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Allogenic Umbilical Cord Mesenchymal Secretome for Knee Osteoarthritis: A Clinical Efficacy, Imaging and Safety Study

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ABSTRACT

Background: Osteoarthritis (OA) is a disease that causes disability, limited joint movement, and limitations in daily activities. No agreed-upon therapy or procedure has been proven to prevent the damage caused by osteoarthritis. However, research on the use of conditioned media in experimental animals demonstrated healing of cartilage defects, as proven by macroscopic, microscopic, and immunohistochemical analysis.

Materials and Methods: The research was conducted at Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia. This was a translational clinical trial that included patients with Kellgren-Lawrence grade 2-3 knee joint OA (n=10) treated with intra-articular injections of umbilical cord mesenchymal stem cell-conditioned media. Injections were administered five times at one-week intervals. Patients were evaluated at 2, 4, and 6 months. The data collected included KOOS, KSS, and WOMAC scores, as well as MRI T2 mapping sequence (CartiGram) examination.

Results: Functional score assessment using KOOS, KSS, and WOMAC showed significant differences between pre-treatment scores and those at the 2nd, 4th, and 6th months post-treatment. However, there were no significant differences between the scores at the 2nd and 4th months, or between the 4th and 6th months. MRI T2 mapping sequence (CartiGram) showed improvement in cartilage signal in all samples.

Conclusion: Allogenic umbilical cord mesenchymal stem cell-conditioned media therapy led to improvement in cartilage quality on MRI T2 mapping sequence (CartiGram) and in knee functional scores. No patients experienced direct side effects from the therapy.

Keywords: Mesenchymal stem cell; Umbilical cord; Conditioned media; Osteoarthritis; Magnetic Resonance Imaging (MRI)

INTRODUCTION

Osteoarthritis (OA) is a progressive, chronic degenerative joint disorder with unknown etiology that often occurs and causes disability[1]. This disorder is characterized by an inflammatory reaction in the synovial joints accompanied by a gradual degeneration process in the articular cartilage and sub-chondral bone[2]. The disease is influenced by risk factors age, obesity, physical activity and genetic factors[1]. Based on data from the World Health Organization (WHO), the global prevalence of OA is 9.6% in men and 18% in women aged over 60 years. In Indonesia, the prevalence reaches 15.5% (approximately 39 million) in men and 12.7% (approximately 32 million) in women, based on a total population of 255 million people[34]. OA has a significant impact on social and economic well-being[35]. There is no agreed-upon therapy or procedure to prevent the damage caused by OA.

Current treatments, such as physiotherapy, anti-inflammatory drugs and viscosity supplements are symptomatic treatments and aim only to relieve pain. Other established therapeutic modalities, including bone marrow stimulation (microfracture), osteochondral autograft transplantation (mosaicplasty), and autologous chondrocyte implantation (ACI), are difficult and invasive, rendering them inefficient for widespread use. Moreover, many patients ultimately end up having joint replacement surgery after undergone this therapy[6]. Although joint replacement surgery provides good results in restoring mobility and eliminating pain, this surgical procedure has the risk of causing infection, and thrombosis, and is expensive for hospital treatment and rehabilitation[7]. Currently, cell-based therapies such as mesenchymal stem cells (MSC) have attracted the attention of many researchers and clinicians as promising regenerative therapies[8]. However, despite the many advantages of therapy with mesenchymal stem cells, there are difficulties that must be faced, including expensive operational costs related to cell isolation, producing viable cultures, developing the cells, cell storage, cell application, excessive immune response from the cell recipient (host), and undesirable differentiation of these cells[9,10]. Current research has discovered that stem cells produce conditioned media (secretome, extra vesicles, and exosomes) that have tissue regeneration, immunomodulation, anti-inflammatory, and anti-apoptotic capabilities[6]. The various secretions of these stem cells are in conditioned media, which makes them more stable because they are in the form of protein compounds, with lower immunogenicity than cells, are easier to store, do not have the potential to become tumor cells, and easily reach tissue targets because they are smaller than cells[11]. Research on the use of secretomes, extra vesicles and exosomes in conditioned media in experimental animals has been carried out in previous studies and has resulted in repair of cartilage defects as proven macroscopically, microscopically and immunohistochemically accompanied by increased expression of TGF-β1, SOX-9, type collagen II, and Aggrecan, which play a role in chondrogenesis[12]. Research on conditioned media for umbilical cord mesenchymal stem cells is still at the in vivo stage in experimental animals. For this reason, this study aims to conduct clinical experimental research in patients with knee joint OA who were given umbilical cord mesenchymal stem cell conditioned media via intra-articular injection to assess its efficacy and safety.

