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Research Article

Homologous Use of Umbilical Cord Tissue for Knee Pain

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Abstract

Context: Injection with homologously-used umbilical cord tissue allograft has not been adequately studied in patients suffering from knee pain.

Objectives: The goal of this study is to determine if knee pain subjects who received cryopreserved umbilical cord tissue (UCT) injected into knee joints experience less knee pain, better function, decreased physical limitations, and reduction of medications (e.g., opioid, NSAIDs, and acetaminophen) over a 6-month period.

Methods: Prior to initiation of this study, Institutional Review Board (IRB) approval was obtained. Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritic Index (WOMAC), and medication usage data were recorded for thirty (30) consenting knee pain subjects receiving UCT at a single site in the United States. Subject profile information was also gathered and utilized to gain further insight into any effects of age, gender, and BMI on pain improvement over time.

Results: Mean resting VAS scores improved from 1.95 to 0.83 over 6 months ($p<0.001$), while mean VAS scores with activity improved from 6.28 to 2.87 ($p<0.001$) for the same period. There was no strong evidence of correlation found between gender and VAS scores (resting or with activity). However, there were statistically

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significant correlations found for both BMI vs. Pre-injection VAS with activity scores (r=0.402, p=.028) and Age vs. Pre-injection VAS with activity scores (r=0.434, p=.017).

Mean WOMAC daily activity function scores improved from 44.7 to 18.5 over the same 6 months (p<.001).

Overall, of the patients who used medications at the beginning of the study (18), 77.8% of them reduced or eliminated medication use.

Conclusion: Analysis demonstrates that injection with UCT decreases pain, improves physical function, and allows for less medication use for at least 6 months.

Keywords: Umbilical cord tissue; UCT, knee pain; VAS; WOMAC.

Introduction

Osteoarthritis (OA), the most common type of disease affecting joints, is one of the most predominant causes of chronic pain and disability in developed nations, including the United States. Specifically, knee OA represents over 80% of the types of osteoarthritis, affecting almost one fifth of American adults over the age of 45 [1]. Almost 23% of US adults (an estimated 54.4 million people) report having doctor-diagnosed arthritis. Even without doctor diagnosis, almost half of American adult's experience limitations in performing their activities of daily living secondary to arthritis [2]. In recent decades, high body mass index (BMI) has become rampant in the United States. Being overweight or obese is a risk factor for knee OA, due to joint overloading as well as adiposity-induced inflammation [1]. Based on analysis of data from 2010-2012 from the National Health Interview Survey (NHIS), it is projected that 26% of adults will be diagnosed with arthritis by 2040. Arthritis and other rheumatic conditions are a leading cause of work disability among US adults [2]. Adults with arthritis are almost three times more likely to fall and suffer injury compared to their non-arthritic counterparts [3]. Of knee and hip OA patients, 25% cannot perform major daily activities and 40% report fair to poor health, ranking high in disability adjusted life years [4]. Because knee pain limits physical activities such as walking, bending, and climbing stairs, reducing pain could improve physical activity and conditioning [5].

Senescing joint tissues accumulate more cartilage loss due to inflammation, oxidative stress, and activation of matrix metalloproteases (MMP) [6]. Joint replacement surgeries are most often due to OA [7]. Considering both direct and indirect costs associated with OA, average annual costs from 2008-2014 totaled $486.4 billion. In 2013, the OA treatment costs were $140,300 [8].

Existing treatments for joint pain are limited to medical management, injection therapy and surgery. Medications to reduce pain are associated with significant morbidity and social concern. 10.1 million people over the age of 12 misused opioids over the course of the year 2019, the overwhelming majority of

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which abused prescription pain relievers. Of those, approximately 1.6 million over age 12 were diagnosed with an opioid use disorder [9]. Health care providers face increasing burden and cost of chronic opioid use with increased scrutiny of monitoring patient usage and protecting against abuse. Almost 500,000 deaths were attributed to opioid overdose, including prescription and illicit opioids, from 1999-2019 [10].

Non-steroidal anti-inflammatory drugs (NSAIDs) are often the first line of treatment chosen by patients with chronic pain. Hospital admission rates due to upper and lower gastrointestinal events secondary to NSAID and aspirin drug use was significant with a mortality rate of almost 6% of admitted patients. About 30% of these deaths were attributed to use of low-dose aspirin [11]. While most common NSAIDs have little toxic effect, NSAID use and overdoses continue to increase, as reported by poison control centers nationwide.

Adverse drug interactions, especially in vulnerable patients, increase morbidity and mortality [12].

