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Human Umbilical Cord Tissue Allografts for Cervical Paraspinal Muscle and Entheses

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Abstract

Introduction: Cervical paraspinal enthesopathy is characterized by fatty infiltration and muscle degeneration; current methods only provide symptomatic relief or involve significant postoperative complications. This study provides preliminary results for the clinical potential of umbilical cord tissue allografts (UCTa) in patients with cervical paraspinal enthesopathy and degeneration refractory to standard care. **Materials and Methods:** The Numeric Pain Rating Scale, Western Ontario and McMaster University Arthritis Index, and Quality of Life Scale were used to measure outcomes of thirty-one patients with cervical paraspinal degeneration from an observational repository who received one to three UCT allograft applications. The Wilcoxon Signed-Rank test, Mann-Whitney U test, and Jonckheere-Terpstra test were performed for the analysis. **Results:** Substantial percentage improvements were observed from the patient cohort, with the triple application group reporting the highest percentage improvement. Statistically significant differences were presented in all application groups. No adverse events were reported. **Discussion:** This study provided preliminary findings that UCTas are a safe, minimally invasive application for cervical paraspinal defects. Notable limitations included a lack of a direct comparison group and a small sample size. **Conclusion:** This study highlights the need for continued research to validate the preliminary results for the safety, feasibility, and efficacy of umbilical cord tissue allografts in patients with cervical paraspinal defects.

Keywords: cervical paraspinal muscles; cervical enthesopathy; fatty infiltration; cervical paraspinal degeneration; umbilical cord tissue; umbilical cord tissue allografts; regenerative medicine

1. Introduction

Although neck pain is one of the most common musculoskeletal disorders, its prevalence and impact are often overshadowed by low back pain, which tends to receive more attention in clinical practice and scientific literature due to its higher perceived burden (Kazeminasab, 2022). Across the globe, neck pain is the fourth highest cause of disability and is ranked twenty-first in the total burden of pain (Kim, 2018). The prevalence of neck pain is projected to increase, reflecting broader trends in musculoskeletal health (GBD Collaborators 2021, 2024). Neck pain is widely recognized as a multifactorial disorder, with contributing factors that may include genetic predisposition, various pathological mechanisms, and traumatic injury (Kazeminasab, 2022). In addition, several risk factors such as the female gender, increased age, and work-related factors contribute to neck pain (Kazeminasab, 2022). A systematic review conducted by Kim et al. (2018) found that psychosocial factors such as depressed mood, high perceived muscular tension, and perceived role conflict also play a large part in patients with neck pain (Kim, 2018). Although these factors can contribute to neck pain, most neck pain conditions are associated with neuromusculoskeletal degeneration.

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The paraspinal muscles and entheses surrounding the cervical spine play an important role in assisting with the curvature, stability, and overall function of the spine (Hou, 2019). Changes in paraspinal muscle morphology of the cervical spine are associated with muscle degeneration, which is indicated by fatty infiltration (Liao, 2024; Tamai, 2019; De Pauw, 2016). The accumulation of adipocytes within non-adipose tissues results in fatty infiltration and often impairs normal function (Zhu, 2024). Muscle degeneration associated with high amounts of fat buildup has been implicated in the development of chronic neck pain and progressive spinal degeneration, disrupting normal sagittal balance over time (Tamai, 2019; He, 2023). MRI assessment of paraspinal muscle degeneration showcases multiple paraspinal muscles, including the multifidus, semispinal cervicis, and spinalis cervicis, with decreased muscle mass and increased adipose tissue, appearing as high signal intensity (Liao, 2024; Huber, 2020). Ultrasound imaging demonstrates increased echogenicity in muscles affected by fatty infiltration, causing them to appear brighter than normal muscle tissue (Toto-Brocchi, 2024). Although the degeneration of paraspinal muscles is a significant factor in neck pain, other connective tissues can also contribute. Similar to paraspinal muscles, the entheses, which are attachment sites for tendons and ligaments, allow for stability, ensuring the reduction of mechanical stress in the upper vertebral column (Sudoł-Szopińska, 2015). Enthesopathy denotes a pathological process at these sites that may manifest as pain, swelling, or tissue degeneration, and can serve as a primary contributor to neck pain (Sudoł-Szopińska, 2015). Ligamentous degeneration may result from repetitive microtearing at sites of strain, leading to progressive stiffening due to the replacement of elastic fibers with less flexible collagenous tissue (Kumar Varma Kalidindi, 2022). In response to such injuries, the body prioritizes structural stability over mobility to safeguard adjacent neurovascular elements (Hauser, 2024). While such a mechanism enhances protection of the cervical structure, it compromises normal biomechanical function. The loss of ligamentous elasticity can contribute to chronic neck pain, reducing the range of motion and impairing functional activities (Hauser, 2024). Understanding the mechanism behind cervical tissue degeneration is crucial in the management of dysfunction to prevent long-term structural compromise and functional decline. Non-invasive and invasive strategies for neck pain, specifically for paraspinal muscle degeneration and cervical enthesopathy, are selected based on clinical assessment and imaging findings to optimize patient outcomes.

To determine the best course of action for patients with cervical paraspinal muscle degeneration, practicing physicians usually consider the cross-sectional area (CSA) and fatty infiltration (FI) in the paraspinal muscles. A visual imaging assessment, by MRI, CT, or ultrasound of the CSA of paraspinal muscles, allows physicians to determine the content of lean muscle fibers (Suo, 2023). Three FI assessments (visual qualitative assessment, semiquantitative assessment, and quantitative assessment) can be used to indicate the severity of the atrophic muscles (Suo, 2023). Additionally, prospective assessments such as ultrasound imaging of muscle thickness and dual-energy X-ray absorptiometry have been used to determine the severity of paraspinal muscle degeneration (Suo, 2023). Based on the severity assessment of paraspinal muscle degeneration, various conservative measures have been utilized in response to approaching paraspinal-affected neck pain. Conservative methods include physical therapy, cervical braces, NSAIDs, activity modification, breathing exercises, and steroid injections (Lauweryns, 2009; Pillastrini, 2019; Cefali, 2025). These non-invasive options are often associated with temporary pain alleviation, and they do not address the root cause of neck pain. Invasive procedures are not common for patients' with cervical myofascial pain, and when surgery does arise, it is often associated with complicated spine wounds and injuries (Adapa, 2018). Due to the limited options in cervical paraspinal management, the necessity for an alternative conservative option that goes beyond symptomatic relief and instead targets root pathology is critical in current literature.

An emerging alternative to current conservative intervention is umbilical cord tissue (UCT) allograft supplementation. This human umbilical cord-derived connective tissue consists of a structural matrix rich in collagen types I, II, III, IV, V, VI, XII, and XIV, as well as other ECM components, including proteoglycans, glycosaminoglycans, fibronectin, fibrillin, and hyaluronic acid

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(Roy, 2022). Despite the limited research on UCT, recent studies have demonstrated its clinical relevance for musculoskeletal disorders (Main, 2021; Roy, 2022). UCT supplementation has been utilized in over 180 homologous use sites, underscoring its clinical potential as an alternative intervention. A 2024 study demonstrated the clinical potential of UCTa when applied to rotator cuff defects, reporting significant pain alleviation, reduced stiffness, increased functionality, and improved range of motion (Lai 2024-rotator cuff). Another study conducted with this repository showed the effectiveness of UCTa in replacing cartilage in patients with treatment-resistant hip osteoarthritis, reporting significant reductions in pain and stiffness, leading to a better overall quality of life (Lai 2024-hip). Research has yet to be published on the outcomes of UCTa applications to degenerated connective tissues in treatment-resistant paraspinal-related neck pain. With the growing interest in expanding current standard-of-care protocols, the need for safe and effective alternative methods with positive outcomes is essential. This observational research study aims to report the safety and efficacy of umbilical cord tissue for the supplementation of cervical paraspinal muscle and entheses degeneration.

2. Materials and Methods

2.1. Study Design

This study utilized data from the Regenative Labs observational repository, which has been maintained in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2022-311) since January 2022. The design of the repository and the protocols for UCTa processing have been described in detail in other studies derived from the database (Davis, 2022; Lai, 2024). Informed consent was collected from all patients in this study. Observer bias was minimized by having multiple observers at multiple clinic sites across the country. Patients were included in this analysis if they received UCTa applications for cervical paraspinal defects and had complete initial and follow-up data. Patients were excluded if they were lost to follow-up, had data outside the respective time range (± 15 days for 30-day follow-up, ± 30 days for 90-day and 120-day follow-ups), had multifaceted defects, or received more than three applications. No exclusions were made based on gender, body mass index (BMI), or age. A total of thirty-one patients met the criteria, and final group sizes by dosage for patients with one, two, and three applications are fifteen, nine, and seven, respectively. Figure 1 displays a flow chart of this study's design.

