THE EUROPEAN SOCIETY OF MEDICINE

Published 30 June 2026 Medical Research Archives, Volume 14 Issue 6

ORIGINAL RESEARCH

Human Umbilical Cord Tissue Allografts for Cervical Paraspinal Muscle and Entheses

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ABSTRACT

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Introduction: Cervical paraspinal enthesopathy is characterized by fatty infiltration and muscle degeneration; current methods only provide symptomatic relief or involve significant postoperative complications. This observational study provides preliminary results for the clinical potential of umbilical cord tissue allografts in patients with cervical paraspinal enthesopathy and degeneration refractory to standard care.

Materials and Methods: Thirty-one patients with cervical paraspinal degeneration that failed three months of conservative care were identified from the observational repository. Patients received one to three ultrasound-guided umbilical cord tissue allograft applications to the muscle or attachment sites with damage. The Numeric Pain Rating Scale, Western Ontario and McMaster University Arthritis Index, and Quality of Life Scale were used to measure outcomes. 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 (42% male, 55% female, 3% unreported), with the triple application group reporting the highest percentage improvement. Statistically significant Bonferroni-adjusted differences were present in all application groups. No adverse events were reported. Discussion: This small observational study provides preliminary findings that umbilical cord tissue allografts 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 and clinical value 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

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DOI : https://doi.org/10.18103/mra.2026.0299

CITATION

Tamea, C., Buchalter, J., et al., 2026. Human Umbilical Cord Tissue Allografts for Cervical Paraspinal Muscle and Entheses. Medical Research Archives, [online] 14(6). https://doi.org/10.18103/mra.2026.0299

ISSN

2375-1924

Abbreviations

The following abbreviations are used in this manuscript:

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

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[1]. Across the globe, neck pain is the fourth highest cause of disability and is ranked twenty-first in the total burden of pain[2]. The prevalence of neck pain is projected to increase, reflecting broader trends in musculoskeletal health[3]. Neck pain is widely recognized as a multifactorial disorder, with contributing factors that may include genetic predisposition, various pathological mechanisms, and traumatic injury[1]. In addition, several risk factors such as the female gender, increased age, and work-related factors contribute to neck pain[1]. 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[2]. Although these factors can contribute to neck pain, most neck pain conditions are associated with neuromusculoskeletal degeneration.

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[4]. Changes in paraspinal muscle morphology of the cervical spine are associated with muscle degeneration, which is indicated by fatty infiltration[5-7]. The accumulation of adipocytes within non-adipose tissues results in fatty infiltration and often impairs normal function[8]. Although exact molecular pathways in paraspinal muscle degeneration are unclear, some studies suggest that Fibro/Adipogenic Progenitor (FAP) activation and circRNA/miRNA regulatory axes are potential molecular targets for early diagnosis and intervention in muscle degeneration[9-11]. Cervical paraspinal 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[6,12]. MRI assessment of paraspinal muscle degeneration showcases multiple paraspinal muscles, including the multifidus, semispinalis cervicis, and spinalis cervicis, with decreased muscle mass and increased adipose tissue, appearing as high signal intensity[5,13]. Ultrasound imaging demonstrates increased echogenicity in muscles affected by fatty infiltration, causing them to appear brighter than normal muscle tissue[14]. 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[15]. 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[15]. Ligamentous degeneration may result from repetitive micro tearing at sites of strain, leading to progressive stiffening due to the replacement of elastic fibers with less flexible collagenous tissue[16]. In response to such injuries, the body prioritizes structural stability over mobility to safeguard adjacent neurovascular elements[17]. 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[17]. 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[18]. Three FI assessments (visual qualitative assessment, semiquantitative assessment, and quantitative assessment) can be used to indicate the severity of the atrophic muscles[18]. 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[18]. 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, non-steroidal anti-inflammatories (NSAID), activity modification, breathing exercises, and steroid injections[19-21]. 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[22]. Due to the limited options in cervical paraspinal management, many patients suffer without relief once exhausting standard approaches. 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 allograft (UCTa) 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[23]. There is an absence of studies on the effectiveness of UCTa applications in refractory neck pain related to cervical paraspinal degeneration; however, recent reports have demonstrated its clinical relevance for musculoskeletal-related defects throughout the body[23,24]. 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[25]. 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[26]. 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.