While steroid injections provide short-term relief of pain, side effects such as diabetes exacerbation, weight gain, cataracts, osteoporosis, difficulty sleeping, menstrual changes, and increased risk of infection should be considered [13]. Disease-Modifying Anti-Rheumatic Drugs (DMARDs) may also increase the risk of infection and can cause liver or kidney damage. Some patients do not tolerate DMARDS, and they may not be safe for those who are or are trying to become pregnant [14].

Finally, surgery for joint replacement associated with chronic pain is very costly and may have a limited effect on pain and disability [7,8]. Given the high cost, limitations, and side effects associated with traditional methods of treatment of chronic joint pain, alternative approaches to relief are needed.

Background on Umbilical Cord Tissue. Umbilical cord tissue (UCT) is clinically available from registered tissue banks globally. The form and methods for preparing umbilical cord tissue allografts may vary affecting the specific contents and clinical results.

UCT from healthy live births contains regenerative, anti-inflammatory, immunomodulatory and wound healing properties due to the many growth factors and cytokines present in UCT at a higher concentration than in other biologics. These may play a factor in their inflammation-reducing, pain-reducing, and musculoskeletal-healing properties [15, 16]. UCT contains prostanoids PGE2, IL-10, VEGF, and TIMPs that suppress cartilage damage. These proteins exhibit potent anti-inflammatory and anti-fibrotic effects in OA joint disease. [17, 18]. Of relevance to OA, PGE2 “reprograms” macrophages from the inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [19].

UCT stimulates many metabolic processes including general protein and collagen

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synthesis, reducing pain. UCT is safe in humans and animals. Uses of UCT include burn and painful chronic wound healing as well as in shoulder, foot and ankle surgeries [20-23].

Placental as well as umbilical cord tissue donated by volunteers free of communicable disease undergoing caesarian section is processed to obtain UCT. The UCT is minimally manipulated under aseptic conditions and cryopreserved with DMSO, retaining much of its original matrix microstructure and cytokine profile. The cryopreserved UCT is used homologously as a protective barrier or cushion of membranous tissue placed in or over damaged joint tissue in patients with osteoarthritic joint pain. Patients receiving UCT for joint pain have failed previous conservative and conventional therapies such as pharmacological and physical therapy, making it medically necessary to proceed with interventional treatment.

Background on Ultrasound-Guided Knee Injection Utilizing the Lateral Supra Patellar Approach.

After patient education and consent, the patient underwent an ultrasound-guided supra patellar injection utilizing 1 ml of thawed cryopreserved UCT along with 4 ml sterile normal saline under direct ultrasound visualization after the knee was prepped with ChloraPrep.

Post procedure evaluation involved alertness, pain, stable vital signs and unchanged neurologic status at 15 minutes and 60 minutes. After postoperative instructions, the patient was discharged in stable condition. While UCT injections in the knee are a daily clinical practice at this institution, outcomes have not been previously reported.

Methods

To report the outcomes after injection of UCT for joint pain, medical charts of 30 consenting adult subjects with knee joint pain previously treated with UCT at a single institution were reviewed for Visual Analogue Scale (VAS) pain scores, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) daily activity function, opioid usage, and NSAID usage as well as for serious adverse events under an IRB- approved protocol.

Pain was evaluated using the VAS as assessed by the patient at baseline, 1 hour, 24 hours, 1 week, 2 weeks, 8 weeks, 12 weeks, and 24 weeks for both resting scenarios and with activity scenarios; this was consistent with the standard patient follow-up schedule at this institution.

Pain, stiffness, and physical function were assessed using WOMAC questionnaire at baseline, 2 weeks, 8 weeks, 12 weeks, and 24 weeks.

Presence of opioid, NSAID usage, and other medications were recorded at baseline, 24 hours, 1 week, 2 weeks, 8 weeks, 12 weeks, and 24 weeks.

Results

Medical records for 30 patients provided substantially complete data regarding

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demographics and outcomes. The mean age was 63.0 ± 10.9 years, range 36-84.

Table 1 shows the details of patient age versus gender.

Age (In Years)	Overall	Female	Male
Sample Size	30	19	11
MEAN Age	63	64.2	61
Min Age	36	36	49
Max Age	84	84	78
Std. Dev.	10.94	12.1	8.75

Table 1: Patient Age vs. Gender Summary.

There was no strong evidence of difference found between Genders and VAS scores (resting or with activity) at the 6-month review, based on independent sample T-tests. See Figure 1. Gender vs. VAS (Rest, Active) for details.