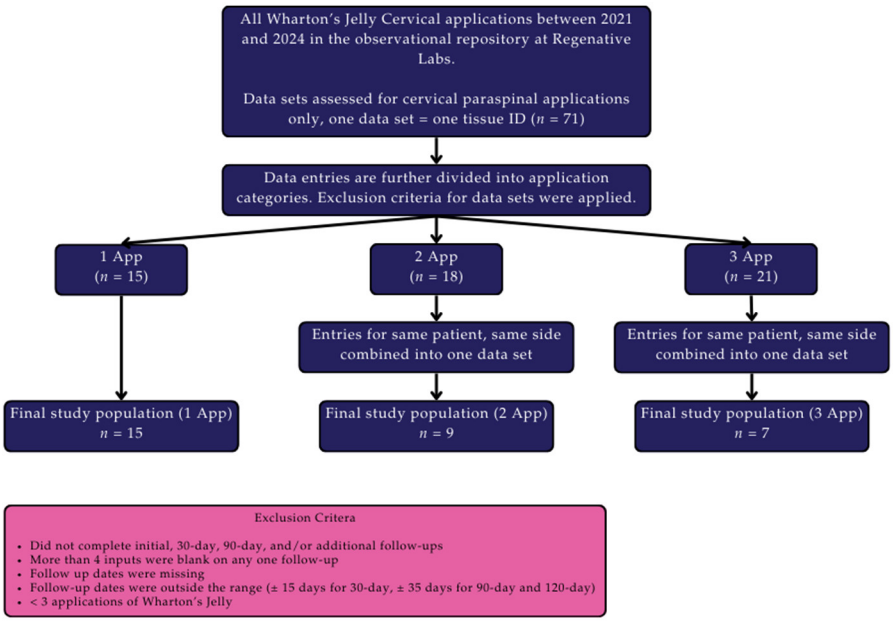

Figure 1. Flow chart of the study's design.

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2.2. Study Population

The participants in this study included 31 patients, 42% male, 55% female, and 3% unreported. Based on the severity of the defect as determined through imaging and by the physician's discretion, five males and ten females received one application, four males and four females received two applications, and four males and three females received three applications. A total of 15 patients were in the single application group, and all patients reported their final scores at the 90-day mark. In the multi-application groups, final patient score dates varied depending on when they received their final application. For data sets with multiple applications, completion of the observation period was established by one last score sheet at 30 days following their final UCTa application. In the double application group, the reapplication took place at either the 30- or 90-day visits, in the triple application group all reapplications were completed by the 120-day visit. Eight out of nine patients in the double application group reported final scores at the 120-day mark, and one reported at the 90-day mark. Two out of seven patients in the triple application group reported completion at the 120-day mark, two reported final scores at the 150-day mark, and three reported completion at the 180-day mark. All participants presented with neck pain and underwent imaging assessment at their initial consultation. MRI and ultrasound imaging were used to determine the specific location, the severity of fatty infiltration, and associated muscle degeneration in the cervical paraspinal region. Prior to umbilical cord tissue allograft application, all patients completed a minimum of three months of conservative care, including steroid injections, topical and oral medications, physical therapy, home exercise, and activity modification with failure to improve. The study cohort opted to receive umbilical cord allografts to avoid more invasive intervention.

2.3. Patient Procedures

All procedures were performed under sterile conditions with ultrasound guidance. Patients were instructed to avoid anti-inflammatory drugs (NSAIDs) and all corticosteroids for at least two weeks prior to application, and to avoid intra-articular corticosteroid injections within 90 days prior to the procedure. A procedure pause was conducted to verify correct patient identity, the procedure to be performed, the proper side and site, the correct patient position, the availability of implants, and the need for special equipment or special requirements. After verification, a sterile technique was used to prepare the application site. Physicians at each site maintained their individual preference on the choice of anesthetics such as a topical coolant anesthetic, local anesthetics, or no anesthetic. Using a 25-gauge 1.5-inch needle, 2 cc of 150 mg of UCTa (Regenative Labs, Pensacola, FL, USA) was applied into the targeted degeneration sites on the cervical paraspinal muscles and entheses, identified with ultrasound. Following application of the allograft, the area was gently mobilized through its full range of motion, and a sterile dressing was applied. All patients were advised to use ice or heat as needed for discomfort and to avoid strenuous activity for the first few days.

2.4. Data Analysis

Three patient-reported scales, NPRS, WOMAC total and subscales (Pain, Stiffness, and Physical Function), and QOLS were utilized to report scores at initial and follow-up visits. Descriptive statistics (mean, minimum, maximum, standard deviation, skewness, and kurtosis) were calculated for all scales across all time intervals for each dosage group. Due to the skewness of the data, nonparametric testing was conducted on the data. The Wilcoxon Signed-Rank test (WSRT) was performed on the three dosage groups to evaluate the statistical differences between the initial to 30-day, to 90-day, and the initial to final visit. The Mann-Whitney test was used to determine where the statistical significance is found between the dosage groups. The correlation coefficient, r, was added to the WSRT and Mann-Whitney to indicate effect size.

An outcome range analysis was performed to characterize the distribution of clinical responses across the three application groups. Only the WOMAC scale and subscales (Pain, Stiffness, and

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Physical Function) were evaluated due to limited missing data. For each scale within each application group, the following indices were calculated:

1. Mean Change, representing the mean difference between the initial and final visit scores;
2. Best Response, defined as the greatest improvement observed;
3. Worst Response, defined as the least favorable change;
4. Outcome Range, calculated as the difference between the best and worst responses.

Clinical improvement is consistently indicated by values that are lower and more negative. Given the non-normal distribution of the data, this analysis was descriptive and aimed at summarizing the variability of responses as application frequency increased.

The Jonckheere-Terpstra (J-T) test was applied to assess ordered trends across categorical groups. This nonparametric test was selected as an alternative to post hoc ANOVA pairwise comparisons since the data did not meet normality assumptions. Age categories (30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and 90-99) and BMI categories (Underweight, Normal weight, Overweight, and Obese) were compared against differences in scores (initial-final) for NPRS (DNPRS), pain (DP), stiffness (DS), physical function (DPF), and quality of life (DQ). Negative differences in scores indicated greater improvement in five scales (DNPRS, DP, DS, DPF, and DW), whereas positive values reflected worsening of symptoms. Only positive differences in DQ were considered as greater improvement. A Bonferroni correction was applied to control for Type I error within each outcome, specifically within each set of three comparisons (where the adjusted $\alpha = 0.05/3 = 0.017$) for all tests used. Significant values are bolded in the tables below. This study performed no imputation, and all data sets analysed were complete. Data sets excluded from this study included those lost to follow-up or missing more than four data points on any given sheet. Statistical tests were two-tailed, with a significance threshold of $p < 0.05$ before correction using the Bonferroni method. Statistical analyses were performed using SPSS Statistics (Version 31, IBM Corp, Armonk, New York).

3. Results

The patient cohort of 31 participants was divided into three different application groups based on dosage frequency. Table 1 summarizes patient characteristics. The mean ages for the single, double, and triple application groups were 63.6, 73.75, and 75 years, respectively. The average BMI in this study was 25.32, 27.02, and 30.4 for single, double, and triple applications, respectively. The majority of patients in the single-application groups were female, while the multi-application groups were evenly split between the sexes. Only one patient's sex remained unrecorded.

Table 1. Patient age, BMI, and gender by application amount and their mean age and BMI for each application category.

Age in range	**1 app**	**2 app**	**3 app**	**total**	**BMI in range**	**1 app**	**2 app**	**3 app**	**total**
20-29	0	0	0	0	Underweight (<18.5)	0	0	0	0
30-39	0	0	0	0	Healthy weight (18.5-24.9)	4	2	0	6
40-49	0	0	0	0	Overweight (25.0-29.9)	1	3	1	5
50-59	0	0	0	0	Obese (>30.0)	1	1	2	4
60-69	3	1	2	6	NA	9	3	4	16
70-79	11	6	3	20	Mean BMI	25.32	27.02	30.4	
80-89	1	1	2	4	**Gender**	**1 app**	**2 app**	**3 app**	**total**
90-99	0	0	0	0	Male	5	4	4	13
NA	0	1	0	1	Female	10	4	3	17
Mean Age	73.6	73.75	75		NA	0	1	0	1

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A reduction in NPRS and WOMAC scores represents improvement, while an increase in QOLS scores represents improvement. In the single application group, five out of ten patients reported improvement in NPRS scores, thirteen out of fifteen reported improvement in total WOMAC scores, and ten out of fifteen reported improvement in QOLS scores. Five out of eight patients who reported NPRS scores indicated improvement, seven out of nine reported improvement in total WOMAC scores, and six reported improvement in QOLS scores. The triple application group recorded that all six patients who reported NPRS scores experienced improvement, five out of seven reported improvement in QOLS scores, and all seven reported improvement in total WOMAC scores. Table 2 presents the average percentage improvement in all application groups from initial to the last reported data set for each application category. Multi-application group scores will fluctuate from visit to visit in all scales due to rises in pain that indicate the need for additional applications at the physician's discretion; however, despite the variations at intermediate follow-ups, reductions in overall score differences are observed from the initial visit to the final follow-up. A visual representation of the average scores from the initial to final visit in all dosage groups is displayed in Figure 2.

