Wharton Jelly derived-Mesenchymal Stromal Cell (WJ-MSC) therapy in orthopedics: description of evidence and experience in the treatment of shoulder overuse injuries.

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ABSTRACT

Statement of the Problem.

Shoulder pain syndrome is a multifaceted condition that requires a comprehensive approach for effective management. This approach should encompass both the conventional orthopedic perspective and regenerative medicine strategies. The direct and indirect costs associated with the management of shoulder pain in primary care can be substantial, including expenses related to sick leave, medication, absenteeism from work and sports, sleep disturbances, financial burden, and delayed functional return to sports practice, among other consequences.

Shoulder injuries, particularly those caused by overuse such as rotator cuff tendinopathy (RCT), impingement, labrum injuries, and bursitis, can significantly impact the quality of life of athletes and the wider population. Furthermore, even after arthroscopic surgery, re-tears can occur, leading to ongoing shoulder pain and loss of function. Managing these injuries solely through arthroscopic repair and physical therapy can be challenging in orthopedics due to issues such as poor healing, adhesion formation, and fatty tissue accumulation.

The above justifies the need for research and innovation in the development of ortho-regenerative therapies that contribute, in a complementary manner to conventional orthopedic management, to the reduction of pain and functional limitation.

Mesenchymal stromal cells (MSCs) are a variety of ortho-biologicals that have demonstrated considerable potential in promoting tendon remodeling and fibrocartilage formation, leading to enhanced biomechanical strength in the tendon. MSCs are characterized by their remarkable proliferation capacity, potent paracrine action, and pluripotency for the differentiation into various cell types. Moreover, the extracellular vesicles originating from MSCs can facilitate collagen production, reduce inflammation, and minimize adhesion formation by transporting regulatory proteins and microRNAs. Consequently, MSC-based therapy shows great promise as a therapeutic strategy for the healing of rotator cuff.

Despite the significant surgical advancements to address rotator cuff tears, the effective connection between tendon tissue and bone remains a persistent challenge. However, MSCs offer a glimmer of hope, as they have demonstrated remarkable paracrine, anti-inflammatory, and angiogenic benefits. The MSC-based therapy, which entails growth factors and specific scaffolds, aims to enhance the biomechanical strength of the rotator cuff and promote fibrocartilage formation. While the studies have shown great promise, more research is necessary to evaluate the long-term safety and efficacy of the therapy in shoulder and elbow injuries, including clinical trials and observational studies.

For this reason, we are delighted to share the experience of a clinical and research center that has treated patients with shoulder overuse injuries (SOI) such as RCT, impingement syndromes, labrum injuries, and bursitis using Wharton Jelly Derived-Mesenchymal Stromal Cells (WJ-MSC). These MSCs were delivered locally, both into the glenohumeral joint and by intratendinous injections.

Methodology.

One retrospective cohort was analyzed according to the effects following therapy based on WJ-MSC in SOI patients. Ethical approval was obtained by an institutional review board (IRB). Patients signed an informed consent form.

SOI patients were treated with a single dose of $70x10^6$ WJ-MSC per target shoulder (MSCs were delivered $20x10^6$ by intra-articular and $50x10^6$ by intratendinous injections) by an ultrasound-guided procedure. Previously, the allogeneic WJ-MSCs

were expanded in a culture medium supplemented with 10% human platelet lysate (hPL) up to passage 7. Cell marker expression and in vitro differentiation to mesodermal lineage and microbiological tests were verified.

Clinical outcomes were measured by the Short-Form12 questionnaire, Visual-Analog-Scale (VAS), and Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at baseline (pre-therapy time), followed by 3-, 6- and 12-month measurements.

Following previous literature, a responder to therapy was defined as a patient with a reduction of at least 2 points or more in the VAS score and a reduction of 10 points or more in the DASH score at the last available follow-up to baseline (pre-therapy scores).

Findings.

From November 2021 to May 2023, 88 patients were treated at the institution and met the eligibility criteria for therapy, of which all responded to the 6-month follow-ups, and 25 (28.41%) completed the questionnaires at 12-month follow-ups. The mean age was 52.36 years old (SD 13.85). The mean body mass index (BMI) was 26.92 (SD 4.30). 84% (n= 74) were men. The most frequent country of origin was the USA (n= 68, 77%). 56% (n= 49) of patients had both shoulders treated, 20% (n= 18) received WJ-MSC in the left shoulder only and 25% (n= 21) in the right shoulder only. 47/88 patients (53.41%) responded favorably to therapy at 6 months, and 18/25 (72%) responded to therapy at 12 months.