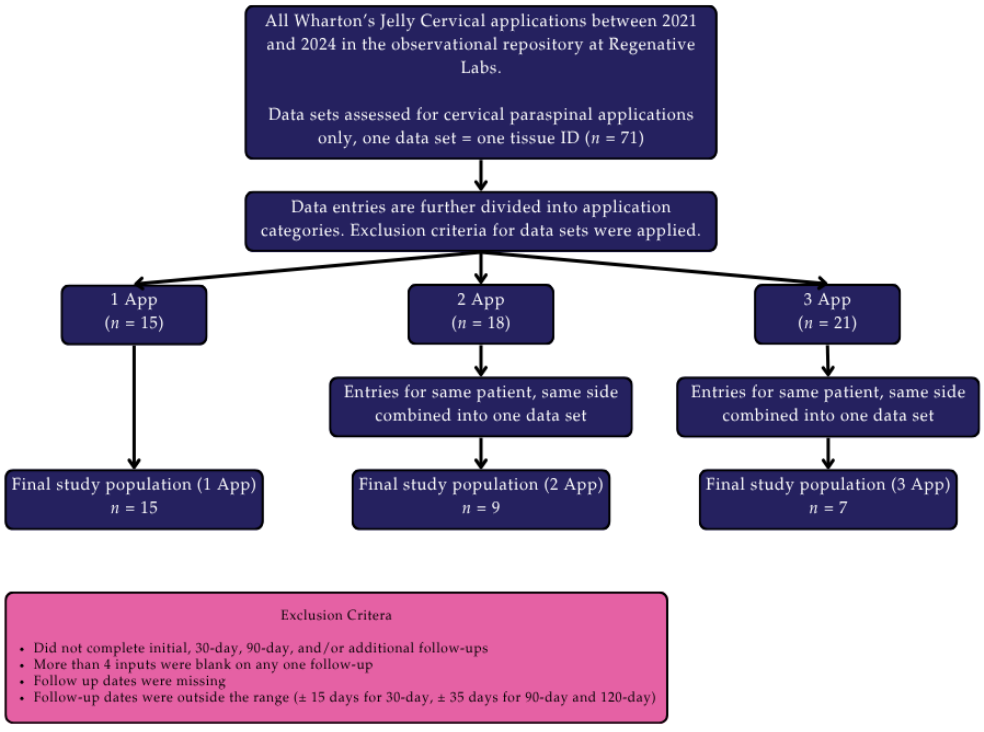
2. Materials and Methods

2.1. STUDY DESIGN

This observational research 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 protocol covers observational data collection on all human perinatal tissue allografts offered by Regenative Labs between 2022 and 2025. Eligible participants had justifiable homologous use of the product, i.e., evidence of tissue degeneration, damage, or missing tissue, and exhausted and failed standard care for said site as defined by Medicare for at least three months. As the data is observational, all application amounts and techniques were up to the discretion of each provider based on the severity and placement of the affected tissue. Patients submitted data at their initial application visit, 30 days post-allograft, and the primary endpoint was a 90-day follow-up to allow sufficient time for meaningful improvements after a single application, as clinically relevant changes are often observed within weeks and can be assessed by approximately 3 months[27-29]. Any reapplication of the product extended the timeline by an additional 90 days. The design of the repository and the protocols for UCTa processing have been described in detail in other studies derived from the database[25,26,30,31]. 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. For this post-observation period analysis, patients were included 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), or had multifaceted defects. All patients identified received 2 mL, 150 mg UCTa from Regenative Labs (Pensacola, FL, USA) per application, manufactured following the FDA's 361 guidelines for minimally manipulated human cell and tissue products. 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.



