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Chondrogen™ Injection for Knee Osteoarthritis using Stem Cells from Wharton's Jelly

(Suntikan Kondrogen™ untuk Osteoartritis Lutut menggunakan Sel Stem daripada Jeli Wharton)

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ABSTRACT

Knee osteoarthritis constitutes a prominent source of pain and functional impairment, with its prevalence showing a consistent yearly increase. Current therapeutic strategies primarily revolve around addressing symptoms and, in severe cases, resorting to prosthetic joint replacement, yet they fail to target the underlying pathophysiological mechanisms driving degeneration. In this context, there is a growing interest in investigating mesenchymal stem cell (MSC) therapy as a potential remedy for osteoarthritis. Among the various MSC types under scrutiny, using Wharton's Jelly-derived mesenchymal stem cells (WJ-MSCs) has garnered relatively scant attention. The present study represents a Phase I clinical trial of an open-label, single-arm design within this context. Its principal aim is to assess the safety and efficacy of administering mesenchymal stem cells derived from Wharton's Jelly via intra-articular injection for patients diagnosed with knee osteoarthritis. Throughout six months, this investigation discerned a statistically significant overall improvement in clinical presentation relative to baseline. This improvement manifested as reduced analgesic consumption, diminished Visual Analog Scale (VAS) scores (19.5 to 18.7 mm, $p = .00$), and augmented functional assessment scores, including the IKDC Score (enhanced from 62.2 to 100, $p = .00$), KOOS Symptoms and Stiffness subscales (elevated from 76.8% to 10.6%, $p = .00$), as well as KOOS Pain subscale (upgraded from 74.4% to 10.1%, $p = .00$). The study encouragingly reported no significant adverse effects during the observation period. However, upon radiographic evaluation, no significant alterations were observed in terms of deformity angle ($p = 0.957$) or medial ($p = 0.871$) and lateral ($p = 0.520$) compartment joint space widths. To further elucidate the comparative efficacy of this treatment, it is prudent to contemplate a randomised controlled trial comparing it against the conventional hyaluronic acid regimen, thereby contributing to an enriched understanding of its therapeutic potential.

Keywords: Knee; mesenchymal stem cell; osteoarthritis; percutaneous injection; Wharton's Jelly

ABSTRAK

Osteoartritis lutut merupakan sumber kesakitan dan kemerosotan fungsi yang ketara dengan kelazimannya menunjukkan peningkatan tahunan secara tekal. Strategi terapeutik pada masa ini kebiasaannya berkisar untuk menangani gejala dan dalam kes yang teruk, menggunakan pengganti sendi prostetik, namun ia gagal menyasarkan mekanisme patofisiologi yang menyebabkan kemerosotan. Dalam konteks ini, terdapat minat yang semakin meningkat untuk mengkaji terapi sel stem mesenkima (MSC) sebagai penyembuh berpotensi untuk osteoartritis. Antara pelbagai jenis MSC yang dikaji, penggunaan sel stem mesenkima (WJ-MSC) yang diperoleh daripada Jeli Wharton kurang mendapat perhatian. Kajian semasa ini mewakili percubaan klinikal Fasa I bagi label terbuka, reka bentuk lengan tunggal dalam konteks ini. Matlamat utamanya adalah untuk menilai keselamatan dan keberkesanan mentadbir sel stem mesenkima yang diperoleh daripada Jeli Wharton melalui suntikan intra-artikul untuk pesakit yang didiagnosis dengan osteoartritis lutut. Sepanjang enam bulan, kajian ini melihat peningkatan keseluruhan yang ketara secara statistik dalam

pembentangan klinikal berbanding garis dasar. Peningkatan ini dimanifestasikan sebagai pengurangan penggunaan analgesik, pengurangan skor Skala Analog Visual (VAS) (19.5 hingga 18.7 mm, p = .00) dan skor penilaian fungsian yang ditambah, termasuk Skor IKDC (ditingkatkan daripada 62.2 kepada 100, p = .00), subskala Simptom KOOS dan Kekakuan (dinaikkan daripada 76.8% kepada 10.6%, p = .00) serta subskala Sakit KOOS (dinaik taraf daripada 74.4% kepada 10.1%, p = .00). Kajian ini melaporkan tiada kesan buruk yang ketara semasa tempoh pemerhatian. Walau bagaimanapun, selepas penilaian radiografi, tiada perubahan ketara diperhatikan dari sudut kecacatan (p = 0.957) atau medial (p = 0.871) dan sisi (p = 0.520) kelebaran petak ruang sendi. Untuk penjelasan lebih lanjut tentang keberkesanan perbandingan rawatan ini, adalah bijak mempertimbangkan percubaan terkawal rawak dan membandingkannya dengan rejimen asid hialuronik konvensional yang menyumbang kepada lebih pemahaman tentang potensi terapeutiknya.