The 6-month VAS was significantly reduced compared to baseline (median baseline VAS= 5, IQR 2.25, median 6m VAS= 2, IQR 4, *p< 0,001* Wilcoxon W test, p= 0,018 Shapiro-Wilk assumption-normality test), as was the 12-month VAS (median baseline VAS= 5, IQR 2.25, median 12m VAS= 2, IQR 3, *p< 0,001* Wilcoxon W test, *p= 0,042* Shapiro-Wilk assumption-normality test). The 6-month DASH was significantly reduced compared to baseline (median baseline DASH= 31.25, IQR 24.99, median 6m DASH= 13.33, IQR 20.21, *p< 0,001* Wilcoxon W test, *p< 0,001* Shapiro-Wilk assumption-normality test), as was the 12-month DASH (median baseline DASH= 31.25, IQR 24.99, median 12m DASH= 11.67, IQR 18.34, *p< 0,001* Wilcoxon W test, *p= 0,011* Shapiro-Wilk assumption-normality test).

The 6-month SF-12 Physical score was significantly increased compared to baseline (median baseline SF12-physical= 57.14, IQR 35.72, median 6m SF12-physical= 64.29, IQR 35.71, *p <0,001* Wilcoxon W test, *p= 0,047* Shapiro-Wilk assumption-normality test), as did the 12-month SF-12 Physical score (mean baseline SF12-physical= 53.40, SD 21.50, mean 12m SF12-physical= 70.78, SD 21.06, *p= 0,008* t-paired test, *p= 0,064* Shapiro-Wilk assumption-normality test) and the 6-month SF-12 Mental score (median baseline SF12-mental= 61.90, IQR 38.09, median 6m SF12-mental= 76.19, IQR 40.48, *p <0,001* Wilcoxon W test, *p= 0,011* Shapiro-Wilk assumption-normality test).

No adverse events were noted.

Conclusion and significance.

This study´s findings contribute to our understanding of the therapeutic benefits of WJ-MSC in SOI-diagnosed patients, who sought treatment for failure of conservative therapy and pain and functional limitation. The improvements evidenced involve changes in the patient's quality of life. There were no serious adverse events reported, demonstrating that this therapy is safe.

BIOGRAPHY



Alejandro Ramirez is a medical doctor and specialist in sports medicine who graduated from the University of Antioquia, Colombia. He has worked as a sports doctor in regional teams and Colombian national cycling and soccer leagues. He has extensive knowledge in the treatment and rehabilitation of musculoskeletal injuries derived from sports and similar activities. He is currently one of the pioneering Latin American doctors in ortho-regenerative therapies, with more than 10 years of experience in applying treatments for osteoarticular injuries, especially from WJ-MSC. Over the past few years, he has honed his skills in musculoskeletal interventionism, training in ultrasound-guided procedures at the MSKUS Institute in Virginia, USA., and has also received hands-on training at the OAA Medical Center in Allentown, Pennsylvania, USA., in the orthopedic service.

ABOUT RESEARCH TOPIC

Shoulder pain, the third most common complaint in primary care according to the British Elbow and Shoulder Society (BESS) guidelines, encompasses a variety of syndromes affecting the shoulder joint and tendons. The anatomical complexity of this region makes it susceptible to injuries, inflammations and degenerative pathologies, representing a significant cause of pain and disability. With around 4.5 million visits and substantial healthcare costs, shoulder pain affects all ages, from 5% to 10% in those under 20 years of age to more than 60% in those over 80 years of age. Treatment begins with conservative approaches, such as changes in physical activity and physical therapy, but in severe cases, surgery, including procedures such as total shoulder arthroplasty, may be necessary. Ortho-biological regenerative therapies, particularly the application of MSCs, have emerged as promising for accelerating the repair of damaged tendon tissues, gaining acceptance as a treatment option in the orthopedic, sports and patient communities.