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
6 Months VAS rest vs Gender	**Equal variances not assumed**	4.212	.050	.834	26.994	.411	.3110	.3728	-.4539	1.0759
6 Months VAS w/ activity vs Gender	**Equal variances assumed**	.485	.492	-.243	28	.810	-.2105	.8671	-1.9867	1.5656

Figure 1: Gender vs. VAS (Rest, Active) Independent Sample Tests.

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However, a statistically significant correlation was found between Age and the Pre-injection VAS (resting) score (r=0.434, p=0.017), showing higher Pre-injection VAS (resting) scores for older patients. See Figure 2. Age vs. VAS Correlation Test Results for details.

Correlations					
		Age	**Pre-Inject VAS rest**	**Pre-Inject VAS w activity**	**6 Months VAS rest**
Pre-Inject VAS rest	**Correlation**	.434*			
	Sig. (2-tailed)	.017			
Pre-Inject VAS w activity	**Correlation**	.103	.362*		
	Sig. (2-tailed)	.589	.049		
6 Months VAS rest	**Correlation**	.079	.080	.148	
	Sig. (2-tailed)	.680	.676	.434	
6 Months VAS w activity	**Correlation**	-.042	-.167	.210	.548**
	Sig. (2-tailed)	.826	.377	.264	.002
*. Correlation is significant at the 0.05 level (2-tailed).					
**. Correlation is significant at the 0.01 level (2-tailed).					

Figure 2: Age vs. VAS Correlation Test Results.

Two-thirds of the patients received treatment for their right knee, and one-third received treatment for their left knee. Table 2 shows the details of patient gender versus injection (treatment) sight.

Injection Site	**Overall**	**Female**	**Male**
Sample Size	30	19	11
Right Knee	20	12	8
Left Knee	10	7	3

Table 2: Injection Sight vs. Gender Summary.

The Body Mass Index (BMI) for the patient population was 29.2 ± 7.0, range 18.0-50.2. Table 3 shows the details of BMI versus gender.

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BMI	Overall	Female	Male
Sample Size	30	19	11
MEAN BMI	29.2	26.9	33.1
Min BMI	18	18	23.8
Max BMI	50.2	39.3	50.2
Std. Dev.	6.97	5.54	7.71

Table 3: Patient BMI vs. Gender Summary.

A statistically significant correlation was found between BMI and the Pre-injection VAS (active) score (r=0.402, p=0.028), showing higher Pre-injection VAS (with activity) score for higher BMI patients. See Figure 3. BMI vs. VAS Correlation Test Results for details.

Correlations					
		BMI	**Pre-Inject VAS rest**	**Pre-Inject VAS w/activity**	**6 Months VAS rest**
Pre-Inject VAS rest	**Correlation**	-.076			
	Sig. (2-tailed)	.691			
Pre-Inject VAS w activity	**Correlation**	.402*	.362*		
	Sig. (2-tailed)	.028	.049		
6 Months VAS rest	**Correlation**	.017	.080	.148	
	Sig. (2-tailed)	.931	.676	.434	
6 Months VAS w activity	**Correlation**	.212	-.167	.210	.548**
	Sig. (2-tailed)	.260	.377	.264	.002
*. Correlation is significant at the 0.05 level (2-tailed).					
**. Correlation is significant at the 0.01 level (2-tailed).					

Figure 3: BMI vs. VAS Correlation Test Results.

Mean VAS scores (resting) improved from 1.95 to 0.83 over 6 months (p<0.001), while mean VAS scores (with activity) improved from 6.28 to 2.87 (p<0.001) for the same period figure 4. ANOVA tests with Tukey HSD Analysis were conducted for VAS at rest scores over the 6-month period and VAS with activity scores over the 6-month period. Results from those analyses revealed:

- Mean VAS scores with activity were statistically different (higher) than the mean VAS scores at rest for every time interval,
- When comparing the mean VAS scores with activity (Figure 4), there was a decrease in the mean for VAS with activity scores after the injection:

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Mean vas score for this PERIOD	Is statistically different from the mean vas score for these periods							
	VAS_PRE	VAS_1HR*	VAS_1D	VAS_1WK	VAS_2WK	VAS_2MO	VAS_3MO	VAS_6MO
VAS_PRE		X	X	X	X	X	X	X
VAS_1HR*	X					X	X	X
VAS_1D	X							
VAS_1WK	X							
VAS_2WK	X							
VAS_2MO	X	X						
VAS_3MO	X	X						
VAS_6MO	X	X						

Table 4: Mean VAS Score (with Activity) Comparisons.