Kata kunci: Jeli Wharton; lutut; osteoartritis; sel stem mesenkima; suntikan perkutaneus

Introduction

Osteoarthritis of the knee is the most prevalent form of arthritis, characterised by pain, stiffness, and impaired function. It is also a primary cause of disability among non-institutionalised individuals (Helmick et al. 2008; Toyoda et al. 2021). The literature describes over 50 different treatments for this condition, including pharmacological, non-pharmacological, and surgical techniques (Zhang et al. 2008). However, with the exception of joint replacement, most current treatments offer only modest but clinically significant benefits and may result in significant adverse effects or expenses (Lohmander & Roos 2007). Furthermore, these treatments are generally designed to alleviate pain, improve joint function, and reduce impairment, rather than regenerate articular cartilage. This is noteworthy given that osteoarthritis is typified by extracellular matrix degradation and subsequent articular cartilage loss (Jo et al. 2003; Zhu, Wu & Qu 2021). Various methods, such as cell therapy and tissue engineering, have been attempted to regenerate articular cartilage.

The therapeutic benefits of chondrocytes have garnered significant attention in the field of medical research (Knutsen et al. 2007; Grande et al. 1989; Lu et al. 2020; Vanlauwe et al. 2011). However, chondrocyte implantation has limitations, including a two-stage surgical procedure that may lead to additional cartilage damage and degeneration. Furthermore, chondrocyte dedifferentiation during culture is a concern that can result in the formation of fibrocartilage instead of hyaline cartilage (Gurer et al. 2018; Lee et al. 2000; Vanlauwe et al. 2011). Additionally, this approach is only applicable to localised cartilage defects arising from injury and cannot be used to address generalised cartilage loss caused by osteoarthritis (Gurer et al. 2018; Knutsen et al. 2007). As a result, there is a pressing need for a new, innovative approach to regenerate cartilage in patients with osteoarthritis.

Mesenchymal stem cells (MSCs) have been investigated as a potential method for regenerating cartilage, particularly in cases of articular cartilage damage. Unlike chondrocyte implantation, the use of MSCs for cartilage regeneration is still experimental in nature (Matsumoto et al. 2010; Wakitani et al. 2002; Zhu, Wu & Qu 2021). Recent literature has highlighted the results of direct intra-articular injections of MSCs into the knee joint for the treatment of isolated defects or more extensive cartilage loss in cases of osteoarthritis (Al Faqeh et al. 2012; Arshi et al. 2020; Barrachina et al. 2020; Chang et al. 2011; Jiang et al. 2021; Mokbel et al. 2011). If this technique could be translated into clinical practice, it would offer significant benefits, such as avoiding complications associated with surgeries, including periosteal hypertrophy and ossification, immune response, and disease transmission caused by xenograft coverage. Furthermore, the simplicity and ease of use of the injection may result in improved therapeutic options, particularly for the elderly with comorbidities. Although there have only been a few case reports published on the subject, we conducted phase I clinical research as a proof-of-concept to evaluate the safety of direct intra-articular injection of MSCs. The present investigation aims to evaluate the safety of MSC injections in a limited patient sample, laying the groundwork for prospective larger-scale clinical trials.

Materials and Methods

Study design and patients

The investigation received endorsement from the UKM Research Ethics Committee (UKM PPI/111/8/JEP-2018-521) on December 28, 2018. This study is a phase I,

open-label, single-arm clinical trial that aims to evaluate the safety and effectiveness of Chondrogen™ injection in patients suffering from knee osteoarthritis. The target population consisted of individuals aged between 42 and 71 years old that were recruited between December 2018 and January 2019 at Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) in Kuala Lumpur. The participants were chosen based on the inclusion and exclusion criteria outlined in Table 1. Before participation, each selected patient was provided with and signed a written informed consent form. Out of the 11 patients in the trial, 8 received WJ-MSC injections in one knee, and 3 received injections in both knees. All the patients received baseline injections and were monitored for six months. The Chondrogen™ injection consisted of 15×10^6 cells in 2 mL of saline and was administered along with 2 mL or 20 mg equivalent of Biovisc™, a 3 million Dalton hyaluronic acid.

MSC CULTIVATION AND PREPARATION

Chondrogen™, a proprietary culture-expanded Wharton's Jelly-derived MSC (WJ-MSC), was prepared and characterised for this investigation at a National Pharmaceutical Regulatory Agency (NPRA) Grade A laboratory Putrajaya, a subsidiary of Meluha Life Sciences Sdn. Bhd. In brief, therapy was performed in a Good Manufacturing Practice (GMP)-type laboratory certified by the International Organization for Standardisation 14644-1:1999E, which also adhered to the Cellular and Gene Therapy Products and Good Tissue Practice (GTP) guidelines.

The WJ-MSCs were obtained from umbilical cords of full-term human placentas by elective caesarean section after informed consent from healthy donors. They were aseptically stored in sterile phosphate-buffered saline (PBS) supplemented with 1% antibiotics. The umbilical cord blood was sent for HIV, Hepatitis B and C, Cytomegalovirus (CMV), and syphilis screening. The umbilical cord is sectioned into smaller pieces (approximately 2 cm per piece), and the blood vessels are removed and digested with collagenase to break down the extracellular matrix overnight. The collagenase was then neutralized by Complete Culture Media (CCM), and the cords were then transferred into a sterile T-flask and incubated for seven days (Figure 1).