2.2. STUDY POPULATION

The participants identified from the registry in this post-observational analysis 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 a single application, four males and four females received two applications (double application group), and four males and three females received three applications (triple application group). 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. Unlike controlled intervention studies, the timing of re-application was not standardized; patients could receive a subsequent application at any point determined by the care provider. 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 completions at the 180-day mark. Cases with more than three cervical paraspinal applications were not present in the registry but would have been acceptable if deemed necessary by the care provider. 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. All patients had exhausted and failed at least three months of conservative care, including but not limited to steroid injections, topical and oral medications, physical therapy, home exercise, and activity modification, prior to umbilical cord tissue allograft application. Any injection of steroid or medication must have occurred greater than one month prior to the UCTa application, although submission of exact prior care was not required. It should be noted that while the precise timing of allograft applications relative to the conclusion of conservative care was not captured, the study cohort opted to receive umbilical cord allografts after a period of evaluation, indicating that UCTa applications were not applied immediately following the cessation of prior management strategies.

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. Multiple target sites were selected within the cervical region depending on the areas of degeneration in each patient, spanning anywhere from C1 to C7. Following application of the allograft, the area was gently mobilized through its full range of motion, and a sterile dressing was applied. A 30-minute waiting period after the application was required to monitor potential side effects. Patients were instructed

to inform the provider at once if any issues or symptoms surfaced during their evaluation. 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, the numeric pain rating scale (NPRS), Western Ontario and McMaster University Arthritis Index (WOMAC) total and subscales (Pain, Stiffness, and Physical Function), and the quality of life scale (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. The calculation of the effect was a z-based calculation (Equation 1).

$$r = \frac{z}{\sqrt{N}}$$

Equation 1: Effect size (*r*) formula, where z is the standardized test statistic, and N is the total sample size.

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. To address concerns regarding multiple comparisons across the J-T tests, the Benjamini-Hochberg (BH) false discovery rate (FDR) correction was applied with a significance threshold of $\alpha = 0.05$. The FDR correction was chosen instead of the Bonferroni correction in these analyses, given the exploratory nature of the J-T analyses and the correlation among the WOMAC subscale outcomes. The correlation coefficient, *r*, was also added to the J-T Tests to indicate effect size. This study performed no imputation, and all data sets analyzed 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

3.1. PATIENT CHARACTERISTICS

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 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)	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

3.2. IMPROVEMENT IN PATIENT REPORTED SCALES

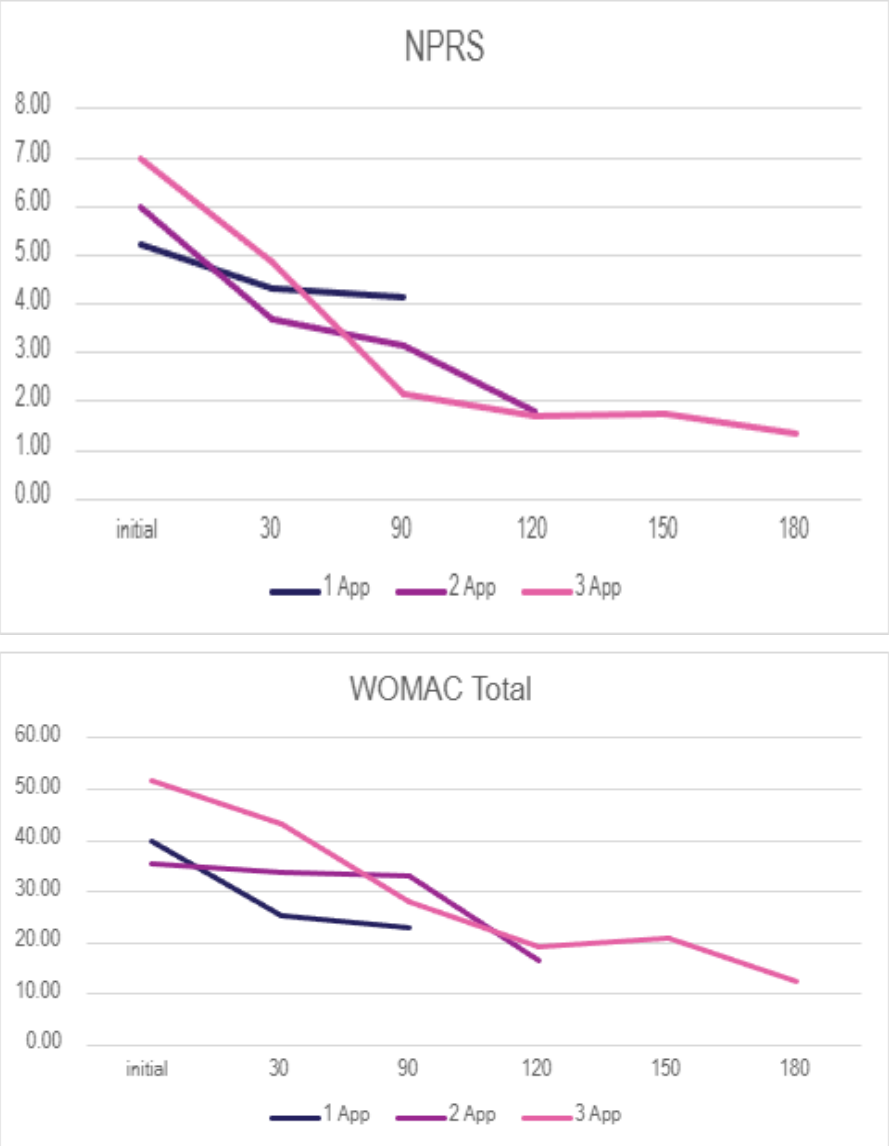
A reduction in NPRS and WOMAC scores represents improvement, while an increase in QOLS scores represents improvement. In the single application group, five out of ten patients reported improvement in NPRS scores, thirteen out of fifteen reported improvement in total WOMAC scores, and ten out of fifteen 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.

