC Stiffness	WOMAC Function	WOMAC Total	QOLS	Direction of Difference [ⓧ]
1 App vs. 2 App (Bonferroni $\alpha = 0.0167$)							
Initial Score	$p = 0.0001$ $r = 0.449$	$p = 0.3921$	$p = 0.3280$	$p = 0.1832$	$p = 0.2130$	$p = 0.9001$	1 App higher at baseline
Final Score	$p = 0.0247$	$p = 0.2680$	$p = 0.4970$	$p = 0.1546$	$p = 0.2106$	$p = 0.2223$	—
Δ Change Score	$p = 0.0051$ $r = 0.350$	$p = 0.5351$	$p = 0.8150$	$p = 0.8842$	$p = 0.8763$	$p = 0.1239$	1 App greater improvement
1 App vs. 3 App (Bonferroni $\alpha = 0.0167$)							
Initial Score	$p = 0.3885$	$p = 0.6437$	$p = 0.1345$	$p = 0.5006$	$p = 0.4384$	$p = 0.8176$	—
Final Score	$p = 0.1904$	$p = 0.8384$	$p = 0.6737$	$p = 0.6880$	$p = 0.7784$	$p = 0.3466$	—
Δ Change Score	$p = 0.8480$	$p = 0.4504$	$p = 0.1314$	$p = 0.3562$	$p = 0.3147$	$p = 0.4683$	—
2 App vs. 3 App (Bonferroni $\alpha = 0.0167$)							
Initial Score	$p = 0.0019$ $r = 0.391$	$p = 0.2017$	$p = 0.0123$ $r = 0.305$	$p = 0.0449$	$p = 0.0397$	$p = 0.7675$	2 App lower at baseline
Final Score	$p = 0.1409$	$p = 0.1641$	$p = 0.2688$	$p = 0.0604$	$p = 0.0537$	$p = 0.7625$	—
Δ Change Score	$p = 0.0096$ $r = 0.330$	$p = 0.8006$	$p = 0.1434$	$p = 0.4215$	$p = 0.3819$	$p = 0.3746$	3 App greater improvement
Bold = statistically significant after Bonferroni correction ($\alpha = 0.05/3 = 0.0167$). Effect size r: small $\geq .10$, medium $\geq .30$, large $\geq .50$. r reported only where significant. Initial Score = baseline (visit 1) values compared between groups. Final Score = endpoint scores compared between groups. Δ Change Score = Final – Initial. Negative Δ = improvement for NPRS/WOMAC; Positive Δ = improvement for QOLS. [ⓧ] Direction of Difference indicates which group had the lower score (Initial/Final) or greater improvement (Δ), based on group medians. Shown only for rows containing at least one significant result. No significant differences were found between 1 App and 3 App groups on any scale or measure. Sample sizes: 1 App $n = 35-48$; 2 App $n = 26-31$; 3 App $n = 33-35$ (NPRS lower due to missing data at some visits).							

The univariate analyses identified no significant confounders after Bonferroni correction ($\alpha = 0.0028$) and therefore were not reported tabularly. Age and BMI showed no significant Spearman correlations with Δ change scores in any dosage group or scale. A trend toward greater NPRS improvement in older patients was observed in the triple application group ($\rho = -0.433$, $p = .013$), though this did not survive correction. Gender was not a significant predictor after correction, though unadjusted comparisons suggested females tended toward greater NPRS improvement in the single and triple application groups ($p = .035$ and $p = .048$, respectively).

Rank-based multiple regression on the combined sample confirmed these findings in a multivariate framework. Baseline severity was the only significant predictor across all six outcome scales (all $p \leq .0002$), with negative coefficients throughout ($B = -0.342$ to -0.745), indicating that patients with greater initial symptom burden achieved greater improvement after controlling for all other variables (Table 5). Age, gender, and dosage group were non-significant in all models (all $p > .07$), confirming that none of these variables independently predicted treatment outcomes after adjustment for baseline severity.

Table 5

Rank-based multiple regression — unstandardized coefficients (B), standard errors, t-statistics, and two-tailed p-values for each predictor. All variables were converted to ranks prior to analysis. Dosage rows are shown in *italic*. Bold text indicates a statistically significant predictor ($p < .05$, unadjusted within model).