The complete culture medium (CCM) is formulated with KnockOut DMEM (Gibco, Thermo Fisher) as its base, supplemented with carefully selected components. These include 1.25% Human Serum AB Plasma (Sigma), 1% GlutaMAX supplement (Gibco, Thermo Fisher), and Gentamicin (50 mg/mL) (Gibco, Thermo Fisher), with an addition of 1 mL per 1L of CCM. Furthermore, incorporating Human recombinant bFGF (50 ug/mL) (StemCell Technologies) is advised, with a recommended volume of 80 uL for each 1 L of CCM.

MSC CHARACTERISATION

The cultivation of Wharton's Jelly-derived Mesenchymal Stem Cells (WJ-MSCs) was conducted with meticulous monitoring at 48-hour intervals until they reached 80-90% confluence, indicating optimal growth. The WJ-MSCs were cultivated using a monolayer construct to ensure controlled and consistent expansion. An expected yield of approximately 15×10^6 WJ-MSCs was achieved after a seven-day incubation period. The cells were then carefully harvested and reseeded for seven days to

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Symptomatic knee osteoarthritis (defined by daily pain at the affected knee joint for at least three months before inclusion)	1. On anticoagulant therapy, e.g., warfarin or aspirin
2. Grade 2 to 3 Kellgren-Lawrence radiographic changes in the affected knee	2. Active skin infection over the knee
	3. Underlying inflammatory arthritis, e.g., gouty arthritis, rheumatoid arthritis, and psoriatic
	4. History or family history of malignancy or immunosuppressed

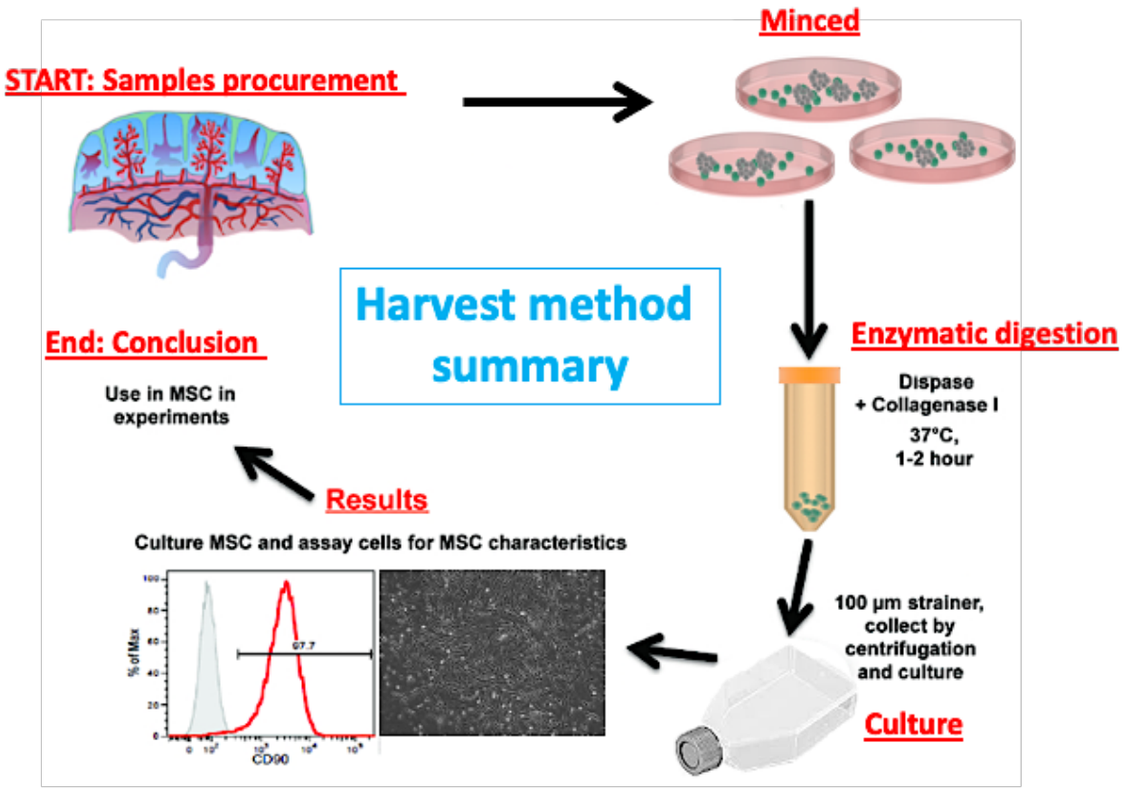

FIGURE 1. Preparation and characterization of Chondrogen™, a proprietary culture-expanded Wharton's Jelly-derived MSCs (WJ-MSCs) diagram

promote further propagation. At the critical stage of passage 3, the WJ-MSCs underwent characterisation following the stringent guidelines set forth by the International Society for Cellular Therapy (ISCT). The comprehensive characterisation of the cells involved an analysis of specific cell surface markers such as CD73, CD90, CD105, CD34, and CD45, which were determined to be present or absent using flow cytometry analysis.