*A 1-hour evaluation with activity was not recorded; this comparison is an at rest score to scores with activity.

- The p-value for the ANOVA for VAS scores with activity was 1.18 x 10^{-15}.
- Comparing the mean VAS scores at rest revealed that the mean VAS score pre-injection was statistically different (higher) than the mean VAS scores at all other time intervals, but there was no statistical difference in the means for all the post injection scores. Overall, there is a decrease in the mean for VAS at rest scores after the injection, and
- The p-value for the ANOVA for VAS scores with at rest was 0.000561.

Graphical representation of the Mean Plots with 95% CI for VAS scores (at rest and with activity) is shown in Figure 4. In addition, ANOVA test results for the VAS scores (at rest and with activity) over time are provided in Figure 5 and Figure 6.

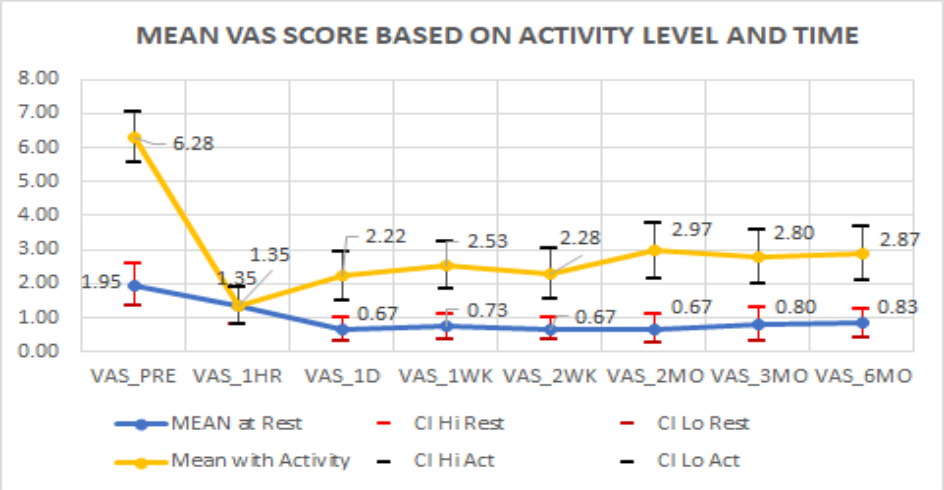

Figure 4: Mean Plots of VAS Scores (Resting and With Activity) with 95% CI.

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Anova: Single Factor		*VAS Scores at Rest*				
Summary						
Groups	Count	Sum	Average	Variance	Std. Error	Std. Dev
VAS_PRE-REST	30	58.5	1.95	3.092241	0.315656	1.728921
VAS_1HR	30	40.5	1.35	2.55431	0.286889	1.571358
VAS_1D REST	30	20	0.666667	0.91954	0.172133	0.942809
VAS_1WK REST	30	22	0.733333	1.081609	0.186687	1.022524
VAS_2WK REST	30	20	0.666667	0.850575	0.165552	0.906765
VAS_2MO REST	30	20	0.666667	1.402299	0.212568	1.164283
VAS_3MO REST	30	24	0.8	1.958621	0.251219	1.375984
VAS_6MO REST	30	25	0.833333	1.367816	0.209938	1.149879
Anova						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	44.5	7	6.357143	3.844946	0.000561	2.049195
Within Groups	383.5833	232	1.653376			
Total	428.0833	239				

Figure 5: ANOVA Results for VAS at Rest Scores over Time.

Anova: Single Factor		VAS Scores with Activity				
Summary						
Groups	Count	Sum	Average	Variance	Std. Error	Std. Dev
VAS_PRE w/ACTIVITY	30	188.5	6.283333	4.49454	0.380558	2.0844
VAS_1HR	30	40.5	1.35	2.55431	0.286889	1.571358
VAS_1D w/ACTIVITY	30	66.5	2.216667	4.184195	0.367184	2.011149
VAS_1WK w/ACTIVITY	30	76	2.533333	3.791954	0.34955	1.914564
VAS_2WK w/ACTIVITY	30	68.5	2.283333	4.477299	0.379827	2.080398
VAS_2MO w/ACTIVITY	30	89	2.966667	5.395402	0.416955	2.283759
VAS_3MO w/ACTIVITY	30	84	2.8	5.062069	0.40387	2.212088
VAS_6MO w/ACTIVITY	30	86	2.866667	5.067816	0.404099	2.213343
Anova						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	445.3625	7	63.62321	14.531	1.18E-15	2.049195
Within Groups	1015.8	232	4.378448			
Total	1461.163	239				

Figure 6: ANOVA Results for VAS with Activity Scores over Time.