Scale	Predictor	B (rank units)	SE	t	p
<i>☐ Dosage predictors: dummy-coded, reference = 1 Application. Positive B = that group improved more than 1 App after adjustment; Negative B = improved less. Neither represents a causal dose effect — see footnotes.</i>					
NPRS	Baseline Score	-0.745	0.085	-8.798	< .0001 **
	Age	0.013	0.070	0.189	0.8507
	Gender (Male = 1)	0.117	0.085	1.387	0.1690
	<i>2 App vs. 1 App ☐</i>	-0.037	0.109	-0.344	0.7320
	<i>3 App vs. 1 App ☐</i>	-0.088	0.092	-0.954	0.3425
Pain	Baseline Score	-0.616	0.075	-8.250	< .0001 **
	Age	0.129	0.074	1.734	0.0858
	Gender (Male = 1)	0.117	0.086	1.350	0.1798
	<i>2 App vs. 1 App ☐</i>	-0.149	0.105	-1.417	0.1593
	<i>3 App vs. 1 App ☐</i>	-0.055	0.101	-0.549	0.5843
Stiffness	Baseline Score	-0.681	0.071	-9.524	< .0001 **
	Age	0.104	0.069	1.503	0.1360
	Gender (Male = 1)	0.086	0.080	1.073	0.2857
	<i>2 App vs. 1 App ☐</i>	-0.118	0.098	-1.204	0.2312
	<i>3 App vs. 1 App ☐</i>	-0.068	0.095	-0.715	0.4762
Physical Function	Baseline Score	-0.662	0.074	-8.933	< .0001 **
	Age	0.112	0.073	1.537	0.1274
	Gender (Male = 1)	0.025	0.085	0.293	0.7698
	<i>2 App vs. 1 App ☐</i>	-0.156	0.104	-1.508	0.1345
	<i>3 App vs. 1 App ☐</i>	-0.064	0.099	-0.649	0.5179
WOMAC Total	Baseline Score	-0.647	0.075	-8.631	< .0001 **
	Age	0.117	0.074	1.588	0.1154
	Gender (Male = 1)	0.056	0.086	0.655	0.5139
	<i>2 App vs. 1 App ☐</i>	-0.142	0.105	-1.361	0.1766
	<i>3 App vs. 1 App ☐</i>	-0.058	0.100	-0.582	0.5618
QOLS	Baseline Score	-0.342	0.090	-3.793	0.0002 **
	Age	-0.023	0.091	-0.256	0.7987
	Gender (Male = 1)	-0.023	0.105	-0.218	0.8278
	<i>2 App vs. 1 App ☐</i>	-0.228	0.128	-1.778	0.0784
	<i>3 App vs. 1 App ☐</i>	-0.104	0.123	-0.848	0.3984
B = unstandardized regression coefficient in rank units. Sign indicates direction; magnitude is not directly interpretable in original score units.					
SE = Standard Error					

Scale	Predictor	B (rank units)	SE	t	p
t = t-statistic (t = B/SE)					
** = predictor significant at p < .05 within the model.					
Baseline Score: significant in all six models (all p ≤ .0002). Negative B throughout confirms that patients with higher initial symptom severity improved more, after controlling for all other predictors including dosage.					
Age and Gender: non-significant in all models (all p > .08), confirming no independent confounding effect on treatment response.					
☐ Dosage dummies (italic rows, blue tint): non-significant in all models (all p > .07). This indicates that after adjusting for baseline severity, patients receiving 2 or 3 applications did not improve significantly more or less than patients receiving 1 application.					

Discussion

The outcomes of this study demonstrated the potential benefits of using umbilical cord tissue allografts for cartilage supplementation in patients with treatment-resistant chondromalacia of the shoulder. Patients were divided into three groups by the number of applications. Patients in all dosage groups averaged lower NPRS and WOMAC scores and higher QOLS scores at the final visit compared to the initial visit, indicating a positive trend of improvement in all scales. All statistical analyses were nonparametric due to the skewed distribution of the data, with Bonferroni adjustments made in the Wilcoxon Signed-Rank test (WSRT) and the Mann-Whitney U test to reduce Type I error (Tables 3 & 4). In the analysis of the single application group, significant differences were found between initial and 30-day scores and initial and 90-day scores. The evaluation of the statistical significance indicates that considerable improvement occurred within the first month of application, with maintained improvement past the 30-day mark. In the double application group, significant improvements were observed from the initial to 30-day visit, the initial to 90-day visit, and the initial to the endpoint visit in all scales except QOLS. The triple application group observed significance in all scales by the endpoint visit, but did not achieve significance in the WOMAC pain subscale or QOLS from the initial to the 30 or 90-day visit. Falling short at the 30 and 90 day visits in those two scales may reflect the need for additional applications that the patients required in the triple application group. All significant results across each group had a large effect size with $r > 0.50$. The consistent response patterns across all application cohorts suggest a potential relationship between UCTa applications and patient outcomes.