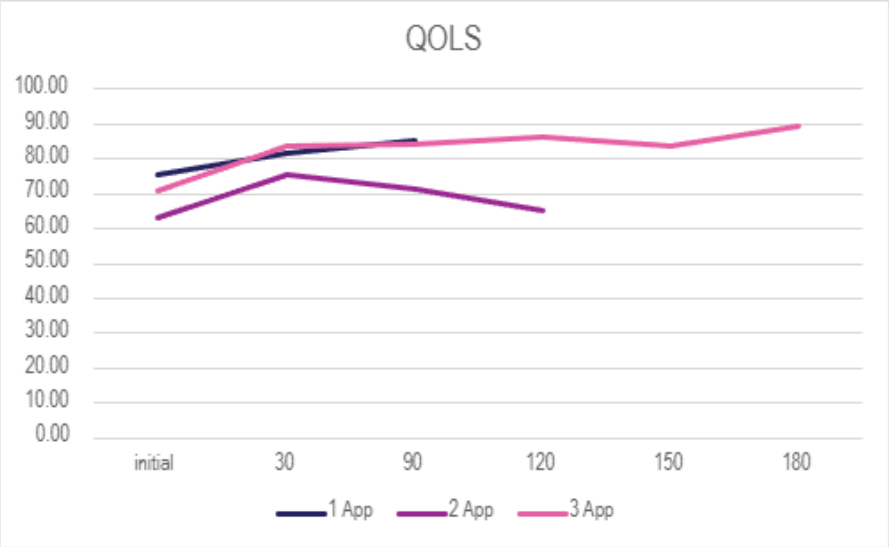
Table 2: Percent improvement in each scale by number of applications from the initial to the last visit submitted

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%

Fluctuations in patient-reported outcomes from visit to visit in the multi-application groups are present due to rises in pain that indicate the need for additional applications at the physician's discretion. 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.

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





The descriptive statistics, mean, standard deviation, skewness, and sample size (n), for the three major scales for the initial, 30 day, 90 day, and endpoint visits are presented in table 3.

Table 3: Descriptive statistics for all major scales across application groups.