MATERIALS AND METHODS

The research was carried out as a clinical trial (Registration NCT06688318), translational study, with a single group treated with intra-articular secretome injection therapy from hypoxic umbilical cord mesenchymal stem cell conditioned media. This research was conducted at the Orthopedic and Traumatology Polyclinic at Dr. Moewardi Hospital, Surakarta, Central Java, Indonesia. This research is a single-arm study without a control group. A purposive sampling method, taking into account the inclusion and exclusion criteria of 10 respondents. The inclusion criteria were age over 45 years, primary knee joint OA Kellgren-Lawrence grade 2 or 3, no history of surgery or intra-articular injection, no history of trauma, and agreement to participate as a research respondent with informed consent. Exclusion criteria: currently experiencing local or systemic infection; a history of autoimmune disorders or immunodeficiency; prior surgery or injection in the target knee joint; or refusal to participate in the study.

In this procedure, umbilical cord–derived mesenchymal stem cells (UC-MSCs) were used at passage four, after cultures had reached approximately 80% confluence. Cells cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, antibiotics, and fungizone were washed with sterile PBS, and the medium was replaced with 10 mL of complete medium without serum. Cells were incubated under normoxic conditions (37 °C, 5% CO_2) for 48 hours**.** All procedures were performed aseptically under laminar flow to maintain sterility. The collected conditioned medium was stored at −20 °C until further use. Mesenchymal stem cell conditioned media is taken as much as 3 cc in one injection[13]. Patients with knee joint OA were screened with physical examination and X-rays of the knee joint, then patients with Kellgrance-Lawrence grade 2 and 3 knee joint OA who met the inclusion criteria were given prior informed consent to undergo intra-articular injections. This study uses a single group that will be given an injection of 3 cc in one injection on one side of the knee [13,14]. The reason for administering the dose is based on the guidelines for intra-articular injections in the knee joint with a maximum dose of 9 cc, and the recommended dose for

hyaluronic acid injection doses in the knee joint is 3 cc. Before the injection is carried out, the patient must first undergo a clinical examination with KOOS, KSS, and WOMAC scoring, then carry out an MRI examination of the knee joint. The patient will then be positioned sitting with the knee flexed at 90^o and an aseptic technique applied to the knee joint. The entry point is done from the anterolateral side (lateral to the inferior pole of the patella). After the injection, the wound is covered with plaster, and the patient is asked to move the knee joint (flexion and extension). After being observed for 10 minutes, the patient was asked to walk. The patient is then asked to go home and carry out daily activities. Injections were carried out 5 times with an interval of 1 week. Next, the patient will be evaluated for two months and four months after the fifth injection to collect clinical data using KOOS, WOMAC, and KSS scoring. In the 6th month, the patient will have clinical data collected using KOOS, KSS, and WOMAC scoring, then evaluated using X-rays and MRI. The result was then calculated for data distribution and analyzed for differences in outcomes using SPSS 30. This research had an ethic recommendation by the Ethics Committee Team at Dr. General Hospital, Moewardi Surakarta (No. 932/VII/HREC/2022).

RESULT

There were 10 respondents with Kellgren-Lawrence grade II and III knee OA. Among them, there were 3 men and 7 women. The mean age of patients was 61.4 (SD±9.7) years. The youngest is 52 years old and the oldest is 80 years old. The mean body mass index (BMI) was 27.15 (SD±6.34) Kg/m2. Laboratory examinations have also been carried out and the results showed that all patients had normal routine blood laboratory levels and were not experiencing systemic infections.

Functional SCORE

The functional examination was obtained using the Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), and Knee Society Score (KSS) scoring methods. The score was obtained at the 0th month or pre-injection examination, the average patient functional score was KOOS pain 63.61 (SD ± 16.59), KOOS symptoms 68.93 (SD ± 12.49), KOOS Activity daily living (ADL) 68.68 (SD ± 16.52), KOOS sport/recreational 30 (SD ± 26.46), KOOS quality of life (QOL) 15.63 (SD ± 19.59), WOMAC 34.27 (SD ± 17 .98), KSS 67.3 (SD ± 15.94) (Table 1). Evaluations of functional scores in the second, fourth and sixth months were shown in Table 2, Table 3, and Table 4.

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Table 1: Means Functional Score of Treatment

Functional Score	Before	2 Months	4 Months	6 Months
KOOS pain	63,61	79,01	79,32	79,01
KOOS symptoms	68,93	93,65	94,05	93,65
KOOS activity daily living	68,68	84,64	85,62	84,64
KOOS sport/recreational	30	38,89	41,11	38,89
KOOS quality of life	15,63	20,14	22,22	20,14
WOMAC score	34,27	14,24	14,23	14,24
KSS score	67,3	86,89	87,44	86,89

The results of the statistical analysis of functional scores were obtained from the KOOS pain score. Based on the results of the Shapiro-Wilk normality test, it was found that all data were normally distributed ($p < 0.05$). Then, continuing with the ANOVA test, significant differences were obtained

($P < 0.05$) in all months of examination. Likewise, the Bonferroni post-hoc test showed a statistically significant difference in KOOS pain with $p=0.001$ ($p < 0.05$) at months 2, 4, and 6 compared to month 0 (before treatment). The highest score was obtained at month 4. Meanwhile, there was no significant difference between months 2 and 4 ($p=0.317$), then months 4 and 6 ($p=0.317$).