The Mann-Whitney U test was used to determine any dose relationship present in the cohort. Between the initial and double groups, the NPRS baseline scores were higher in the single application group, with no difference in final scores, which means greater improvement overall in the single application group is expected due to higher initial scores and greater room for improvement. Between the double and triple application groups, the double group had lower baseline NPRS and WOMAC stiffness scores, but the triple group achieved greater improvement in NPRS overall. No significance was found in any scale between the single and triple application groups. The sample size for NPRS fluctuated at each time point due to missing data, which therefore weakens any results based on NPRS alone. Because no significance was found in the initial, final, or overall change from initial to final in the WOMAC scales, no conclusion about increased dosage benefit can be made; it does suggest that, because the baseline was equivalent, patients who received additional applications may have required a greater dosage to achieve the same results as the single application group. In other cohorts or use sites published from this repository, there has been evidence of greater improvement relating to additional applications; however, the small sample size and non-specific scale may have skewed any relationship observable in this cohort [23]. Future studies with larger sample sizes are warranted to determine dose-related outcome results. The regression analysis also confirms baseline score and severity-dependent dosing while evaluating potential confounding by age, BMI, sex, and baseline severity. Baseline severity was the only consistent significant predictor across all six outcome models (all p ≤ .0002), with negative coefficients throughout (B = − 0.342 to − 0.745), indicating that it acts as a facilitating rather than confounding variable; patients who started worse improved more, which is compatible with structural supplementation dosage proportional to the degree of cartilage loss (Table 5). Age and BMI were non-significant in all multivariate models, indicating that these demographic factors did not meaningfully influence the response within the observed range. Age, gender, and dosage group were non-significant in all models (all p > .07), confirming that none of these variables independently predicted outcomes after adjustment for baseline severity. The gender finding warrants measured interpretation: while univariate analyses suggested females tended toward greater NPRS improvement, this did not survive Bonferroni correction within dosage groups, and the gender coefficient was non-significant in all regression models after controlling for baseline severity. This pattern suggests the apparent sex effect observed overall may partly reflect differences in baseline symptom burden between male and female patients rather than an independent biological sex effect on allograft response. Current literature identifies a range of biological and psychosocial factors

that may contribute to higher pain reporting in females. Biologically, studies have shown that hormonal fluctuations, particularly in estrogen and progesterone, may heighten sensitivity to pain in women [24, 25]. Psychosocial contributors include cultural expectations in gender and the expression of pain, biases in clinical care, and established sex differences in pain thresholds and coping mechanisms [25, 26]. These findings make it difficult to demonstrate clear sex-based differences, and future studies are encouraged to focus on sex-related reporting differences when evaluating UCTa applications.

Despite the statistically significant results from this study, several limitations must be considered when interpreting the results. Nonparametric testing was employed to address the distributional characteristics of the data, which ensured appropriate handling of skewness and outliers. However, compared to parametric alternatives, these methods typically provide less statistical power and more limited options for incorporating covariates. In addition to the limited statistical power of testing, the observational nature of the study inherently has the risk of selection bias, as each provider determined the eligibility of patients and the appropriate number of applications, and recall bias, as the data reported were exclusively patient-reported outcome measures without any objective imaging assessments. The WOMAC scale was used to cover a wide range of homologous use sites submitted to the repository. Still, the American Shoulder and Elbow Surgeons (ASES), Constant-Murley Score (CMS), Shoulder Pain and Disability Index (SPADI), or Western Ontario Osteoarthritis of the Shoulder (WOOS) would be more specific to evaluate shoulder function regarding cartilage degeneration. Reliance on self-reported scales limited the ability to capture functional or structural improvements with UCTa fully. Additionally, the absence of a comparison group receiving standard conservative care alone reduced the capacity to evaluate the relative effectiveness of UCT, despite all patients failing the standard of care for at least three months. The use of a single commercial UCTa product while ensuring homogeneity of the allograft limits comparison to other similar products. The preliminary findings from this study provide a foundational hypothesis for UCTas in chondromalacia, encouraging future prospective studies to incorporate imaging assessments and comparative analysis with other conservative interventions. Such studies would validate the efficacy, clarify optimal dosage protocols, and allow the use of parametric models for more robust statistical evaluation.