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

Scale	1 app	2 app	3 app
NPRS	20.67%	58.33%	79.59%
WOMAC Total	42.62%	37.93%	68.70%
Pain	46.03%	21.15%	74.03%
Stiffness	36.67%	56.82%	62.86%
Functionality	42.44%	38.12%	67.87%
QOLS	13.46%	11.99%	21.37%

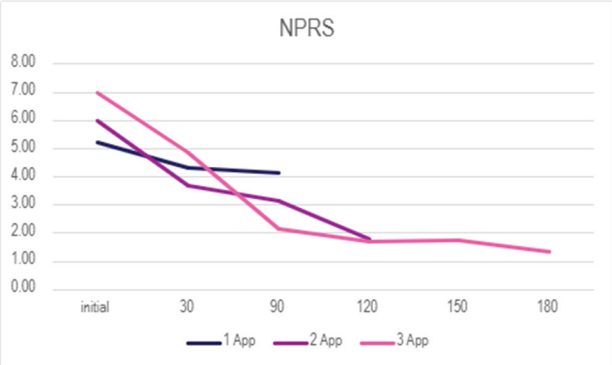

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Figure 2. Average score improvement of all application groups in all scales from initial to last possible visit.

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The WSRT analyzed outcomes between initial and follow-up visits (initial to 30-day, initial to 90-day, and initial to final visit) for within-group changes over their respective timelines (Table 3). Positive trends of improvement are evident through the statistically significant values identified across multiple scales in each application group. Strong significant differences were seen across the single application group in all comparisons and in all six patient-reported measures. Double application participants reflected similar outcomes to the single application group; however, no significant differences were found in the QOLS. In the triple application group, significant differences were found in multiple scales, and the most prominent differences were found when comparing the initial visit to the final visit, reporting $p < 0.001$ in all six scales.

Table 3. Wilcoxon Signed-Rank Test Statistics in all application groups from initial to follow-up visits (Bonferroni adjustment $\alpha = 0.05/3 = 0.017$).

Test Statistics[a]						
Dosage		NPRS2 - NPRS1	P2 - P1	S2 - S1	PF2 - PF1	W2 - W1
Single Application	Z	-4.846[b]	-3.032[b]	-4.105[b]	-3.651[b]	-3.960[b]
	Asymp. Sig. (2-tailed)	**<.001**	**.002**	**<.001**	**<.001**	**<.001**
Double Application	Z	-3.859[b]	-3.761[b]	-3.310[b]	-4.488[b]	-4.544[b]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**
Triple Application	Z	-3.504[b]	-2.369[b]	-2.599[b]	-2.489[b]	-2.715[b]
	Asymp. Sig. (2-tailed)	**<.001**	.018	**.009**	**.013**	**.007**
Dosage		Q2 - Q1	NPRS3 - NPRS1	P3 - P1	S3 - S1	PF3 - PF1
Single Application	Z	-3.443[c]	-4.873[b]	-3.886[b]	-4.226[b]	-4.049[b]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**
Double Application	Z	-2.233[c]	-2.694[b]	-3.715[b]	-3.203[b]	-3.988[b]
	Asymp. Sig. (2-tailed)	.026	**.007**	**<.001**	**.001**	**<.001**
Triple Application	Z	-1.416[c]	-3.911[b]	-1.956[b]	-3.384[b]	-2.942[b]
	Asymp. Sig. (2-tailed)	.157	**<.001**	.050	**<.001**	**.003**
Dosage		W3 - W1	Q3 - Q1	FNPRS - NPRS1	FP - P1	FS - S1
Single Application	Z	-4.218[b]	-3.565[c]	-4.873[b]	-3.886[b]	-4.226[b]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**
Double Application	Z	-3.981[b]	-1.208[c]	-3.429[b]	-4.294[b]	-4.179[b]
	Asymp. Sig. (2-tailed)	**<.001**	.227	**<.001**	**<.001**	**<.001**
Triple Application	Z	-3.070[b]	-1.446[c]	-4.591[b]	-4.325[b]	-4.668[b]
	Asymp. Sig. (2-tailed)	**.002**	.148	**<.001**	**<.001**	**<.001**
Dosage			FPF - PF1	FW - W1		FQ - Q1
Single Application	Z		-4.049[b]	-4.218[b]		-3.565[c]
	Asymp. Sig. (2-tailed)		**<.001**	**<.001**		**<.001**
Double Application	Z		-4.487[b]	-4.686[b]		-1.443[c]
	Asymp. Sig. (2-tailed)		**<.001**	**<.001**		.149
Triple Application	Z		-4.361[b]	-4.636[b]		-3.452[c]
	Asymp. Sig. (2-tailed)		**<.001**	**<.001**		**<.001**

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, 2: 30-Day Visit, 3: 90-Day Visit, 4: 120-Day Visit. a. Wilcoxon Signed Ranks Test; b. Based on positive ranks.; c. Based on negative ranks.; d. The sum of negative ranks equals the sum of positive ranks.

Coupled with the WSRT, the Mann-Whitney U test was used to analyze which specific dosage groups improved the most compared to the others. Prior to performing the Mann-Whitney test, a Kruskal-Wallis test was utilized to determine if significance was found across all dosage groups. Once

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significance was confirmed, the Mann-Whitney test was conducted to analyze specific significant differences between the dosage groups. The analysis of initial scores, final scores, and the difference between initial and final scores was conducted between single and double patients, single and triple patients, and double and triple patients (Tables 4–6). Data sets were completed with a 30-day follow-up after the last application in multi-application groups. This led to fluctuating final visit dates for patients, as the practicing physician determined the reapplication schedule. The last visit data was used for each patient, regardless of the timeline, to analyze the differences in final visit scores among all dosage groups for the Mann-Whitney. In the analysis between single and double application patients, no significant differences were identified. Comparisons between the single and triple application patients identified that triple application patients had significantly greater improvement of NPRS scores compared to single application patients, $U = 2.50$, $z = -2.92$, $p = 0.003$. When comparing double and triple application patients, triple application patients experienced significantly greater improvement in pain scores than double application patients, $U = 7.00$, $z = -2.61$, $p = 0.009$.

Table 4. Test Statistics for single vs double application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017).

Single vs Double Applications[a]							
	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	30.500	44.000	53.000	65.000	62.000	53.000	13.500
Wilcoxon W	85.500	89.000	173.000	110.000	107.000	98.000	34.500
Z	-.861	-1.412	-.884	-.149	-.329	-.866	-1.365
Asymp. Sig. (2-tailed)	.389	.158	.377	.881	.742	.386	.172
Exact Sig. [2*(1-tailed Sig.)]	.408[b]	.174[b]	.411[b]	.907[b]	.770[b]	.411[b]	.181[b]
	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	67.000	57.000	66.000	67.000	50.500	5.000	41.500
Wilcoxon W	112.000	102.000	111.000	112.000	95.500	20.000	161.500
Z	-.030	-.650	-.090	-.030	-1.016	-2.275	-1.556
Asymp. Sig. (2-tailed)	.976	.516	.929	.976	.310	.023	.120
Exact Sig. [2*(1-tailed Sig.)]	1.000[b]	.558[b]	.953[b]	1.000[b]	.318[b]	.030[b]	.123[b]
	DS		DPF		DW		DQ
Mann-Whitney U	46.500		61.000		59.000		60.500
Wilcoxon W	91.500		181.000		179.000		105.500
Z	-1.275		-.389		-.508		-.419
Asymp. Sig. (2-tailed)	.202		.697		.612		.675
Exact Sig. [2*(1-tailed Sig.)]	.215[b]		.726[b]		.640[b]		.682[b]

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final - Initial). a. Grouping Variable: Dosage; b. Not corrected for ties.

Table 5. Test Statistics for single vs triple application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017).