ABOUT INSTITUTION

BioXcellerator is a company headquartered in the USA and Colombia, specializing in WJ-MSC and other regenerative medicine therapies. The company is dedicated to the research and development of advanced medical treatments based on WJ-MSC to address a variety of medical conditions, injuries, and chronic diseases. BioXcellerator has excelled in the field of regenerative medicine and has worked on the application of these therapies to treat conditions such as osteoarthritis, sports injuries, neurodegenerative diseases, autoimmune diseases and other health problems. The company has researched to evaluate the safety and efficacy of these treatments.

REFERENCES

1. Nourissat G, Diop A, Maurel N, Salvat C, Dumont S, Pigenet A, et al. Mesenchymal Stem Cell Therapy Regenerates the Native Bone-Tendon Junction after Surgical Repair in a Degenerative Rat Model. PLOS ONE. 2010;5(8):e12248.
2. Costa-Almeida R, Calejo I, Gomes ME. Mesenchymal Stem Cells Empowering Tendon Regenerative Therapies. Int J Mol Sci. 2019;20(12):3002.
3. Hevesi M, LaPrade M, Saris DBF, Krych AJ. Stem Cell Treatment for Ligament Repair and Reconstruction. Curr Rev Musculoskelet Med. 2019;12(4):446-50.
4. Russo E, Caprnda M, Kruzliak P, Conaldi PG, Borlongan CV, La Rocca G. Umbilical Cord Mesenchymal Stromal Cells for Cartilage Regeneration Applications. Stem Cells Int. 2022;2022:e2454168.

5. Trebinjac S, Gharairi M. Mesenchymal Stem Cells for Treatment of Tendon and Ligament Injuries-clinical Evidence. Med Arch. 2020;74(5):387-90.
6. Ackerman IN, Fotis K, Pearson L, Schoch P, Broughton N, Brennan-Olsen SL, et al. Impaired health-related quality of life, psychological distress, and productivity loss in younger people with persistent shoulder pain: a cross-sectional analysis. Disabil Rehabil. 2022;44(15):3785-94.
7. Parikh N, Martinez DJ, Winer I, Costa L, Dua D, Trueman P. Direct and indirect economic burden associated with rotator cuff tears and repairs in the US. Curr Med Res Opin. 2021;37(7):1199-211.
8. Holtedahl R, Bøe B, Brox JI. The clinical impact of retears after repair of posterosuperior rotator cuff tears: a systematic review and meta-analysis. J Shoulder Elbow Surg. 2023;32(6):1333-46.
9. Mora MV, Ibán MAR, Heredia JD, Laakso RB, Cuéllar R, Arranz MG. Stem cell therapy in the management of shoulder rotator cuff disorders. World J Stem Cells. 2015;7(4):691-9.
10. Liu F, Meng Q, Yin H, Yan Z. Stem Cells in Rotator Cuff Injuries and Reconstructions: A Systematic Review and Meta-Analysis. Curr Stem Cell Res Ther. 2019;14(8):683-697. doi: 10.2174/1574888X14666190617143952. Erratum in: Curr Stem Cell Res Ther. 2020;15(7):646.
11. Jo CH, Chai JW, Jeong EC, Oh S, Kim PS, Yoon JY, et al. Intratendinous Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Rotator Cuff Disease: A First-In-Human Trial. Stem Cells. 2018 Sep 1;36(9):1441–50.
12. Cho WS, Chung SG, Kim W, Jo CH, Lee SU, Lee SY. Mesenchymal Stem Cells Use in the Treatment of Tendon Disorders: A Systematic Review and Meta-Analysis of Prospective Clinical Studies. Ann Rehabil Med. 2021 Oct 31;45(5):410–410.
13. Mirghaderi SP, Valizadeh Z, Shadman K, Lafosse T, Oryadi-Zanjani L, Yekaninejad MS, et al. Cell therapy efficacy and safety in treating tendon disorders: a systemic review of clinical studies. J Exp Orthop. 2022 Aug 30;9(1):85.
14. Havlas V, Kotaška J, Koníček P, Trč T, Konrádová Š, Kočí Z, et al. [Use of cultured human autologous bone marrow stem cells in repair of a rotator cuff tear: preliminary results of a safety study]. Acta Chir Orthop Traumatol Cech. 2015;82(3):229–34.
15. Hernigou P, Flouzat Lachaniette CH, Delambre J, Zilber S, Duffiet P, Chevallier N, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. Int Orthop. 2014;38(9):1811–8.