Scale	Visit	Single Application*				Double Application				Triple Application			
		n	**Mean**	**SD**	**Skew**	**n**	**Mean**	**SD**	**Skew**	**n**	**Mean**	**SD**	**Skew**
NPRS	*Initial*	**10**	5.20	2.440	−.289	**8**	6.000	2.563	−.204	**6**	7.000	1.897	.000
	30-Day	**9**	4.333	2.739	.209	**9**	3.667	1.803	.969	**7**	4.857	4.472	.423
	90-Day	**8**	4.125	2.232	−.824	**7**	3.143	1.676	−.582	**7**	2.143	1.069	−1.520
	Endpoint	**-**	-	-	-	**9**	3.111	2.088	.817	**7**	1.857	1.464	.337
WOMAC Total	*Initial*	**15**	39.733	15.252	−.294	**9**	35.444	15.840	.500	**7**	51.571	17.709	.570
	30-Day	**15**	36.800	25.688	1.190	**9**	23.333	12.052	.623	**7**	29.143	15.097	−.507
	90-Day	**15**	22.800	11.434	.896	**9**	33.667	17.095	.372	**7**	43.286	22.515	.817
	Endpoint	**-**	-	-	-	**9**	33.667	17.095	.372	**7**	43.286	22.515	.817
QOLS	*Initial*	**15**	81.933	11.774	−.093	**9**	75.667	20.944	−.047	**7**	83.571	10.163	−.042
	30-Day	**15**	75.267	17.123	−.619	**9**	63.000	30.203	−1.038	**7**	70.857	32.698	−2.174
	90-Day	**15**	85.400	11.438	−.216	**9**	70.556	31.976	−1.453	**7**	86.000	9.574	−.426
	Endpoint	**-**	-	-	-	**9**	70.556	31.976	−1.453	**7**	86.000	9.574	−.426

n = valid observations. SD = standard deviation. Skew = skewness. Visits: Initial = baseline; 30-Day, 90-Day = scheduled follow-up visits; Endpoint = last available visit (90-day for single application; last recorded visit for double and triple application groups). NPRS = Numerical Pain Rating Scale; Pain/Stiffness/Phys. Func./WOMAC Total = WOMAC subscales and total; QOLS = Quality of Life Scale. * The 90 day visit is the end point for the single application group

3.3. WITHIN-GROUP STATISTICAL ANALYSES

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. Negative Z-scores define positive trends of improvement and 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 4 displays the significant findings from the WSRT analyses.

Table 4: Wilcoxon Signed-Rank Test within-group analyses for all application groups: Each cell shows Z statistic, p-value, and rank-biserial r (effect size). Presented values are significant after Bonferroni-adjusted α ($p < 0.017$). NS = tested but not significant. NPRS = Numerical Pain Rating Scale; Pain, Stiffness, Phys. Func., WOMAC Total = WOMAC subscales totaled; QOLS = Quality of Life Scale. Endpoint = 90-day for single application; last available visit for double and triple application groups.

Comparison	NPRS	Pain	Stiffness	Phys. Func.	WOMAC Total	QOLS
Single application (n = 15) — endpoint: 90-day						
Initial → 30-Day	**−4.846**	**−3.032**	**−4.105**	**−3.651**	**−3.960**	**−3.443**
	p=<.001	p=.002	p=<.001	p=<.001	p=<.001	p=<.001
	r=0.80	r=0.44	r=0.59	r=0.53	r=0.57	r=0.50
Initial → 90-Day	**−4.873**	**−3.886**	**−4.226**	**−4.049**	**−4.218**	**−3.565**
	p=<.001	p=<.001	p=<.001	p=<.001	p=<.001	p=<.001
	r=0.80	r=0.56	r=0.59	r=0.58	r=0.61	r=0.52
Double application (n = 9) — endpoint: last available visit						
Initial → 30-Day	**−3.859**	**−3.761**	**−3.310**	**−4.488**	**−4.544**	
	p=<.001	p=<.001	p=<.001	p=<.001	p=<.001	NS
	r=0.76	r=0.68	r=0.60	r=0.81	r=0.82	
Initial → Endpoint	**−3.429**	**−4.294**	**−4.179**	**−4.487**	**−4.686**	
	p=<.001	p=<.001	p=<.001	p=<.001	p=<.001	NS
	r=0.67	r=0.77	r=0.75	r=0.81	r=0.61	
Triple application (n = 7) — endpoint: last available visit						
Initial → 30-Day	**−3.504**		**−2.599**	**−2.489**	**−2.715**	
	p=<.001	NS	p=.009	p=.013	p=.007	NS
	r=0.62		r=0.44	r=0.42	r=0.46	

Comparison		NPRS	Pain	Stiffness	Phys. Func.	WOMAC Total	QOLS
Initial	→	**−4.591**	**−4.325**	**−4.668**	**−4.361**	**−4.636**	**−3.452**
Endpoint		p=<.001	p=<.001	p=<.001	p=<.001	p=<.001	p=<.001
		r=0.81	r=0.73	r=0.79	r=0.74	r=0.79	r=0.58

3.4. BETWEEN-GROUP COMPARISONS

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 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. 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 5 presents the significant values between each application comparison.