The Mack-Wolfe Test is a non-parametric technique used to test for a "U" or "Umbrella" shape in the median (i.e., a peak or valley). It works even when the curve is very non-symmetrical about the valley (i.e., when a quadrative regression would not fit well). Execution of the Mack-Wolfe Test on the VAS scores revealed that there was strong evidence of a valley in the VAS (resting) score median at 2 months and a valley in the VAS (with activity) score median at 2 weeks. See Figures 7 and 8 for graphical representation of the Mack-Wolfe Test results for the VAS scores at rest and with activity, respectively.

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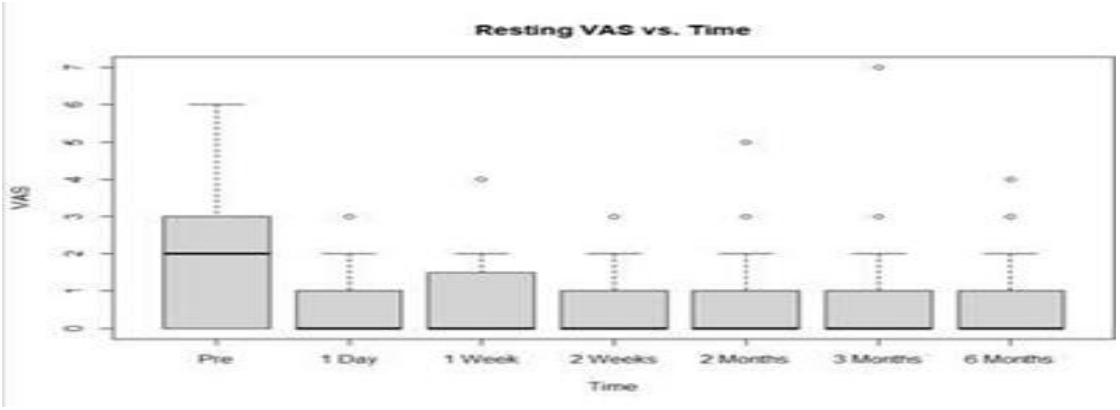

Figure 7: Mack-Wolfe Test Results for VAS (at rest) Scores vs. Time Since Injection. data: x and g Ap*=-3.0623, p-value=0.008 alternative hypothesis: theta_1<=...<=theta_p>=... >=theta_k, p=5 (the fifth bar graph).

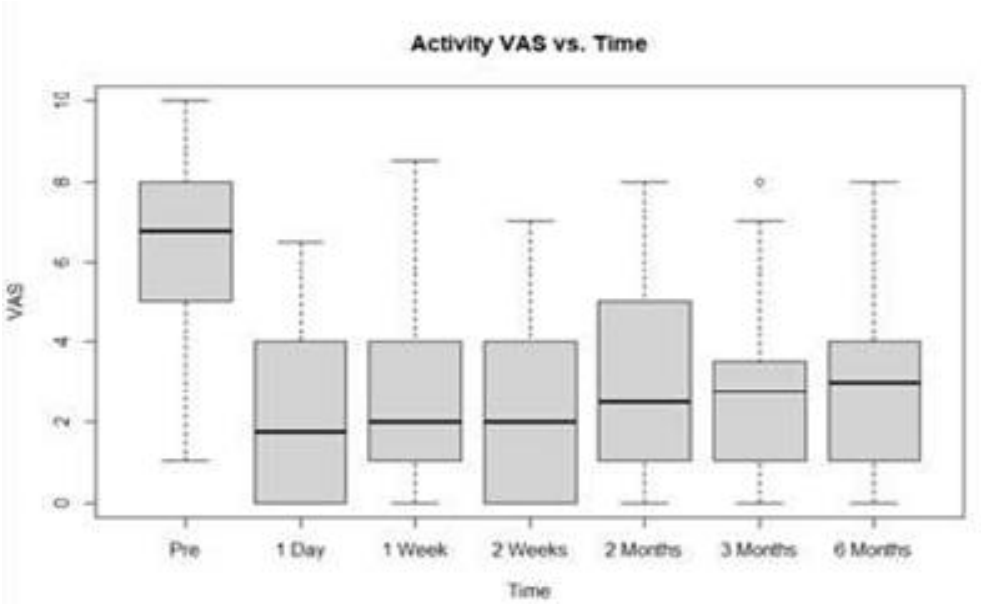

Figure 8: Mack-Wolfe Test Results for VAS (with activity) Scores vs. Time Since Injection. data: x and g Ap*=1.9614, p-value=6e-04 alternative hypothesis: theta_1<=...<=theta_p>=...>=theta_k, p=4 (the fourth bar graph.