	Single vs Triple Applications[a]						
	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	15.500	36.000	34.000	30.500	30.000	50.000	8.500
Wilcoxon W	70.500	156.000	154.000	150.500	150.000	170.000	36.500
Z	-1.592	-1.172	-1.336	-1.556	-1.597	-.176	-2.275
Asymp. Sig. (2-tailed)	.111	.241	.181	.120	.110	.860	.023
Exact Sig. [2*(1-tailed Sig.)]	.118[b]	.267[b]	.210[b]	.123[b]	.123[b]	.891[b]	.021[b]
	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	38.500	42.500	39.000	38.500	52.000	2.500	21.500
Wilcoxon W	66.500	70.500	67.000	66.500	80.000	23.500	49.500

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Z	-1.009	-.725	-.954	-.989	-.035	-2.920	-2.195
Asymp. Sig. (2-tailed)	.313	.469	.340	.323	.972	**.003**	.028
Exact Sig. [2*(1-tailed Sig.)]	.332[b]	.490[b]	.368[b]	.332[b]	1.000[b]	.003[b]	.026[b]
r						**.78**	

	DS	DPF	DW	DQ
Mann-Whitney U	29.500	22.000	22.000	52.000
Wilcoxon W	57.500	50.000	50.000	80.000
Z	-1.663	-2.154	-2.153	-.035
Asymp. Sig. (2-tailed)	.096	.031	.031	.972
Exact Sig. [2*(1-tailed Sig.)]	.106[b]	.032[b]	.032[b]	1.000[b]

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final - Initial). a. Grouping Variable: Dosage.

Table 6. Test Statistics for double vs triple application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017).

	Double vs Triple Applications[a]						
	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	16.500	9.500	27.500	21.000	19.000	23.500	14.500
Wilcoxon W	52.500	54.500	72.500	66.000	64.000	68.500	42.500
Z	-.996	-2.337	-.431	-1.119	-1.326	-.848	-.954
Asymp. Sig. (2-tailed)	.319	.019	.666	.263	.185	.396	.340
Exact Sig. [2*(1-tailed Sig.)]	.345[b]	.016[b]	.681[b]	.299[b]	.210[b]	.408[b]	.366[b]
	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	26.000	31.000	27.500	28.000	23.000	5.000	7.000
Wilcoxon W	54.000	59.000	55.500	56.000	68.000	26.000	35.000
Z	-.592	-.054	-.425	-.372	-.901	-1.864	-2.605
Asymp. Sig. (2-tailed)	.554	.957	.671	.710	.368	.062	**.009**
Exact Sig. [2*(1-tailed Sig.)]	.606[b]	1.000[b]	.681[b]	.758[b]	.408[b]	.082[b]	.008[b]
r							**.65**

	DS	DPF	DW	DQ
Mann-Whitney U	26.500	12.000	10.000	25.500
Wilcoxon W	54.500	40.000	38.000	70.500
Z	-.535	-2.067	-2.276	-.639
Asymp. Sig. (2-tailed)	.593	.039	.023	.523
Exact Sig. [2*(1-tailed Sig.)]	.606[b]	.042[b]	.023[b]	.536[b]

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final - Initial). a. Grouping Variable: Dosage; b. Not corrected for ties.

Beyond the statistical testing performed both between and within dosage groups, the outcome range analysis provides a deeper understanding of application response in individuals (Tables 7-9, Figure 3). Participants receiving a single application demonstrated consistent improvements across all WOMAC scales. The mean change for the WOMAC total was −16.93, with responses ranging from −44 to 8 (outcome range: 52). Improvements were also observed for Pain (mean −3.87; outcome range: 13), Stiffness (mean −1.47; outcome range: 8), and Functionality (mean −11.6; outcome range: 35) (Table 7). In the double application group, patients also demonstrated overall improvement, though mean changes were slightly smaller in specific scales compared with the single application group. WOMAC Total improved by a mean of −13.44 (outcome range: 46). Mean changes for Pain, Stiffness, and Functionality were −1.22 (outcome range: 12), −2.78 (outcome range: 5), and −9.44 (outcome range: 32), respectively (Table 8). Triple application patients observed the greatest mean improvements in several scales. WOMAC Total showed a mean change of −35.43 (outcome range:

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44), indicating the most pronounced overall reduction across groups. Mean improvements for Pain, Stiffness, and Functionality were −8.14 (outcome range: 11), −3.14 (outcome range: 5), and −24.14 (outcome range: 31), respectively (Table 9).

Table 7. Outcome ranges for WOMAC outcome domains across the single application group.

Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome Range (Δ)
WOMAC Total	-44	8	-16.93	52
Pain	-10	3	-3.87	13
Stiffness	-5	3	-1.47	8
Functionality	-32	3	-11.6	35

Table 8. Outcome ranges for WOMAC outcome domains across the double application group.

Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome Range (Δ)
WOMAC Total	-37	9	-13.44	46
Pain	-6	6	-1.22	12
Stiffness	-6	-1	-2.78	5
Functionality	-25	7	-9.44	32

Table 9. Outcome ranges for WOMAC outcome domains across the triple application group.

Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome Range (Δ)
WOMAC Total	-51	-7	-35.43	44
Pain	-12	-1	-8.14	11
Stiffness	-5	0	-3.14	5
Functionality	-37	-6	24.14	31

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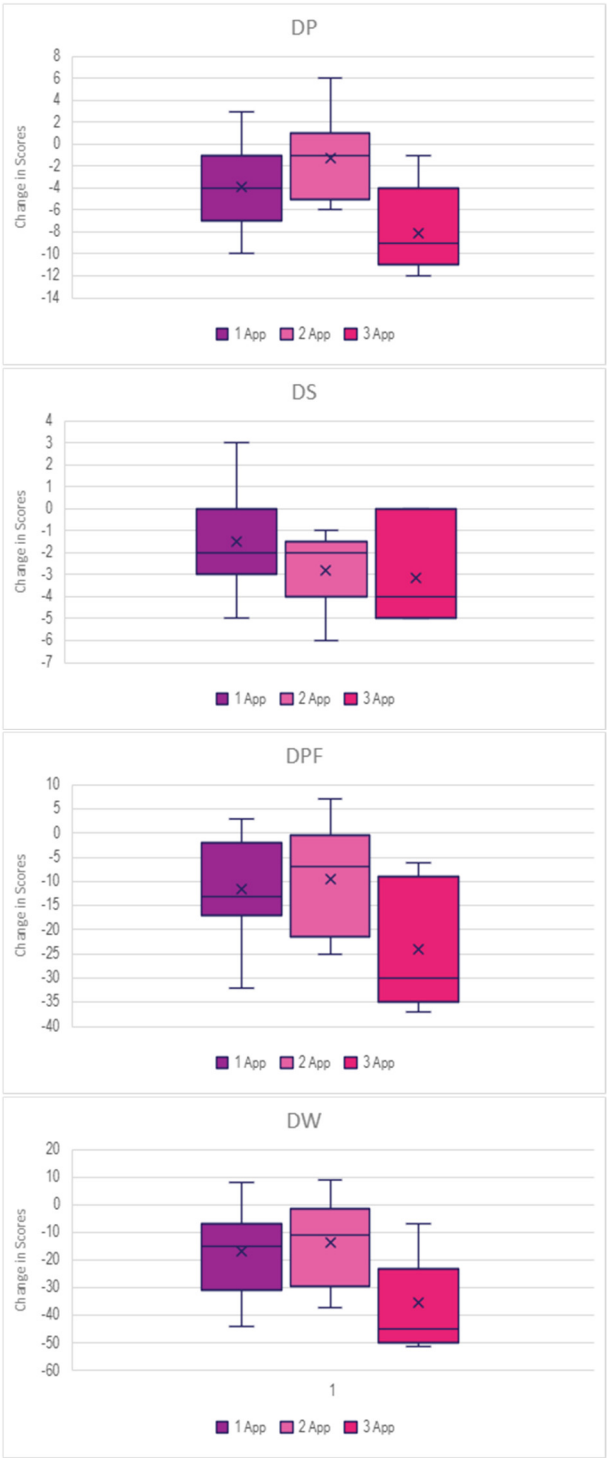

Figure 3. Distribution of Change Scores Across Application Frequencies (Boxplots depict change scores (final minus initial) for DP, DS, DPF, and DW across participants receiving 1, 2, or 3 applications.).

Jonckheere-Terpstra (J-T) analyses were conducted to assess whether there were ordered trends in overall change in scores in all measures across various factors (dosage, age category, and BMI category). Results indicated a statistically significant trend in overall change in NPRS scores, with additional applications related to greater improvement ($J\text{-}T$ = -3.578, p = 0.001), as shown in Table 10. The findings in Table 11 revealed a statistically significant pattern in the overall change of stiffness scores, indicating that older individuals experienced less improvement in stiffness (J-T = 2.691, p = 0.007). Due to the strong significance in the overall change in stiffness scores, another J-T test was conducted to analyze specifically where the significant trend appeared. Triple application patients reported a significant trend in overall stiffness scores, indicating that younger patients in this patient

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group experienced better outcomes than older patients (Table 12). A statistically significant trend in Table 13 was evident in the monotonic change of stiffness, physical function, and total WOMAC scores, indicating that an increased BMI was associated with greater improvement. The p-values indicated in the table were not strongly significant, and therefore, the J-T test was not performed. Figures 4–6 display line charts for the Jonckheere-Terpstra tests. A Mann-Whitney U test was performed to determine if any statistically significant differences were identified in the overall change in scores across all measures between patient sex. Because no statistically significant differences were found, the test was excluded from this study.