In addition, the morphological characteristics of the cells were observed under a microscope, confirming the anticipated fibroblast-like morphology with a distinct spindle shape. Furthermore, differentiation assays were conducted to assess the potential of WJ-MSCs to differentiate into adipocytes, osteocytes, and chondrocytes, demonstrating their multipotent capacity as a critical aspect of their characterisation process. After being characterised, it is cryopreserved in a liquid nitrogen storage tank at −190 °C until needed. Before use, the cells are thawed, centrifuged, and resuspended within an infusion medium comprising 0.9% Sodium Chloride. They are then sealed, labelled, and packaged into syringes in preparation for administration to patients at a medical facility. The package is transferred to a carrier that includes an ice pack, thus maintaining a temperature range of 2 to 6 °C throughout the transport process.

INJECTION TECHNIQUE

The patient is lying supine with the knee flexed to 30 degrees. A lateral mid-patellar approach is used. After cleaning the intended injection area with povidone-iodine followed by alcohol 70%, the prefixed syringe with WJ-MSCs is injected using a 24-gauge needle. A plaster is applied after the injection. If both knees are affected, the other knee will also receive the injection. The patients are advised to return immediately to Pusat Perubatan Universiti Kebangsaan Malaysia Emergency Department if there is worsening knee pain, fever, and inability to move the knee. The researcher is to be informed of the admission.

OUTCOME MEASURES

The primary objective of the trial is to guarantee the safety of intra-articular injections using mesenchymal stem cells derived from Wharton's Jelly. Adverse events were closely monitored and meticulously documented at each visit, following the Common Terminology Criteria for adverse events to categorise them. These events, such as Arthralgia, Joint Swelling, Joint Stiffness, Injection-Site Joint Pain, Joint Effusion, Headache, and Peripheral Oedema, were extensively recorded for their occurrence and accompanied by precise dates to enable a comprehensive understanding of their temporal patterns. This rigorous approach ensured that the safety and well-being of the participants were given the utmost priority throughout the study, which allowed for a robust evaluation of the safety profile and tolerability of the percutaneously injected Wharton's Jelly-derived mesenchymal stem cells in individuals with knee osteoarthritis.

The secondary objective of the trial was to comprehensively evaluate the efficacy of the treatment using various clinical outcome measures at specific intervals. Pain levels were measured using the Visual Analogue Scale (VAS) at different time points throughout the study, including during recruitment, at 2 Weeks, 6 Weeks, 12 Weeks, 24 Weeks, and 36 Weeks. Symptoms were systematically analysed using the International Knee Documentation Committee (IKDC) questionnaire, administered at parallel intervals during the study. Additionally, the impact on sports activities was evaluated through relevant questions included in the IKDC assessment at each key time marker. Functionality was assessed through responses to questions of the IKDC questionnaire, which reflected the patients' functional progress during the same intervals. These structured evaluations provided a comprehensive understanding of the effectiveness of the treatment, reflecting changes over time and contributing valuable insights into the impact of percutaneously injected Wharton's Jelly-derived mesenchymal stem cells on knee osteoarthritis patients.

The efficacy of pain relief measures and Sit-to-Stand Tests, which evaluate lower limb strength and endurance, were assessed at each visit. Knee scanography was conducted at the onset and six months later to measure knee angulation and the width of the tibiofemoral joint space using the Midpoint Method (Mehta et al. 2017). This method utilises a digitised scanogram of the lower limb to quantify the widths of the medial and lateral compartments between the tibial and femoral surfaces at midpoints of the lines representing each compartment and aligned with the long axis of the tibia (Figure 2).

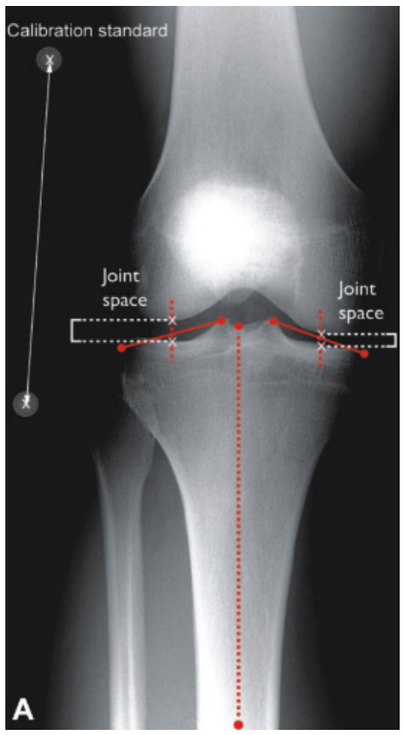

FIGURE 2. The Midpoint Method utilized to evaluate the joint space widths (JSWs) uses a digitized scanogram of the lower limb

STATISTICAL ANALYSIS

The sample description provided the frequency of each category and the mean plus standard deviation for qualitative variables. At baseline and during follow-ups, the Analysis of Variance (ANOVA) was used to analyse parametric data, and the Kruskal-Wallis test was used to analyse non-parametric data. SPSS version 25 (IBM ® Statistics, https://www.ibm.com/products/spss-statistics) was used for all statistical analyses. Statistical significance was defined as P values less than 0.05 ($p < 0.05$).