Table 5: Mann-Whitney U between-group p-values at initial, final, and change scores. Dark green = p ≤ .017; light green = p ≤ .05; gray = no significance.

Single VS Double						
	NPRS	Pain	Stiffness	Phys Fn	Total	QOLS
Initial	0.389	0.158	0.377	0.881	0.742	0.386
Final	0.172	0.976	0.516	0.929	0.976	0.31
Change	0.023	0.12	0.202	0.697	0.612	0.675
Single VS Triple						
	NPRS	Pain	Stiffness	Phys Fn	Total	QOLS
Initial	0.111	0.241	0.181	0.12	0.11	0.86
Final	0.023	0.313	0.469	0.34	0.323	0.972
Change	0.003	0.028	0.096	0.031	0.031	0.972
Double VS Triple						
	NPRS	Pain	Stiffness	Phys Fn	Total	QOLS
Initial	0.319	0.019	0.666	0.263	0.185	0.396

Final	0.34	0.554	0.957	0.671	0.71	0.368
Change	0.062	0.009	0.593	0.039	0.023	0.523

3.6. TRENDS BY AGE AND BMI

Jonckheere-Terpstra (J-T) analyses with FDR correction 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-T* = -3.578, $p = 0.035$), as shown in Table 6. Findings for age and BMI after FDR correction were not significant, suggesting that associations between age and BMI are only exploratory trends, evident in the raw significance. 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 6: Jonckheere-Terpstra test results examining ordered trends in overall score changes in all measures across dosage, age, and BMI groups.

ΔNPRS	ΔPain	ΔStiffness	ΔPhys. Func.	ΔWOMAC	ΔQOLS
Ordered trend by dosage group					
Z=−3.578 p=.055 n=19	Z=−1.096 p=.562 n=31	Z=−1.841 p=.237 n=31	Z=−1.615 p=.318 n=31	Z=−1.612 p=.318 n=31	Z=−.056 p=.955 n=31
Ordered trend by age group					
Z=−.317 p=.897 n=18	Z=1.103 p=.562 n=30	Z=2.691 p=.123 n=30	Z=.410 p=.897 n=30	Z=.841 p=.704 n=30	Z=1.862 p=.257 n=30
Ordered trend by BMI group					
Z=−1.527 p=.342 n=11	Z=−1.602 p=.562 n=15	Z=−2.046 p=.123 n=15	Z=−1.969 p=.245 n=15	Z=−2.018 p=.245 n=15	Z=.376 p=.897 n=15

Each cell shows the Standardized J-T statistic (Z), BH-adjusted p-value (FDR correction), and n (number of observations at the smallest group level). Yellow = significant before but not after FDR correction. Δ = change from initial to endpoint. ΔNPRS = change in NPRS; ΔPain/Stiffness/Phys. Func./WOMAC = WOMAC subscale and total changes; ΔQOLS = change in QOLS. BH correction applied globally across all J-T tests.

4. Discussion

The clinical potential of umbilical cord tissue (UCT) allografts for the supplementation of treatment-resistant paraspinal muscle and enthesis defects in the cervical spine is presented in the positive findings from this observational study. 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. In the WSRT, the single application group displayed significance across all timeline comparisons, all reporting $p < 0.001$, except for initial to

30-day pain ($p = 0.002$)(Table 4). This strong significance demonstrates that a single application of UCTa in the supplementation of cervical paraspinal defects may 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. In the Mann-Whitney analysis, comparisons between the single application patients and double application patients observed no significant differences, suggesting that improvement was similar between these groups. 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. When triple application patients were compared to single application patients, significance was identified in the overall change in NPRS scores, indicating that triple application patients reported better NPRS outcomes than single application patients. Because no significance was identified in the main WOMAC total scale between groups, no dose-related outcomes could be hypothesized. The percentage improvements for the raw average scores in each scale show a greater percentage improvement in the triple application group than the single and double, which most likely correlates to the higher initial scores, leaving room for a greater level of improvement, maintaining the notion that additional applications are based on severity.