Table 10. Jonckheere-Terpstra test results examining ordered trends in overall score changes in all measures across dosage groups.

Jonckheere-Terpstra Test[a]	DNPRS	DP	DS	DPF	DW	DQ
Number of Levels in Dosage	3	3	3	3	3	3
N	19	31	31	31	31	31
Observed J-T Statistic	12.500	122.000	102.500	108.000	108.000	150.000
Mean J-T Statistic	59.000	151.500	151.500	151.500	151.500	151.500
Std. Deviation of J-T Statistic	12.995	26.914	26.611	26.940	26.981	26.875
Std. J-T Statistic	-3.578	-1.096	-1.841	-1.615	-1.612	-.056
Asymp. Sig. (2-tailed)	**<.001**	.273	.066	.106	.107	.955

a. Grouping Variable: Dosage

Table 11. Jonckheere-Terpstra test results examining ordered trends in overall score changes in all measures across age groups.

Jonckheere-Terpstra Test[a]	DNPRS	DP	DS	DPF	DW	DQ
Number of Levels in Age_Category	3	3	3	3	3	3
N	18	30	30	30	30	30
Observed J-T Statistic	40.000	137.500	173.500	121.500	131.500	155.000
Mean J-T Statistic	43.500	112.000	112.000	112.000	112.000	112.000
Std. Deviation of J-T Statistic	11.046	23.128	22.857	23.149	23.187	23.091
Std. J-T Statistic	-.317	1.103	2.691	.410	.841	1.862
Asymp. Sig. (2-tailed)	.751	.270	**.007**	.682	.400	.063

a. Grouping Variable: Age_Category

Table 12. Jonckheere-Terpstra test results examining ordered trends in overall score changes in all measures across age groups split by dosage groups.

Jonckheere-Terpstra Test[a]	Dosage	DNPRS	DP	DS	DPF	DW	DQ
Single Application	Number of Levels in Age_Category	3	3	3	3	3	3
	N	8	15	15	15	15	15
	Observed J-T Statistic	9.000	34.000	33.000	25.000	27.500	26.000
	Mean J-T Statistic	9.500	23.500	23.500	23.500	23.500	23.500
	Std. Deviation of J-T Statistic	3.062	7.697	7.454	7.712	7.719	7.705
	Std. J-T Statistic	-.163	1.364	1.274	.195	.518	.324
	Asymp. Sig. (2-tailed)	.870	.173	.203	.846	.604	.746
Double Application	Number of Levels in Age_Category	—	3	3	3	3	3
	N	—	8	8	8	8	8
	Observed J-T Statistic	—	7.500	9.000	7.500	7.000	13.000

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	Mean J-T Statistic	—	6.500	6.500	6.500	6.500	6.500
	Std. Deviation of J-T Statistic	—	3.003	2.984	3.022	3.041	3.022
	Std. J-T Statistic	—	.333	.838	.331	.164	2.151
	Asymp. Sig. (2-tailed)	—	.739	.402	.741	.869	.031
Triple Application	Number of Levels in Age_Category	3	3	3	3	3	3
	N	6	7	7	7	7	7
	Observed J-T Statistic	5.000	10.000	15.000	8.500	11.000	9.500
	Mean J-T Statistic	5.500	8.000	8.000	8.000	8.000	8.000
	Std. Deviation of J-T Statistic	2.242	3.047	2.957	3.078	3.109	3.047
	Std. J-T Statistic	-.223	.656	2.367	.162	.965	.492
	Asymp. Sig. (2-tailed)	.823	.512	**.018**	.871	.335	.623

a. Grouping Variable: Age_Category.

Table 13. Jonckheere-Terpstra test results examining ordered trends in overall score changes in all measures across BMI groups.

Jonckheere-Terpstra Test[a]	DNPRS	DP	DS	DPF	DW	DQ
Number of Levels in BMI_category	3	3	3	3	3	3
N	11	15	15	15	15	15
Observed J-T Statistic	11.000	22.000	18.000	18.500	18.000	40.500
Mean J-T Statistic	20.000	37.000	37.000	37.000	37.000	37.000
Std. Deviation of J-T Statistic	5.895	9.361	9.288	9.398	9.416	9.308
Std. J-T Statistic	-1.527	-1.602	-2.046	-1.969	-2.018	.376
Asymp. Sig. (2-tailed)	.127	.109	**.041**	**.049**	**.044**	.707

a. Grouping Variable: BMI_category.

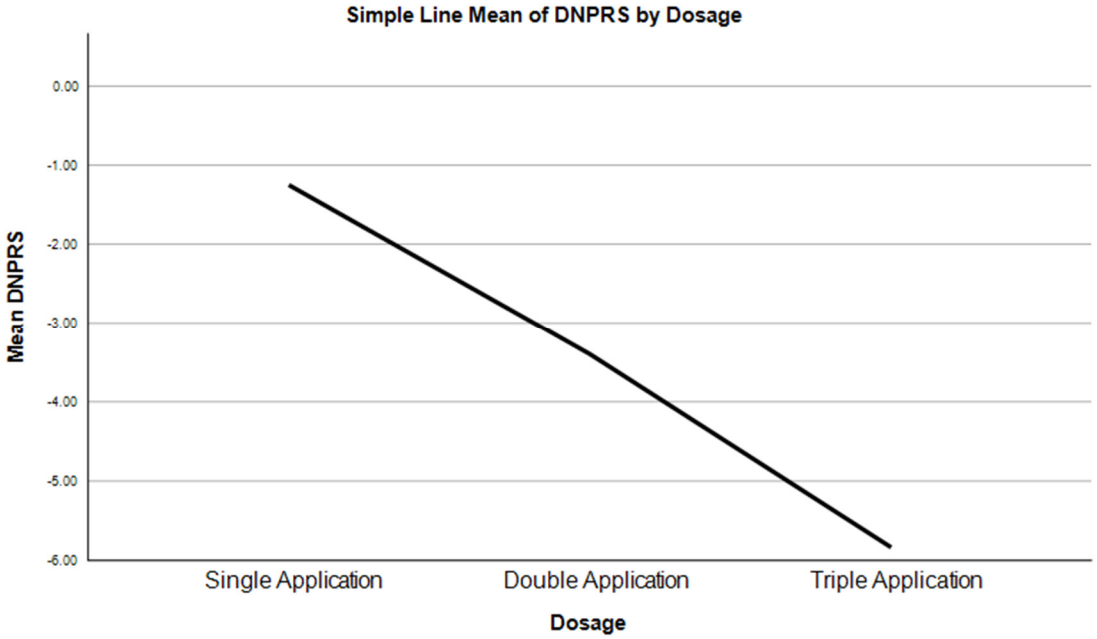

Figure 4. Line graph of overall change in NPRS scores (DNPRS) across dosage groups (1, 2, 3).

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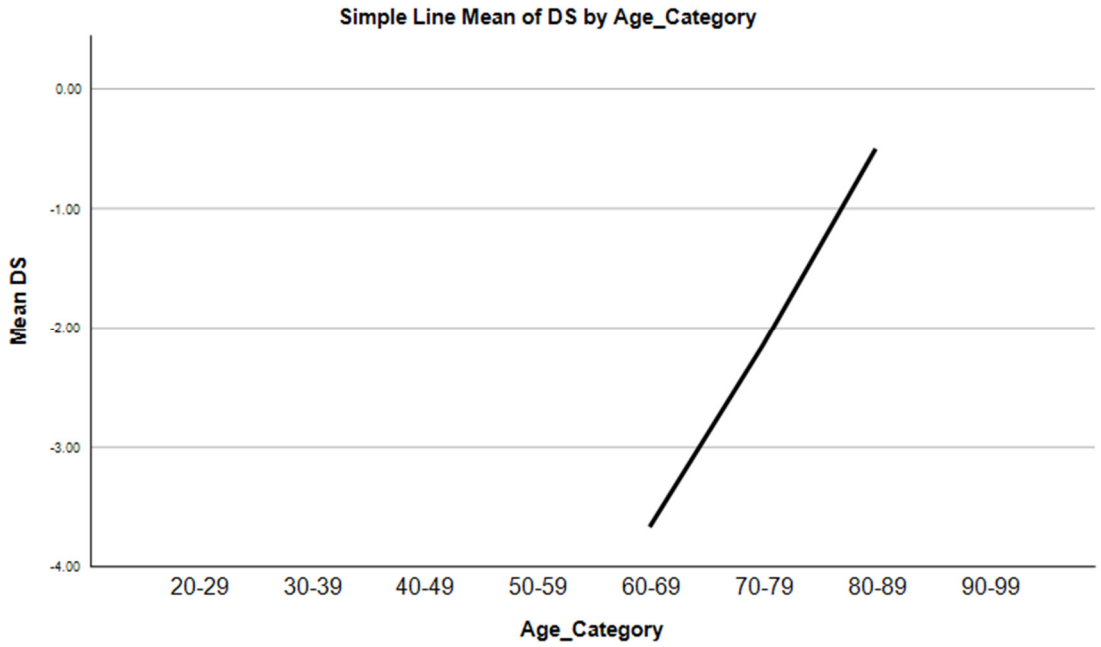

Figure 5. Line graph of overall change in stiffness scores (DS) across all age categories (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-99).