Plotting VAS scores over time revealed a slow linear increase with much uncertainty (p=.1972), suggesting further data needs to be collected over a longer period to draw a strong conclusion; however, this model suggests it would take an estimated 1162 days (3 years, 2 months) to return to Pre-Injection VAS with activity scores without further intervention. (See Figure 9).

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ANOVA for Linear model

Response 1: Activity VAS

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	7.86	1	7.86	1.71	0.1927	not significant
A-Time (Days)	7.86	1	7.86	1.71	0.1927	
Residual	818.42	178	4.60			
Lack of Fit	7.03	4	1.76	0.3770	0.8249	not significant
Pure Error	811.38	174	4.66			
Cor Total	826.28	179				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 1.71 implies the model is not significant relative to the noise. There is a 19.27% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case there are no significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 0.38 implies the Lack of Fit is not significant relative to the pure error. There is a 82.49% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Figure 9: Linear Analysis of VAS Scores with Activity and Estimate of Time to Return to Pre-Injection VAS Scores.

Estimating Time to Return to Pre-Injection VAS Scores

Visually, from Day 1 post injection it appears that there is a slow increase in VAS over time. Therefore, a linear model was fit. The p-value of model=0.1972 indicating lots of uncertainty in the slope estimation suggesting data needs to be collected over a longer period of time (ex. 2 years), however it gives us a ballpark estimate of the longevity of this treatment. A quadratic model was tried but it did not improve the model fit. The Model is below:

Activity VAS=**2.416+0.003326** (*Days Post Injection*)

Given that the average Pre-VAS score is 6.28333 we estimate that it takes about 1162 days post-injection (3 years and 2 months) for VAS scores to return to back to pre-Injection levels, on average.

Days to Return to Pre Injection Scores =*ActivityVAS*–2.416/.003326=6.28333–2.416/ 0.003326 =1,162 *Days*.

WOMAC-measured physical function scores improved from 44.7 to 18.5 over the 6-month review period (p<.001). Table 5 summarizes WOMAC data over time.

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	Pre-Inject WOMAC	2 Weeks WOMAC	2 Months WOMAC	3 Months WOMAC	6 Months WOMAC
N	30	30	30	30	30
Min	11	0	0	0	0
Max	85	62	81	68	65
MEAN	44.73	23	22.63	20.13	18.5
STD DEV	20.42	19.48	20.65	17.67	17.33
Std. Err of Means	3.729	3.556	3.771	3.226	3.164

Table 5: Summary of Womac Data Over Time.

ANOVA for WOMAC scores over the 6-month review period revealed that the mean Pre-injection WOMAC score is statistically different from the mean WOMAC scores at 2 weeks, 2 months, 3 months, and 6 months. This is supported by a p-value of $1.34x10^{-6}$. Otherwise, the mean WOMAC scores at 2 weeks, 2 months, 3 months, and 6 months are NOT statistically different from each other. Graphical representation of the Mean Plots with 95% CI for WOMAC scores is shown in Figure 10. In addition, Paired Sample test results for the WOMAC score over time is provided in Figure 11.