The findings from this study provide evidence for the functional relevance of umbilical cord tissue in chondromalacia of the shoulder. The structural framework of umbilical cord tissue, which consists of high concentrations of collagen types I, II, III, and V, offers protection from tensile stress and cushioning in the umbilical cord [14, 15]. Current literature shows in vitro and in vivo studies of UCTa as a successful scaffold replacement for intra-articular cartilage [20, 27–29]. Connective tissues in the glenohumeral joint assist in stabilization and cushioning to support the joint and adjacent tendons. The structural profile of the cartilage in the glenohumeral joint consists of high concentrations of collagen type II, with other extracellular matrix components, supporting the structural integrity of the joint [30]. The glenoid labrum functions as a passive stabilizing component of the glenohumeral joint, providing attachment for ligaments and acting as a shock absorber to evenly distribute forces across the surfaces of the joint [31, 32]. The structural framework of the glenoid labrum predominantly consists of fibrocartilage, bundled type II collagen fibers with a deeper collagen core [31, 32, 33]. Chondromalacia leads to the disruption of the collagen matrix, which can be replaced with a healthy collagen matrix from UCT.

The results from applying UCTa to patients with treatment-resistant chondromalacia of the shoulder offer guidance for practicing physicians seeking alternative conservative options prior to surgery when conventional care proves ineffective. Routine surgical methods for glenohumeral joint defects, including procedures like palliative, reparative, restorative, or reconstructive surgeries, have not been confirmed as the preferred practice due to complications and risks [34, 35]. Platelet-rich plasma is another widely used regenerative therapy for many intra-articular applications that can outperform the short-term benefits of corticosteroids [36]. Yet randomized control trials present minimal patient outcomes using PRP compared with other cheaper alternatives, such as HA, in part due to its autologous nature, making the final product dependent on patient health [37]. Visco supplementation with hyaluronic acid (HA therapy) has been recommended for cartilage defects in the glenohumeral joint but is often associated with limited efficacy over time [38, 39, 40]. This is further realized by evidence that suggests that the use of isolated materials diminishes therapeutic responses [41, 42]. Umbilical cord tissue, as indicated by this research and other literature, is a better alternative due to its complete tissue structure, consisting of various ECM components, including hyaluronic acid (HA) [14]. A previous study from the same observational repository used in this paper reported similar efficacy of UCTa applications in patients with rotator cuff defects unresponsive to current standard-of-care protocols [43]. Patients reported statistically significant improvements in pain, stiffness, and functionality [43]. The findings from both studies suggest clinical benefits of UCTa in homologous shoulder applications, demonstrating its capacity to supplement various connective tissues in the human body. The favorable effects of UCTa applications in patients with chondromalacia of the shoulder in this observational study provide a reference in evaluating alternative methods to

standard-of-care protocols. Future studies are warranted to validate best practice dosage and application protocols for clinical use of UCTa in chondromalacia of the shoulder.

Conclusions

The cohort of 115 patients in this observational research reported that after the application of umbilical cord tissue allografts, they experienced decreased pain and stiffness and increased functionality, leading to improvements in a patient's quality of life. No adverse events or side effects were reported in the patient group. The results from this investigation are encouraging, but definitive evidence is prevented by its limitations. The current body of literature showcases a rising interest in alternative medicine, primarily due to the complications and side effects associated with surgical practices and the lack of conservative care options. Future randomized and controlled studies are vital in redefining standardized care and incorporating umbilical cord tissue as a primary option for chondromalacia of the shoulder.

Abbreviations

UCTa - Umbilical Cord Tissue allograft

NPRS - Numeric Pain Rating Scale

WOMAC - Western Ontario and McMaster University Arthritis Index

QOLS - Quality of Life Scale

WSRT - Wilcoxon Signed Rank Test

GH - Glenohumoral

NSAID - Nonsteroidal Anti-Inflammatory Drug

OA - Osteoarthritis

HA - Hyaluronic Acid

PRP - Platelet-rich plasma

CMS - Centers for Medicare & Medicaid Services

Declarations

Ethical Review Committee Statement: This data was collected in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (approval number IRCM-2022-311; Approval date: 12 January 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability: The datasets generated and/or analyzed during the current study are not publicly available due to private ownership under Regenerative Labs, but are available from the corresponding author on reasonable request.

Conflicts of Interest: Naomi Lambert, Alexis Lee, and Tyler Barrett are employees at Regenerative Labs. Regenerative Labs was involved in the design of the study, data analysis, and writing. Regenerative Labs influenced the decision to publish.