RESULTS

STEM CELL MORPHOLOGY AND CHARACTERISATION

Upon reaching passage 3 through culture expansion, Wharton's Jelly-Derived Mesenchymal Stem Cells (WJ-MSCs) exhibited a distinctive spindle-shaped morphology, as depicted in Figure 3(A). The rapid attainment of confluency within a week underscored their robust growth potential. Rigorous immunophenotyping was conducted, employing a panel of markers endorsed by the International Society for Cell Therapy to substantiate the MSC identity. As illustrated in Figure 3(B), the findings were compelling - over 95% of the cells expressed CD73 and CD90, recognised hallmarks of MSCs. Additionally, a minority of cells (less than 5%) manifested CD34 and HLA-DR expression, indicative of immune activation, aligning with the expected MSC profile. Most notably, differentiation assays yielded remarkable insights, showing the profound capacity of WJ-MSCs to differentiate into adipocytes, osteocytes, and chondrocytes - a testament to their undeniable multipotency, as illustrated in Figure 3(C

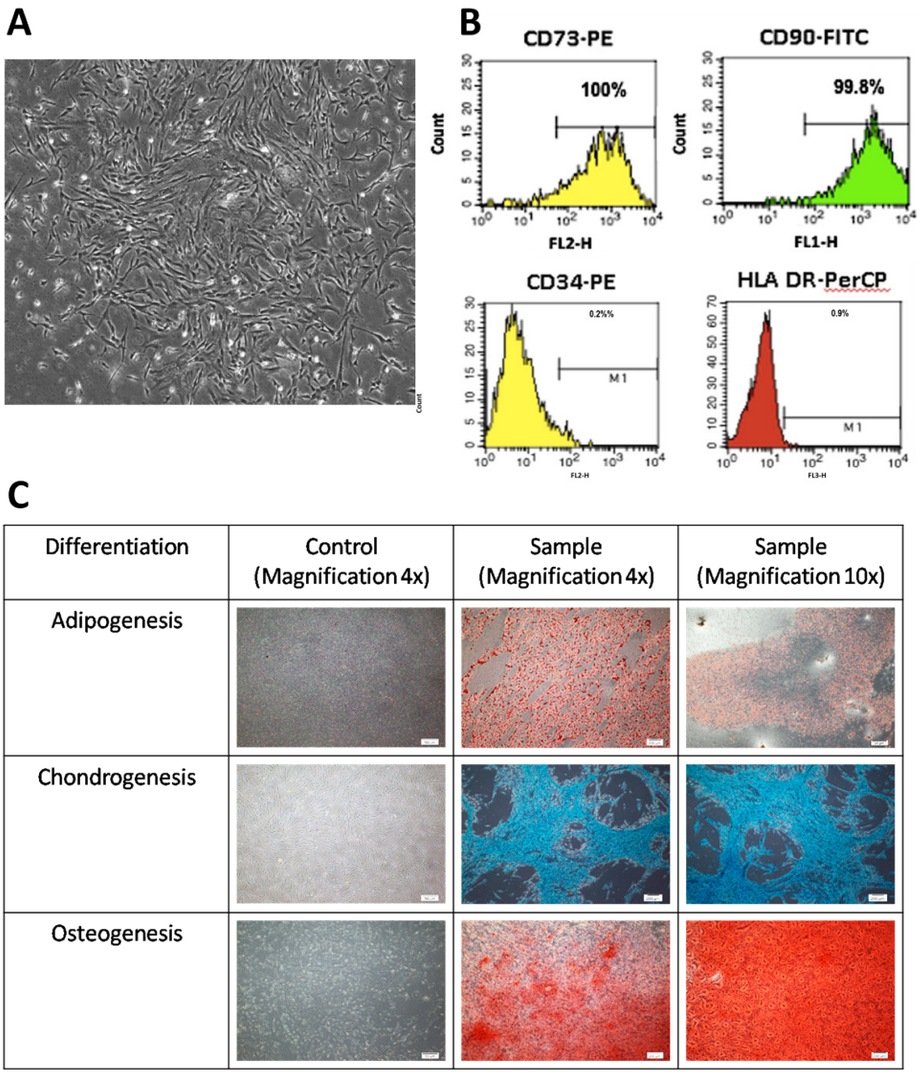

FIGURE 3. Characterization of WJ-MSCs. (A) Morphology of MSCs in 7 days of culture at passage 3 under light microscopy. (B) Percentage and flow cytometric analysis of MSCs surface markers were tested at passage 3 according to the ISCT guidelines. (C) Tri-lineage differentiation of WJ-MSCs. Adipogenic, chondrogenic, and osteogenic staining demonstrates the tri-lineage differentiation potential of WJ-MSCs. (Scale bars indicate 100 μm)