A significant positive trend in stiffness was observed for dosage, indicating that greater numbers of UCTa applications were associated with greater reduction in some scores. While raw significance was found in age and BMI, these findings are only exploratory trends. No meaningful gender differences were found, suggesting that males and females experienced comparable outcomes or that the sample size was too small to determine any difference. Collectively, the analysis revealed that multi-application dosage protocols of UCTa might produce more consistent outcomes 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[32]. Before and after MRI or ultrasound imaging would provide quantitative analysis of physiological changes in the paraspinal tissue. The non-randomized assignment of application frequency introduces the potential for confounding by indication, as providers allocated more applications to more severe cases, precluding definitive dose-response patterns. However, BH FDR correction applied across the J-T tests revealed that age and BMI associations cited as potential confounders did not retain statistical significance, while the dose-response trend in change in NPRS scores remained significant after correction, suggesting these factors do not fully account for the observed differences between application groups. Additionally, the timing of reapplications was determined at the provider's discretion rather than by a standardized protocol, resulting in variable final follow-up windows across and within application groups, which limits the direct comparability of final scores in between -group analyses and should be considered when interpreting the Mann-Whitney results.

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[33,34]. These cross-linking collagen fibers are affected by injury and aging, changing the morphology from type III to abnormal levels of type I[34]. The cervical paraspinal entheses are primarily comprised of fibrocartilage[35]. 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[35]. Comparatively, UCTa consists of collagen types I, II, III, IV, V, VI, XII, and XIV, as well as other ECM components[23]. 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 entheses and UCTa can be analyzed for similarities. Functionally, both the entheses and UCTa rely on their structural framework to distribute and dissipate tensile stress[23,36]. Moreover, the collagenous matrix in UCTa interlaces through a hyaluronic acid and sulfated GAG-rich ground substance, conferring viscoelastic cushioning and hydration[37]. Similarly, type I collagen bundles in the entheses are integrated with the proteoglycans, such as aggrecan, which enhance compressive resistance[35]. 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 provides 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 for 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, many comparisons with a control group reported no statistical significance[38]. These findings may stem from PRP's reliance on platelet concentration, indicating the importance of patient health in the efficacy of PRP therapy[39,40]. 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[41]. 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[25,26,30]. 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 observational 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 preliminary results from this observational research study reported improvements in pain, stiffness, functionality, and quality of life over a 90-180 day period after 31 patients received a single, double, or triple UCTa application(s). The significant improvement in overall scores in the patient-reported outcomes is encouraging; however, the small sample size, no pre- and post-imaging of soft tissues, and the absence of a comparison group precluded definitive evidence regarding the clinical efficacy of UCTa applications that do not pertain to this study's cohort. These preliminary observations serve as the foundation in support of the safety and feasibility of UCTa applications for refractory neck pain related to cervical paraspinal degeneration. To validate these results, randomized controlled trials in future studies can help define the role of this regenerative approach in the clinical management of cervical paraspinal enthesopathy and other related defects.

Author Contributions: Conceptualization, C.T., J.B., J.C., T.G., H.J., L.P., and T.B.; methodology, C.T., J.B., J.C., T.G., H.J., L.P., and T.B.; software, T.B.; validation, N.L, A.L., T.B.; formal analysis, C.T., J.B., J.C., T.G., H.J., L.P., N.L., A.L., and T.B.; investigation, C.T., J.B., J.C., T.G., H.J., and L.P.; resources, N.L. and A.L.; data curation, C.T., J.B., J.C., T.G., H.J., L.P., N.L., A.L., and T.B.; writing—original draft preparation, C.T., J.B., J.C., T.G., H.J., L.P., N.L., A.L., and T.B.; writing—review and editing, C.T., J.B., J.C., T.G., H.J., L.P., 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, C.T., J.B., J.C., T.G., H.J., L.P., and T.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board 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 (protocol code IRCM-2022-311; Approval date: 12 January 2022).

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

Data Availability Statement: Data available upon request.

Acknowledgments: The authors would like to thank the staff at each clinic that submitted data to the repository for their assistance in data collection and submission.

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.

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