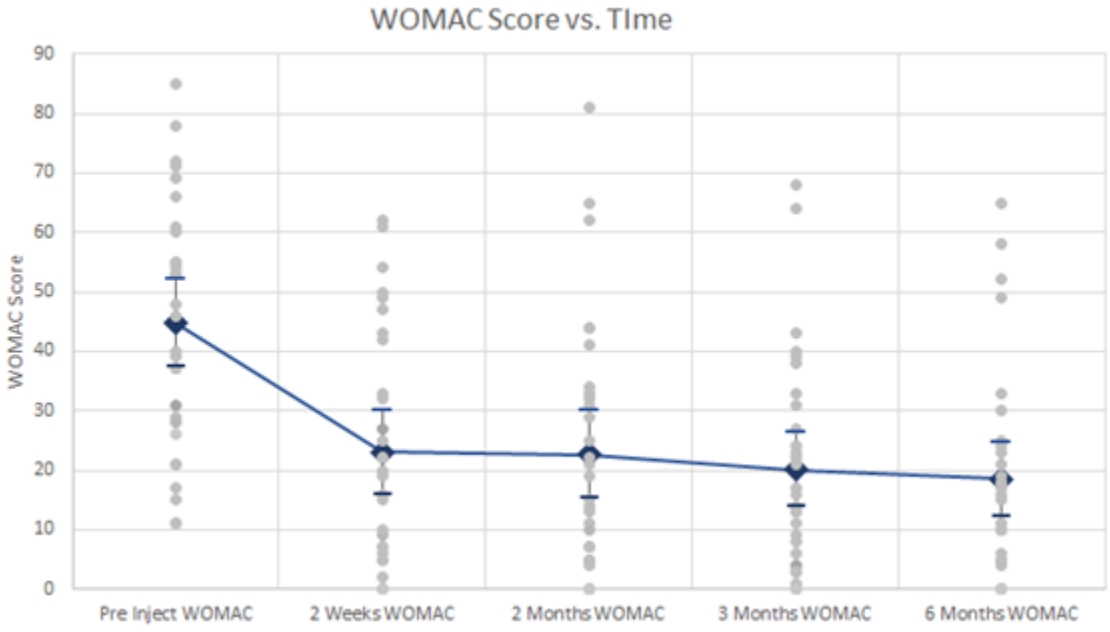

Figure 10: Mean Plot of WOMAC Scores with 95% CI.

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Paired Samples Test									
		Paired Differences					t	df	Sig (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Inject VAS rest - 6 Months VAS rest	1.1167	2.0328	.3711	.3576	1.8757	3.009	29	.005
Pair 2	Pre-Inject VAS w activity - 6 Months VAS w activity	3.4167	2.7483	.5018	2.394	4.4429	6.809	29	.000
Pair 3	Pre-Inject WOMAC - 6 Months WOMAC	26.233	20.397	3.724	18.617	33.850	7.044	29	.000

Figure 11: Paired Sample Test Results for WOMAC Scores over Time.

Drug / Drug Combinations Used	# Taking MEDS_ Pre	# Taking MEDS_ 1WK	# Taking MEDS_ 2WK	# Taking MEDS_ 2MO	# Taking MEDS_ 3MO	# Taking MEDS_ 6MO
Acetaminophen	1	0	0	0	1	1
Anticonvulsant+ Muscle Relaxant	1	0	0	1	0	0
NSAID	7	1	0	3	1	2
NSAID or Acetaminophen	3	2	3	2	1	1
opioid + Anticonvulsant+ NSAID	1	1	1	1	1	1
Opioid-NSAID + Acetaminophen	1	1	0	1	1	1
Opioid	3	2	2	1	1	1
Opioid-NSAID + NSAID or Acetaminophen	0	0	0	1	1	1
Opioid, NSAID, Acetaminophen, EMU	1	0	0	1	1	1
Phyto cannabinoid	0	0	0	0	1	1
Grand TOTAL	18	7	6	11	9	10

Table 6. Summary of Drug Types Used by Patients Throughout Study.

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Overall, of the patients who used medications at the beginning of the study (18), 77.8% of them reduced or eliminated medication use.

Table 6 shows the number of patients using a particular drug/drug combination at each point in the study period:

Analysis of medication use by patients over the study period revealed

- 30%(9) of the patients studied never took medication throughout the course of the study period,
- 13.3%(4) of the patients studied continued to take medications throughout the entire course of the study period,
- 20%(6) of the patients studied went from daily medication use to no medication use by the end of the study period,
- 13.3%(4) of the patients studied reduced their medication frequency from daily to occasional by the end of the study period,
- 13.3%(4) of the patients studied reduced their medication frequency from occasional to none by the end of the study period,
- One person went from using no medications to using CBD oil on the knee at the end of the study period. Although that patient had decreasing WOMAC and VAS at rest scores throughout the study period, their VAS with activity score did not change significantly throughout the study period (VAS range: 3-4).
- One person went from using no medications to occasionally using Tylenol at the end of the study. This patient's VAS and WOMAC scores remained consistent throughout the study.
- One person went from using no medications to using Tylenol or Ibuprofen daily. This person's VAS and WOMAC scores initially decreased after the injection, but increased back up over time to pre-injection scores, and
- The number of patients using opioids decreased by 16.7% from pre-injection to 6-month follow-ups, and the number of patients using NSAID decreased by 46.1% from pre-injection to 6-month follow. (See Figure 12).