ELIGIBILITY ASSESSMENT

The study cohort comprised of individuals with a mean age of 62, ranging from 42 to 71, with females representing the predominant gender. The majority of patients fell into the category of Obesity Type 1 (7 patients), followed by Overweight (3 patients) and Morbid Obesity (1 patient). While eight patients received a single knee injection, the remaining three received injections for both knees. One patient withdrew from the study at Week 20 to undergo knee arthroplasty, as their knee deformity continued to affect low back pain, and their data were excluded from the overall analysis (Figure 4). Throughout the study period, no serious adverse events, deaths, permanent disability, neoplasia, or septic arthritis cases were observed. Knee pain and swelling, which resolved within 72 h post-injection, were the most common adverse events related to intra-articular injection. Two cases of post-injection fever occurred, while isolated incidents of itching at the injection site without rash, diarrhoea, and back pain were also reported, none lasting more than 24 hours. No hospitalisations were necessary.

CLINICAL OBSERVATION AND ANALYSIS

This comprehensive clinical study conducted a meticulous analysis of various parameters to evaluate the impact of the intervention. Notably, the reduction in analgesic intake by Week 2, with mean intake decreasing from 1.3 ± 0.82 to 0.4 ± 0.52, and subsequent absence of analgesia from Week 6 through Week 24 ($p < 0.05$), demonstrated sustained and significant pain management. The Visual Analogue Scale (VAS) indicated a remarkable reduction of approximately 27% by Week 24 (19.5 mm ± 18.7 mm, $p < 0.05$), signifying substantial improvement in perceived pain levels. The Sit-to-Stand Test showcased a noteworthy enhancement in lower limb strength, with a near doubling of initial repetitions from baseline (21.0 reps ± 6.5 reps, $p = 0.006$). Subjective knee evaluation through the IKDC exhibited a notable 69% improvement (62.2% ± 6.4%, $p < 0.05$), indicating enhanced perceived knee-related well-being. The Knee injury and Osteoarthritis Outcome Score (KOOS) demonstrated widespread improvement: Symptoms and Stiffness increased to 76.8% ± 10.6%, Pain escalated to 74.4% ± 16.1%, Function and Daily Living elevated to 78.7% ± 10.5%, Function, Sports and Recreational Activity rose to 52.5% ± 18.4%, and Quality of Life improved to 63.6% ± 14.5% (all $p < 0.05$) (Figure 5). The Lysholm Knee Score exhibited a statistically significant improvement, rising to 67.0 per 100 ± 12.4 per 100 ($p = 0.034$), reflecting enhanced knee functionality. While the Tegner Activity Scale displayed a slight non-significant

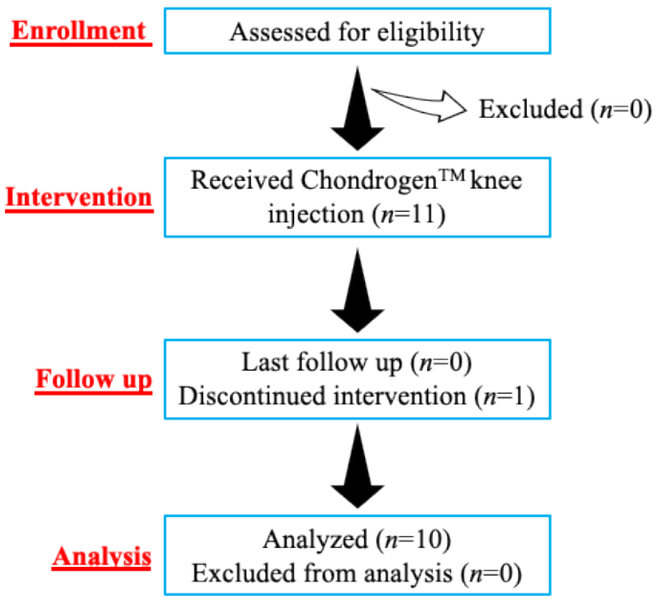

FIGURE 4. Break down of patient enrolment, intervention, follow up and analysis

enhancement from a baseline of 2.0 ± 0.7 to 3.0 ± 1.0 (p = 0.094), the temporal consistency between Week 12 and Week 24 highlighted the maintained positive effects of the intervention. These outcomes underscore the significant and multifaceted benefits of the intervention in pain management, functional improvement, and overall knee health (Table 2).

There were changes from Baseline measurements to Week 24; Medial Compartment Joint Space Width increased by 2% (5.1 mm ± 1.4 mm to 5.2 mm ± 1.5 mm), and Lateral Compartment Joint Space Width increased by 8% (6.2 mm ± 1.7 mm to 6.7 mm ± 1.5 mm). The deformity Angle remained the same with a 3.2° varus. All the radiographic parameters were insignificant, with a p-value > 0.05 (Table 3).