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Author Contribution: Conceptualization, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., and T.B.; methodology, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., and T.B.; software, T.B.; validation, N.L., A.L., T.B.; formal analysis, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., A.L., and T.B.; investigation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., and R.D.; resources, N.L. and A.L.; data curation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., R.D., N.L., A.L., and T.B.; writing—original draft preparation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., R.D., N.L., A.L.,

and T.B.; writing—review and editing, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., A.L., and T.B.; visualization, N.L. and A.L.; supervision, N.L. and T.B.; project administration, R.D. and T.B.; funding acquisition, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., and T.B. All authors have read and agreed to the published version of the manuscript.

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Figures

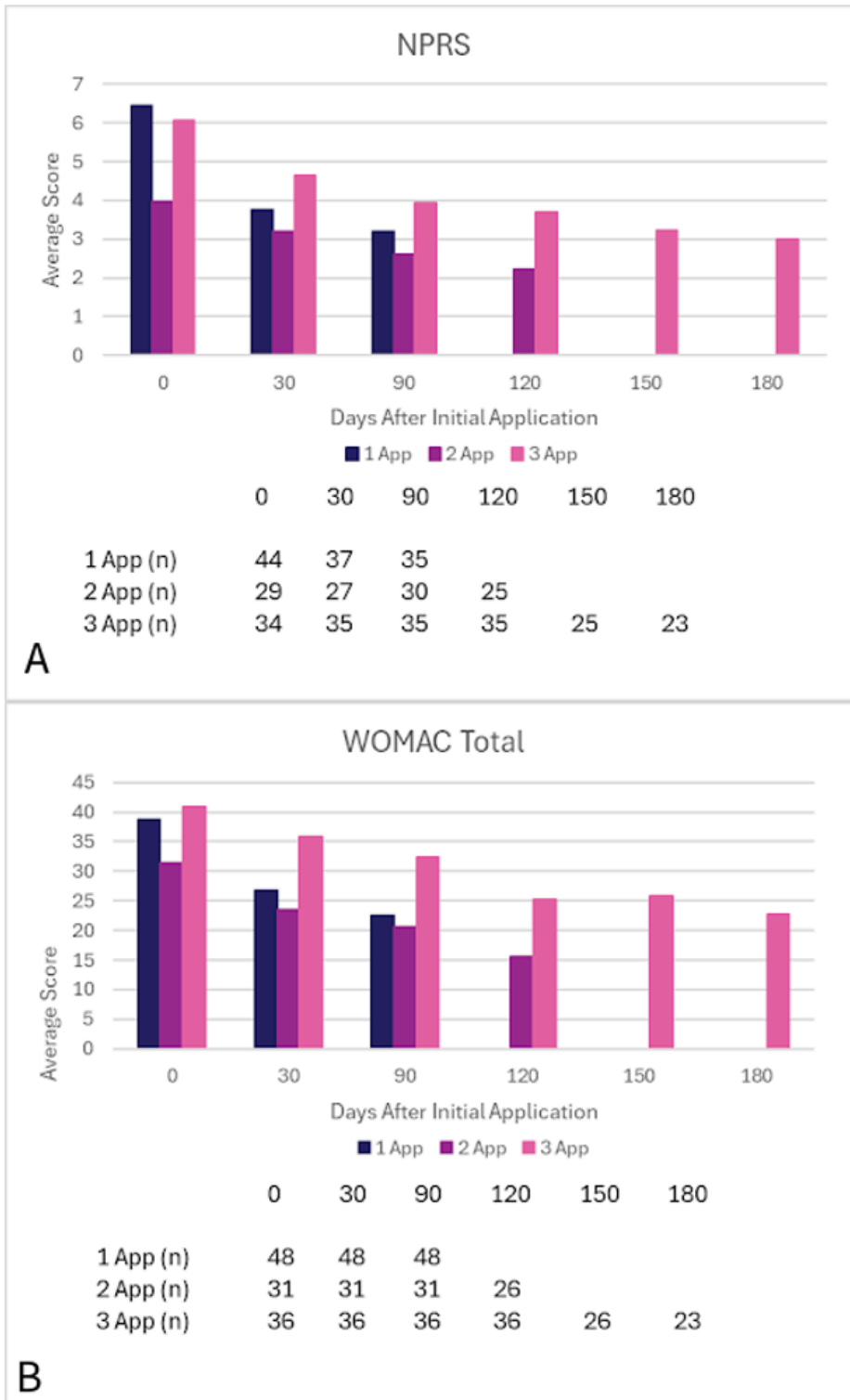


Figure 1

Average scores across time in the three main scales are compared among each application group. **A:** NPRS, **B:** WOMAC Total, **C:** QOLS