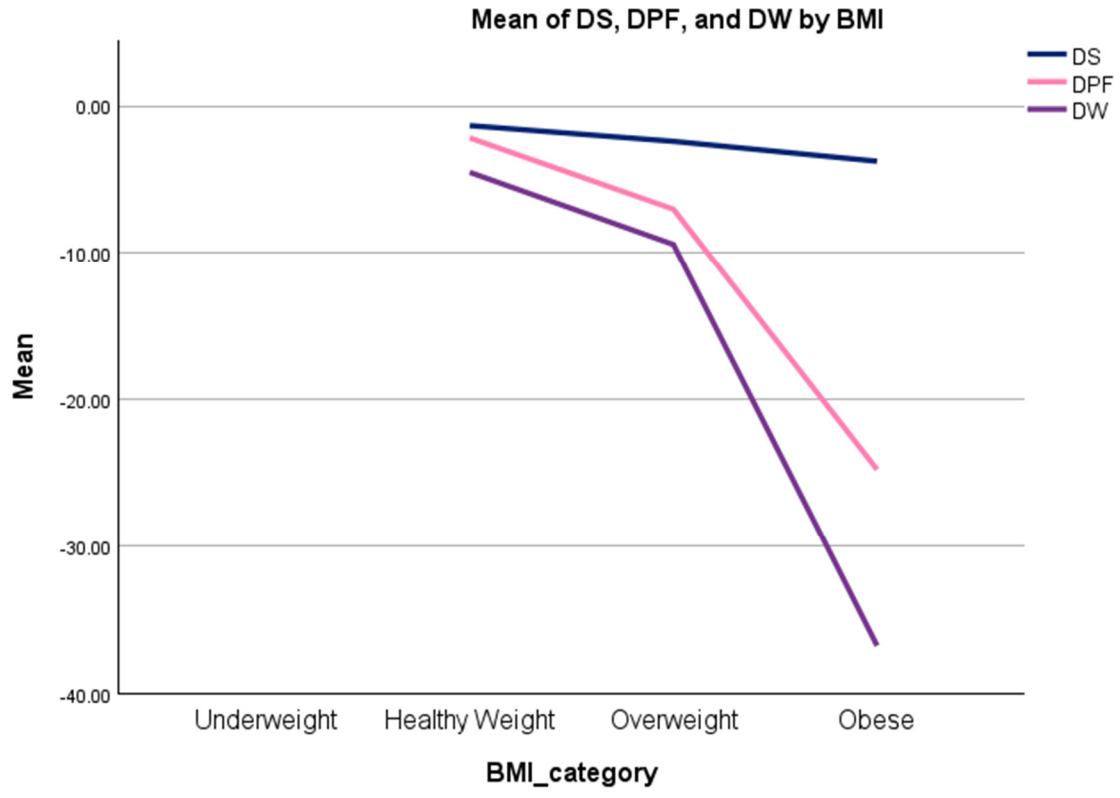

Figure 6. Line graph of overall change in stiffness (DS), physical function (DPF), and total WOMAC (DW) across BMI categories (Underweight, Healthy Weight, Overweight, Obese).

4. Discussion

The clinical potential of umbilical cord tissue (UCT) allografts for the supplementation of treatment-resistant paraspinal defects in the cervical spine is presented in the positive findings from this study. Table 2 presents the overall rate of improvement in all application groups, and Figure 1

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reflects the mean scores over time across each group for all six measures. All patient groups reported lower average NPRS and WOMAC scores and higher average QOLS scores at the final visit compared to the initial visit, demonstrating an overall positive trend of improvement in all scales. Statistical tests used were nonparametric, and a Bonferroni adjustment to the p-value (adjusted $\alpha = 0.05/3 = 0.017$) was made to reduce Type I error in the Wilcoxon Signed-Rank Test (WSRT) and the Mann-Whitney U test. In the WSRT, significant differences in timeline were observed between the initial and 30-day, the initial and 90-day, and the initial and final visits. Each dosage group was stratified and observed individually, with almost all scales reporting significance. The single application group displayed significance across all timeline comparisons, all reporting $p < 0.001$, except for initial to 30-day pain ($p = 0.002$). This strong significance demonstrates that a single application of UCTa in the supplementation of cervical paraspinal defects can significantly improve pain, functionality, and quality of life. The multi-application groups similarly mirror the same results as the single application group, with very few differences that were not significant. Overall, both the double and triple application groups experienced improvement ($p < 0.001$).

In addition to the results presented in the WSRT analyses, Mann-Whitney U tests were performed between the dosage groups to reveal which specific groups performed better (Tables 5-7). The final scores used for the Mann-Whitney test were the last follow-ups submitted for each patient, regardless of where in the timeline that fell. When comparing single application patients to double application patients, no significant differences were observed, suggesting that improvement was similar between these groups. However, in comparisons between the multi-application groups, the results indicated that the triple application group had significantly greater reductions in overall pain scores than the double application patient group. While no other scale displayed meaningful differences, the visual representation of the average scores in Figure 2 and percentage improvements in Table 2 suggest the possibility that triple applications achieved better clinical outcomes than the double application group (Figure 1). When triple application patients were compared to single application patients, statistical significance was identified in the overall change in NPRS scores, indicating that triple application patients reported better NPRS outcomes than single application patients. Despite the lack of significance between the single and triple application patients in other scales, the NPRS and reported averages suggest that triple application patients may have experienced better outcomes than single application patients (Figure 2, Table 2).

Across the WOMAC scales, increasing application frequency was associated with progressively greater mean improvements, with the triple application group demonstrating the largest overall reductions. This pattern was most evident in the WOMAC Total and Functionality scores, both of which showed substantial score improvements with the addition of further applications. However, despite these improvements, the outcome ranges remained high in all dosage groups, particularly for the WOMAC total score, suggesting pronounced variability in individual response to application. Pain and stiffness exhibited lower ranges, but have a lower possible maximum total score than physical function and the total WOMAC. The triple application group displayed narrower outcome ranges than the single application group, and slightly lower ranges than the double application patients, highlighting the potential greater efficacy in triple application protocols (Figure 3, Table 7-9). While this analysis evaluates the application response in individuals, the results remain descriptive due to the non-normal distribution of the data. The observed pattern of increased mean improvement with additional applications suggests the potential for sustained improvement with multi-application care protocols (Figure 3). The wide range of patient response variability underscores the importance of identifying factors that may influence responsiveness. Future studies should focus on a more comprehensive analysis of dose-dependent effects, explore factors associated with individual patient response patterns, and assess whether repeated applications are associated with meaningful changes over more extended follow-up periods.

Given the modest sample size ($n = 31$), the nonparametric Jonckheere-Terpstra (J-T) test was applied to assess monotonic trends in overall change in scores across ordered factors, such as dosage, age, and BMI. To further confirm the results observed from the Mann-Whitney test, a significant

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positive trend in stiffness was observed for dosage, indicating that greater numbers of UCTa applications were associated with greater reduction in some scores. Age also demonstrated a significant trend in stiffness, with patients in the 60-69 category exhibiting greater improvement than 70-79 year-old patients, and more specifically in the triple application group (Table 9), which is concurrent with the literature (Khazzam, 2020; Rupp, 2024). Higher BMI was associated with significant improvements in stiffness, physical function, and total WOMAC scores, suggesting that overall improvement of those with higher BMI was greater than that of patients with lower BMI. These findings may appear counterintuitive to current literature; however, one possible explanation is that leaner patients may have had less room for improvement, whereas patients with higher BMI had greater potential for larger gains of improvement (Giesinger, 2021). Gender differences were evaluated using the Mann-Whitney test, as this factor represents a dichotomous variable rather than an ordered one suitable for J-T analysis. No meaningful differences were found, suggesting that males and females experienced comparable outcomes or the sample size was too small to determine any difference. Collectively, the analysis revealed that multi-application dosage protocols of UCTa might produce more favorable outcomes for supplementing cervical paraspinal muscle degeneration refractory to standard care than single-application protocols, with triple applications being particularly effective. Future studies with randomized controlled trials (RCTs) and larger sample sizes will contribute to a stronger confirmation of the results presented in the study.