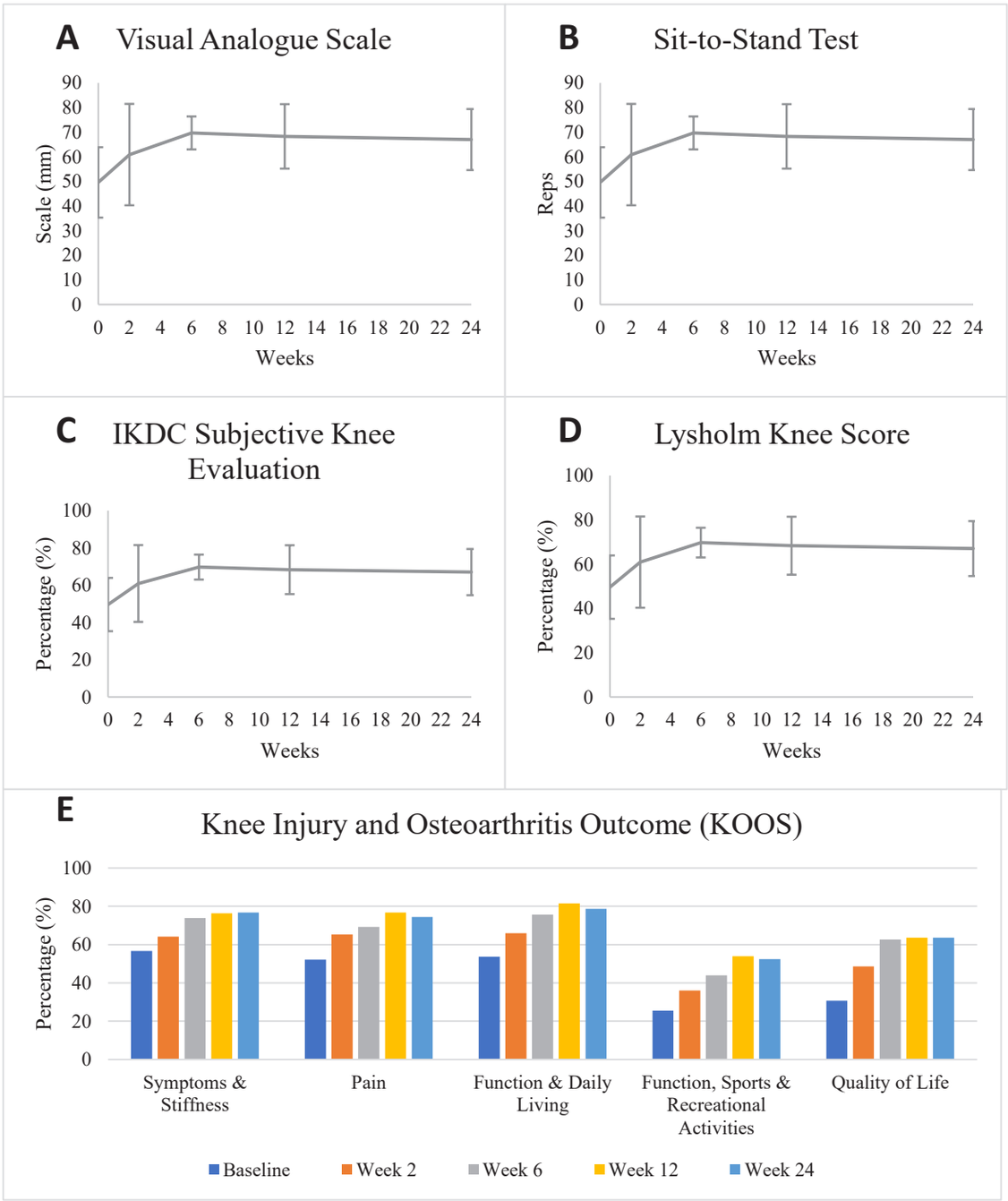

FIGURE 5. Graphs showing a general improvement of scores from Baseline to Week 24 for VAS (A), Sit-to-Stand Test (B), IKDC (C), Lysholm (D), and KOOS overall (E)

TABLE 2. Clinical outcome from baseline to week 24

	Baseline mean = SD	Week 2 mean = SD	Week 6 mean = SD	Week 12 mean = SD	Week 24 mean = SD	P-value
Number of Analgesia[a]	1.3 ± 0.82	0.4 ± 0.52	0	0	0	0.000*
Visual Analogue Scale (VAS) 100 mm	72.2 ± 20.0	47.6 ± 17.9	30.5 ± 18.9	17.2 ± 8.8	19.5 ± 18.7	0.000*
Sit-to-Stand Test (reps)	11.4 ± 4.8	15.2 ± 6.6	18.9 ± 6.0	20.1 ± 7.0	21.0 ± 6.5	0.000*
IKDC Subjective Knee Evaluation (%)	36.9 ± 11.8	48.2 ± 8.9	59.4 ± 11.5	62.2 ± 7.1	62.2 ± 6.4	0.000*
KOOS Symptoms and Stiffness (%)	56.6 ± 15.3	64.2 ± 11.0	73.9 ± 7.6	76.4 ± 8.8	76.8 ± 10.6	0.000*
KOOS Pain (%)	52.2 ± 11.0	65.3 ± 15.8	69.2 ± 17.2	76.7 ± 13.0	74.4 ± 16.1	0.000*
KOOS Function & Daily Living (%)	53.7 ± 12.9	65.9 ± 14.1	75.6 ± 11.4	81.5 ± 8.9	78.7 ± 10.5	0.000*
KOOS Function Sports & Recreational Activities (%)	25.5 ± 18.2	36.0 ± 15.6	44.0 ± 18.7	54.0 ± 14.3	52.5 ± 18.4	0.000*
KOOS QoL (%)	30.7 ± 19.2	48.6 ± 21.2	62.7 ± 13.3	63.7 ± 16.3	63.6 ± 14.5	0.000*
Tegner Activity Scale	2.0 ± 19.2	2.0 ± 0.8	2.0 ± 08	2.7 ± 0.9	3.0 ± 1.0	0.000*
Lysholm Knee Score (per 100)[a]	49.6 ± 14.3	60.9 ± 20.6	69.7 ± 6.7	68.3 ± 13.1	67.0 ± 12.4	0.000*