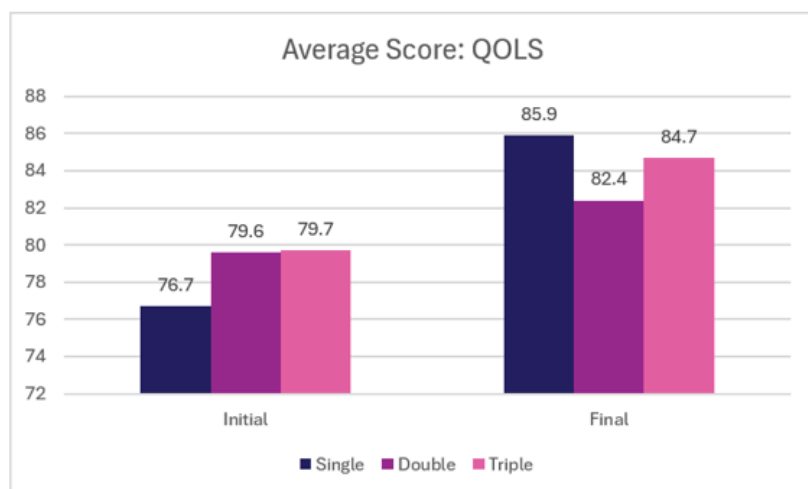
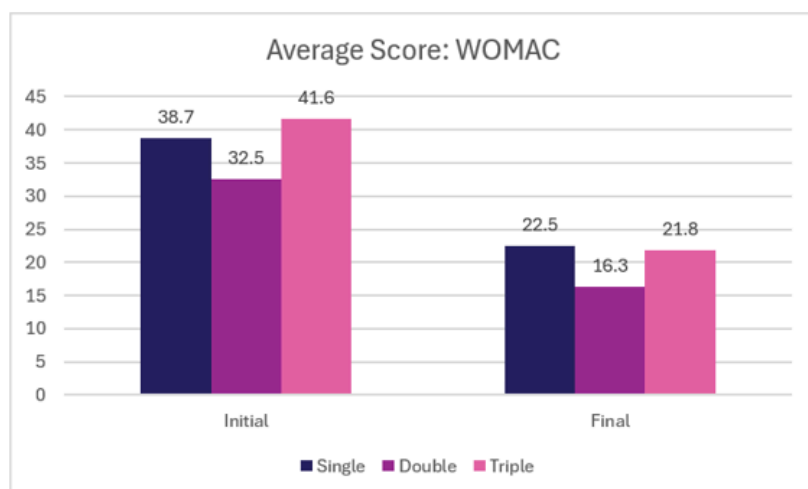
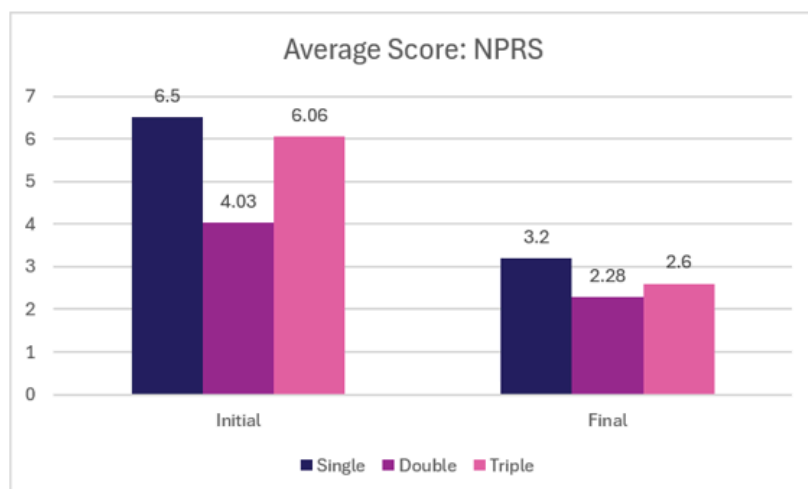


Figure 2

The average scores in each group in each scale at the initial visit and from the last available visit, the end date varied in multi-application groups. NPRS: single group n = 44, double group n = 29, tripple group n = 33. WOMAC & QOLS: single group n = 48, double group n = 31, tripple group n = 35.

Supplementary Files

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- [AppendixA.docx](#)