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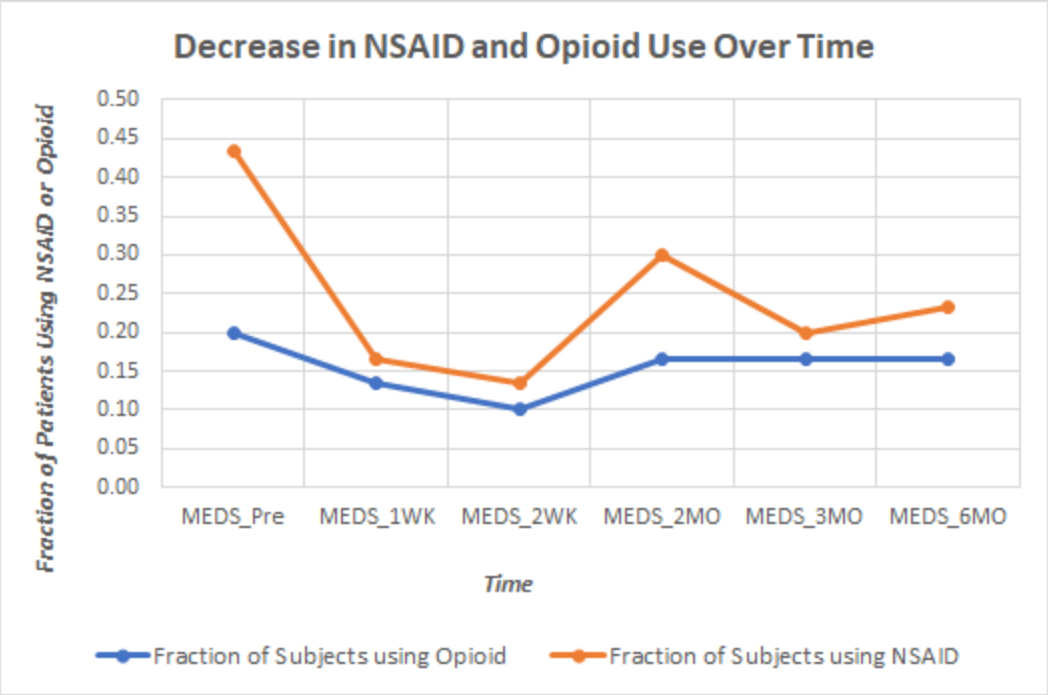

Figure 12: NSAID and opioid use after treatment.

Medication data was made binary at time 6 months (any medicine vs. none).

A Welch two sample t-test showed strong evidence of a difference for VAS with activity scores and those using medications; that is, subjects using medications reported higher VAS active scores (p-value=0.064).

No serious adverse events were reported throughout 6 months. Between 2 weeks and 2 months, one patient fell and reinjured the knee and was reinjected at 5 months. Late intervention was without complications. All three outcomes depict a consistent result with significant improvement. Extended follow-up is expected at 360 days for all patients.

Discussion

Chart review of 30 patients with joint pain revealed the clinical benefits of injecting UCT for knee pain. Improvement in pain, physical function, reduction in medications (opioid use and NSAID) use began promptly after treatment and was sustained over at least a 2-week period, in most cases extending to 6 months. Given that opioid use is a CDC national epidemic secondary to dependency, overdose, and abuse, leading to reluctance in prescribing and difficulty in managing patients on opioid, UCT offers an important alternative [9, 10].

In many instances, patients were physically limited and deconditioned secondary to their pain. Counseling on weight reduction and transition to

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physical activity is a critical adjunctive measure in achieving improvement in normal activities of daily living. Prior to treatment, many patients exhibited increased BMI as well as were physically deconditioned. This, in fact, is a factor that may complicate or hinder recovery and functional restoration. Therefore, it is crucial that patients be counseled on reduction of BMI for sustained outcomes.

This study demonstrated that the injections were effective for 6 months, however we have continued to follow these patients over the course of 2 years. We have observed that many go beyond 24 months of relief compared to baseline with just one injection. This is consistent with extrapolation projection as demonstrated in our ANOVA linear model (Figure 9).

While the cost of a single steroid injection is less expensive than a UCT injection, in a given year, a patient may receive up to four injections of steroid which increases morbidity associated with each injection. This is in comparison with UCT which would require only one injection and has not been associated with any adverse events or increased morbidity and may provide up to 2 years of relief.

While this review supports safety and efficacy, its limitation is that it is not a prospective randomized study against a control depicting the standard of care. It is extremely important that additional studies and confirmation of data substantiating pain relief and improved function be investigated in patients with arthritic joint pain before acquiescing to joint replacement.

Conclusion

UCT injection reduces pain, physical disability, medication usage (specifically opioid and NSAID usage) in patients suffering from knee pain for at least 6 months. As a result, this would allow patients to postpone or delay joint replacement until BMI and physical condition are optimized.

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