Several limitations must be considered when interpreting the findings of this study. This study's small sample size limits the statistical power of the testing, increasing the possibility of Type II error, where the true effect may not have been detected. In addition to the limited sample size, the design of this study was observational, offering no direct comparison to a control group or alternative regenerative interventions, such as platelet-rich plasma (PRP) therapy. The reliance on patient-reported outcomes presents limitations in quantifying functional and physiological changes attributed to UCT. The NPRS and QOLS scales are widely used across various use sites; however, the WOMAC scale primarily assesses lower extremity function, limiting its relevance in this study (Bellmany, 1988; Park, 2020). While no specific scales are designed for cervical paraspinal muscle defects, validated neck pain measures, such as the Neck Disability Index (NDI), Northwick Park Neck Pain Questionnaire (NPQ), Neck Bournemouth Questionnaire (NBQ), and the Copenhagen Neck Functional Disability Scale (CNFDS), may offer greater effectiveness in assessing the functional efficacy of UCTa (Farooq, 2017; Stefanovitch-Lawbuary, 2019). Before and after MRI or ultrasound imaging would provide quantitative analysis of physiological changes in the paraspinal tissue. Future studies with larger patient pools that utilize comparative analysis and site-specific assessment tools are encouraged to validate the benefits of UCTa applications in patients with cervical paraspinal muscle defects.

Despite the limitations, this pilot investigation into the safety and efficacy of UCTa in supplementing cervical paraspinal muscle and entheses defects provides positive results in patient pain reduction and increased functionality. In skeletal muscle, the primary component of the extracellular matrix (ECM) is type I collagen with other minor types including III, V, IX, and XI (Wohlgemuth, 2023; Csapo, 2020). These cross-linking collagen fibers are affected by injury and aging, changing the morphology from type III to abnormal levels of type I (Csapo, 2020). The cervical paraspinal entheses are primarily comprised of fibrocartilage (Apostolakos, 2014). The entheses contain several zones, with Zone 1 consisting of collagen types I and III, Zone 2 consisting of collagen types I-III, Zone 3 consisting of collagen types I, II, and X, and Zone 4 consisting of collagen type I (Apostolakos, 2014). Comparatively, UCTa consists of collagen types I, II, III, IV, V, VI, XII, and XIV, as well as other ECM components (Roy, 2022). The biological plausibility of UCTa in cervical paraspinal defects is supported by the similar compositions presented in the entheses, muscle, and UCT. In addition to the collagenous-rich composition, the structural framework and functionality of the etheses and UCTa can be analyzed for similarities. Functionally, both the entheses and UCTa rely on their structural framework to distribute and dissipate tensile stress (Tits, 2023; Roy, 2022). Moreover, the collagenous matrix in UCTa interlaces through a hyaluronic acid and sulfated GAG-

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rich ground substance, conferring viscoelastic cushioning and hydration (Dubus, 2022). Similarly, type I collagen bundles in the entheses are integrated with the proteoglycans, such as aggrecan, which enhance compressive resistance (Apostolakos, 2014). The integration of the collagenous-rich framework with proteoglycan-rich extracellular matrix in both the entheses and UCTa provides tensile reinforcement, and the ground substance modulates viscoelastic properties. This study's favorable findings corroborate the biological similarities shared by UCTa and entheses, thereby confirming the homologous use of UCTa in addressing paraspinal muscle and entheses defects within the cervical spine, by enabling the integration of healthy collagen structures with damaged native matrices.

While this study's design lacked a comparison group, physicians participating in this study observed that UCTa provide more consistent outcomes in their patients than the autologous regenerative medicine they had previously used, platelet-rich plasma (PRP). While PRP therapy has been commonly used as an alternative in general cervical neck pain, current literature for cervical paraspinal entheses is limited. Positive findings have been observed in studies; however, a 2022 systematic review emphasizes that despite the trend in functional improvement, the majority of comparisons with a control group reported no statistical significance (Masiello, 2022). These findings may stem from PRP's reliance on platelet concentration, indicating the importance of patient health in the efficacy of PRP therapy (Rahman, 2024; Boffa, 2024). In addition to PRP therapy, prolotherapy is another regenerative alternative for cervical neck pain; however, recent literature indicates prolotherapy does not consistently outperform placebo or control groups for tendinopathy or musculoskeletal pain in many studies (Thamrongskulsiri, 2025). UCT allografts have been shown to be consistent in various homologous use sites, offering pain alleviation and increased functionality, as shown in previous publications derived from the same repository (Lai, 2024; Lai, 2024). The minimally manipulated UCTa is rigorously screened with highly regulated processing protocols, ensuring the consistent quality of the connective tissue in each allograft. The structural and functional similarities between UCT and the entheses, as well as the positive preliminary findings in this study, demonstrate UCT allografts' promising clinical potential as a tissue transplant for treatment-resistant cervical paraspinal muscle defects. As a conservative approach, UCT allografts could be beneficial as a standardized option when traditional methods fail to preserve muscular and ligamentous integrity. Continued research with larger sample sizes and comparative analysis is encouraged to validate these preliminary results and provide definitive evidence for the clinical applicability of UCTa supplementation in cases of paraspinal muscle defects in the cervical spine that are unresponsive to standard-of-care methods.

5. Conclusions

The patient cohort of 31 patients, divided into three dosage groups, derived from an observational repository, reported improvements in pain, stiffness, functionality, and quality of life over a 90-180 day period after receiving UCTa applications. No adverse effects or post-procedure complications were recorded. The significant improvement in overall scores in all scales was encouraging; however, the small sample size, reliance on patient-reported outcomes, no pre- and post-imaging of soft tissues, and the absence of a control group precluded definitive conclusions regarding the clinical efficacy of UCTa application. These preliminary findings support the safety and feasibility of UCT allografts for paraspinal muscle defects in the cervical spine and highlight the imperative for randomized controlled trials to validate these results and define the role of this regenerative approach in the clinical management of cervical paraspinal enthesopathy.

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

Data Availability Statement: Data available upon request.

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

Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
UCT	Umbilical Cord Tissue
UCTa	Umbilical Cord Tissue allograft
WOMAC	Western Ontario and McMaster University Arthritis Index
NPRS	Numeric Pain Rating Scale
QOLS	Quality of Life Scale

Appendix A

Table A1. Descriptive Statistics for all application groups in all scales.

Statistics							
Dosage			NPRS1	P1	S1	PF1	W1
Single Application	N	Valid	10	15	15	15	15
		Missing	5	0	0	0	0
	Mean		5.2000	8.4000	4.0000	27.3333	39.7333
	Median		5.5000	9.0000	5.0000	24.0000	44.0000
	Std. Deviation		2.44040	4.35562	2.00000	10.90653	15.52172
	Skewness		-.289	-.002	-1.113	-.132	-.294
	Std. Error of Skewness		.687	.580	.580	.580	.580
	Kurtosis		-.098	-1.280	.242	-1.715	-1.789
	Std. Error of Kurtosis		1.334	1.121	1.121	1.121	1.121
	Minimum		1.00	2.00	.00	11.00	17.00
	Maximum		9.00	14.00	6.00	41.00	56.00
Double Application	N	Valid	8	9	9	9	9
		Missing	1	0	0	0	0
	Mean		6.0000	5.7778	4.8889	24.7778	35.4444
	Median		6.0000	6.0000	5.0000	25.0000	35.0000
	Std. Deviation		2.56348	3.03223	1.83333	11.56263	15.83596
	Skewness		-.204	.237	.052	.524	.500
	Std. Error of Skewness		.752	.717	.717	.717	.717
	Kurtosis		-.057	.006	-.259	-.267	-.047
	Std. Error of Kurtosis		1.481	1.400	1.400	1.400	1.400