*p-value is significant at $p < 0.05$, [a]analysis performed using non-parametric Kruskal Wallis

TABLE 3. Radiological outcomes

	Baseline mean ± SD	Week 24 mean ± SD	p-value
Deformity Angle (°)	3.2 ± 2.4	3.2 ± 2.1	0.957
Medial Compartment Joint Space Width (mm)	5.1 ± 1.4	5.2 ± 1.5	0.871
Lateral Compartment Joint Space Width (mm)	6.2 ± 1.7	6.7 ± 1.5	0.520

DISCUSSION

Chronic and irreversible degeneration of OA joints causes significant pain. It limits patients' mobility, resulting in significant declines in quality of life and higher mortality risks associated with comorbidities such as cardiovascular disease (Hawker et al. 2014). Globally, the rising prevalence of OA and a dearth of effective treatments to halt disease progression have sparked the development of novel treatment options inspired by regenerative medicine, including cell and gene therapy. Recently, MSCs have been employed to treat OA in several preclinical investigations and early-stage clinical trials with some demonstrating promising results (Davatchi et al. 2011; Hawker et al. 2014; Jo et al. 2017; Koh et al. 2013). However, in human trials, systematic assessments of the evidence for employing MSCs intra-articularly to treat knee OA found inconclusive benefits. They indicated a lack of confidence in recommending MSCs as an OA therapy (Xing et al. 2018a, 2018b). Additional human trials utilising various MSCs, such as those generated from different sources or administered to different OA models, are still required before MSC-based cell treatment is considered an ideal treatment for OA. We verified the efficacy of WJ-MSCs, a rarely explored source of MSCs in the OA area, in reversing disease progression following OA induction in a human model.

This trial examines the safety and efficacy of Wharton's Jelly-derived mesenchymal stem cell injection in patients with symptomatic osteoarthritis. After six months, no serious adverse events were reported, and this was to be expected given the immunomodulatory property of the mesenchymal stem cell. The anti-inflammatory capability of the mesenchymal stem cell is seen with the improvement of pain, reflected by improvement in the *Visual Analogue Scale*, *Analgesia Usage* and *KOOS Symptoms & Stiffness,* and KOOS *Pain*. With the improvement of pain, the functional limitation follows suit, which is evident with the improvement of the Sit-to-Stand Test, IKDC, the remaining KOOS subset scores (*Function & Daily Living*, *Function, Sports & Recreational Activities*, *Quality of Life*), and Lysholm Knee Score. One possible restraint to the clinical improvement is the limitation of the untreated knee, as knee osteoarthritis often presents bilaterally with one side more severe than the other. Another limitation to conducting the study in the older population is concurrent arthropathy in other sites (back, hip, and ankle) and thus, limiting overall function.

Tegner Activity Scale hovers between Level 2 and Level 3, i.e., between walking on uneven ground and light work labour. A significant improvement is likely only appreciated in a younger batch of patients. On one exciting note, the improvements in pain and function generally peaked at 12 weeks and continued to maintain until 24 weeks. In their study using mesenchymal stem cells from adipose tissue, Jo et al. (2014) showed a similar pattern of improvement but with a peak at six months. Also, there were no changes in the radiological outcome at 24 weeks compared to the baseline. A longer-term follow-up (two years) is required to further evaluate clinical and radiological outcomes. While Vangsness Jr. et al. (2014) demonstrated a statistically significant increase of joint space noted by 12 months, Matas et al. (2019) have shown no radiological improvement by 12 months despite the mild baseline knee osteoarthritis. Several authors have suggested a repeated stem cell knee injection to improve the clinical and radiological outcomes (Song et al. 2018).

CONCLUSIONS

In this outpatient-based study, patients with knee osteoarthritis were treated with an intra-articular injection of Chondrogen™, a proprietary culture-expanded Wharton's Jelly-derived mesenchymal stem cell. After six months of follow-up, the treatment demonstrated significant functional improvement and pain reduction. However, a larger sample size and longer-term follow-up are necessary to confirm these results.

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