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	Minimum		2.00	1.00	2.00	9.00	12.00
	Maximum		10.00	11.00	8.00	43.00	62.00
Triple Application	N	Valid	6	7	7	7	7
		Missing	1	0	0	0	0
	Mean		7.0000	11.0000	5.0000	35.5714	51.5714
	Median		7.0000	11.0000	6.0000	38.0000	55.0000
	Std. Deviation		1.89737	4.47214	2.70801	12.72605	17.70929
	Skewness		.000	.423	-1.128	.257	.570
	Std. Error of Skewness		.845	.794	.794	.794	.794
	Kurtosis		2.500	2.202	1.021	.499	1.057
	Std. Error of Kurtosis		1.741	1.587	1.587	1.587	1.587
	Minimum		4.00	4.00	.00	19.00	28.00
	Maximum		10.00	19.00	8.00	57.00	83.00
Dosage			Q1	NPRS2	P2	S2	PF2
Single Application	N	Valid	15	9	15	15	15
		Missing	0	6	0	0	0
	Mean		75.2667	4.3333	5.4667	2.8000	16.8667
	Median		74.0000	4.0000	4.0000	3.0000	17.0000
	Std. Deviation		17.12336	2.73861	5.02660	2.17781	12.84449
	Skewness		-.619	.209	.535	.247	.062
	Std. Error of Skewness		.580	.717	.580	.580	.580
	Kurtosis		-.155	-.184	-1.088	-1.113	-1.468
	Std. Error of Kurtosis		1.121	1.400	1.121	1.121	1.121
	Minimum		43.00	.00	.00	.00	.00
	Maximum		99.00	9.00	14.00	6.00	35.00
Double Application	N	Valid	9	9	9	9	9
		Missing	0	0	0	0	0
	Mean		63.0000	3.6667	6.3333	4.0000	23.3333
	Median		65.0000	3.0000	6.0000	4.0000	21.0000
	Std. Deviation		30.20348	1.80278	3.67423	1.80278	12.05197
	Skewness		-1.038	.969	-.147	.165	.623
	Std. Error of Skewness		.717	.717	.717	.717	.717
	Kurtosis		1.399	-.091	-.160	.044	-.181
	Std. Error of Kurtosis		1.400	1.400	1.400	1.400	1.400
	Minimum		.00	2.00	.00	1.00	6.00
	Maximum		96.00	7.00	12.00	7.00	43.00
Triple Application	N	Valid	7	7	7	7	7
		Missing	0	0	0	0	0
	Mean		70.8571	4.8571	9.0000	4.5714	29.7143
	Median		83.0000	5.0000	8.0000	5.0000	30.0000
	Std. Deviation		32.69775	1.67616	5.53775	2.76026	15.09651
	Skewness		-2.174	.309	.915	-.507	.914
	Std. Error of Skewness		.794	.794	.794	.794	.794
	Kurtosis		5.178	-1.468	.604	-.367	.521
	Std. Error of Kurtosis		1.587	1.587	1.587	1.587	1.587
	Minimum		.00	3.00	3.00	.00	15.00
	Maximum		98.00	7.00	19.00	8.00	57.00
Dosage			W2	Q2	NPRS3	P3	S3
Single Application	N	Valid	15	15	8	15	15
		Missing	0	0	7	0	0

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	Mean		25.1333	81.9333	4.1250	4.5333	2.5333
	Median		23.0000	79.0000	4.5000	5.0000	2.0000
	Std. Deviation		19.08577	11.77447	2.23207	3.52272	1.95911
	Skewness		-.001	-.093	-.824	.505	.896
	Std. Error of Skewness		.580	.580	.752	.580	.580
	Kurtosis		-1.638	-.403	.512	-.409	-.586
	Std. Error of Kurtosis		1.121	1.121	1.481	1.121	1.121
	Minimum		.00	58.00	.00	.00	.00
	Maximum		50.00	99.00	7.00	12.00	6.00
Double Application	N	Valid	9	9	7	9	9
		Missing	0	0	2	0	0
	Mean		33.6667	75.6667	3.1429	6.5556	4.1111
	Median		35.0000	70.0000	3.0000	7.0000	4.0000
	Std. Deviation		17.09532	20.90454	1.67616	3.57460	1.69148
	Skewness		.372	-.047	.582	-.482	-.021
	Std. Error of Skewness		.717	.717	.794	.717	.717
	Kurtosis		-.065	-1.446	.052	.296	1.240
	Std. Error of Kurtosis		1.400	1.400	1.587	1.400	1.400
	Minimum		7.00	47.00	1.00	.00	1.00
	Maximum		62.00	104.00	6.00	12.00	7.00
Triple Application	N	Valid	7	7	7	7	7
		Missing	0	0	0	0	0
	Mean		43.2857	83.5714	2.1429	5.2857	2.8571
	Median		39.0000	84.0000	2.0000	6.0000	3.0000
	Std. Deviation		22.51455	10.16296	1.06904	2.62769	1.95180
	Skewness		.817	-.042	-1.520	.030	.088
	Std. Error of Skewness		.794	.794	.794	.794	.794
	Kurtosis		.206	-.269	2.712	-1.690	.318
	Std. Error of Kurtosis		1.587	1.587	1.587	1.587	1.587
	Minimum		20.00	69.00	.00	2.00	.00
	Maximum		83.00	99.00	3.00	9.00	6.00
Dosage			PF3	W3	Q3	FNPRS	FP
Single Application	N	Valid	15	15	15	8	15
		Missing	0	0	0	7	0
	Mean		15.7333	22.8000	85.4000	4.1250	4.5333
	Median		16.0000	23.0000	81.0000	4.5000	5.0000
	Std. Deviation		9.13757	14.02141	11.43803	2.23207	3.52272
	Skewness		.913	.797	-.216	-.824	.505
	Std. Error of Skewness		.580	.580	.580	.752	.580
	Kurtosis		1.807	1.091	-1.084	.512	-.409
	Std. Error of Kurtosis		1.121	1.121	1.121	1.481	1.121
	Minimum		2.00	2.00	64.00	.00	.00
	Maximum		39.00	57.00	100.00	7.00	12.00
Double Application	N	Valid	9	9	9	6	9
		Missing	0	0	0	3	0
	Mean		22.3333	33.0000	71.4444	2.5000	4.5556
	Median		23.0000	35.0000	68.0000	2.5000	6.0000
	Std. Deviation		12.15525	17.07337	15.66933	2.07364	4.18662
	Skewness		.267	.109	.133	.807	-.149
	Std. Error of Skewness		.717	.717	.717	.845	.717

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	Kurtosis		-.222	.138	-.624	1.109	-2.376
	Std. Error of Kurtosis		1.400	1.400	1.400	1.741	1.400
	Minimum		4.00	5.00	47.00	.00	.00
	Maximum		43.00	62.00	96.00	6.00	9.00
Triple Application	N	Valid	7	7	7	7	7
		Missing	0	0	0	0	0
	Mean		20.0000	28.1429	84.4286	1.4286	2.8571
	Median		18.0000	28.0000	84.0000	1.0000	1.0000
	Std. Deviation		6.21825	10.22136	9.10782	1.27242	2.96808
	Skewness		.833	.736	.155	.222	.889
	Std. Error of Skewness		.794	.794	.794	.794	.794
	Kurtosis		-.574	-.525	-.774	-1.715	-1.242
	Std. Error of Kurtosis		1.587	1.587	1.587	1.587	1.587
	Minimum		13.00	17.00	73.00	.00	.00
	Maximum		30.00	45.00	98.00	3.00	7.00

Dosage			FS	FPF	FW	FQ
Single Application	N	Valid	15	15	15	15
		Missing	0	0	0	0
	Mean		2.5333	15.7333	22.8000	85.4000
	Median		2.0000	16.0000	23.0000	81.0000
	Std. Deviation		1.95911	9.13757	14.02141	11.43803
	Skewness		.896	.913	.797	-.216
	Std. Error of Skewness		.580	.580	.580	.580
	Kurtosis		-.586	1.807	1.091	-1.084
	Std. Error of Kurtosis		1.121	1.121	1.121	1.121
	Minimum		.00	2.00	2.00	64.00
	Maximum		6.00	39.00	57.00	100.00
Double Application	N	Valid	9	9	9	9
		Missing	0	0	0	0
	Mean		2.1111	15.3333	22.0000	70.5556
	Median		2.0000	18.0000	26.0000	72.0000
	Std. Deviation		2.08833	12.96148	18.82153	31.97699
	Skewness		1.083	.196	.149	-1.453
	Std. Error of Skewness		.717	.717	.717	.717
	Kurtosis		.233	-1.198	-1.434	2.331
	Std. Error of Kurtosis		1.400	1.400	1.400	1.400
	Minimum		.00	.00	.00	.00
	Maximum		6.00	36.00	51.00	100.00
Triple Application	N	Valid	7	7	7	7
		Missing	0	0	0	0
	Mean		1.8571	11.4286	16.1429	86.0000
	Median		1.0000	10.0000	12.0000	89.0000
	Std. Deviation		1.46385	9.67569	13.89758	9.57427
	Skewness		.337	.621	.656	-.426
	Std. Error of Skewness		.794	.794	.794	.794
	Kurtosis		-1.537	-1.015	-1.187	-1.263
	Std. Error of Kurtosis		1.587	1.587	1.587	1.587
	Minimum		.00	2.00	2.00	73.00
	Maximum		4.00	27.00	38.00	98.00

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Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, 2: 30-Day Visit, 3: 90-Day Visit, 4: 120-Day Visit.

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