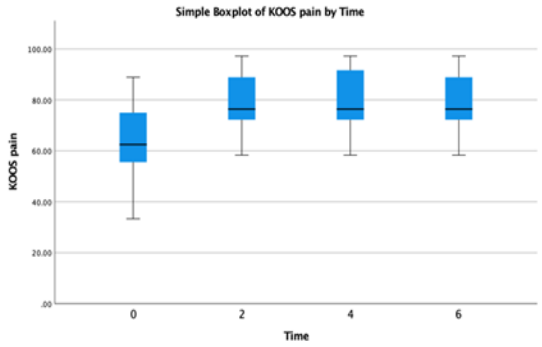

Figure 1. KOOS Pain

The results of the statistical analysis of functional scores were obtained from the KOOS pain score. Based on the results of the Shapiro-Wilk normality test, it was found that all data were normally distributed ($p < 0.05$). Then, continuing with the ANOVA test, significant differences were obtained ($p < 0.05$) in all months of examination. Likewise, the Bonferroni post-hoc test showed a statistically significant difference in KOOS pain with $p=0.001$ ($p < 0.05$) at months 2, 4, and 6 compared to month 0 (before treatment). The highest score was obtained at month 4. Meanwhile, there was no significant difference between months 2 and 4 ($p=0.317$), then months 4 and 6 ($p=0.317$).

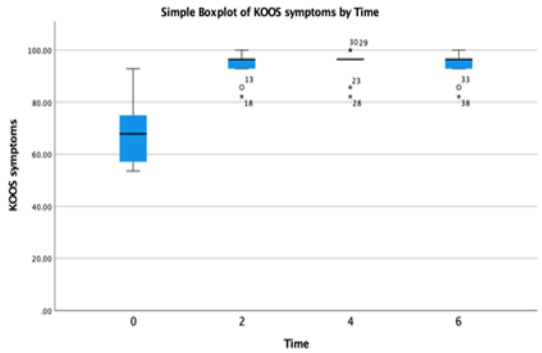

Figure 2. KOOS Symptoms

The results of the functional score statistical analysis carried out on the KOOS Activity Daily Living (ADL) score, based on the results of the Shapiro-Wilk normality test, showed that all data were normally distributed ($p < 0.05$). Then, continuing with the ANOVA test, significant differences were obtained $p= 0.024$ ($p < 0.05$) in all months of examination. Likewise, using the Post-hoc Bonferroni test, statistically significant differences were found ($p < 0.05$) at months 2, 4 and 6 compared to month 0 (before treatment). The highest score was obtained at month 4. Meanwhile, there was no significant difference between months 2 and 4, then months 4 and 6.

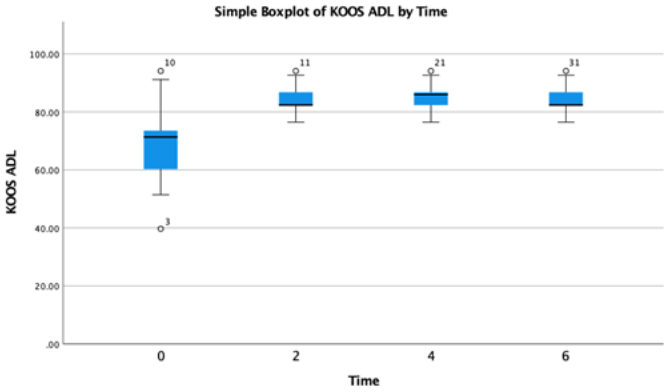

Figure 3.KOOS Activity Daily Living (ADL)

The results of statistical analysis of functional scores carried out on KOOS sport/recreational scores, based on the results of the Shapiro-Wilk normality test, showed that all data were not normally distributed. Then, continuing with the Friedman test, significant differences were found with $p = 0.003$ ($p < 0.05$) in all months of examination. Likewise, using the Post-hoc Wilcoxon test, statistically significant differences were found ($p < 0.05$) at months 2 ($p = 0.005$), 4 ($p = 0.005$) and 6 ($p = 0.005$) compared to month 0 (before treatment). The highest score was obtained at month 4. Meanwhile, there was no significant difference between months 2 and 4 ($p = 0.317$), then months 4 and 6 ($p = 0.317$).

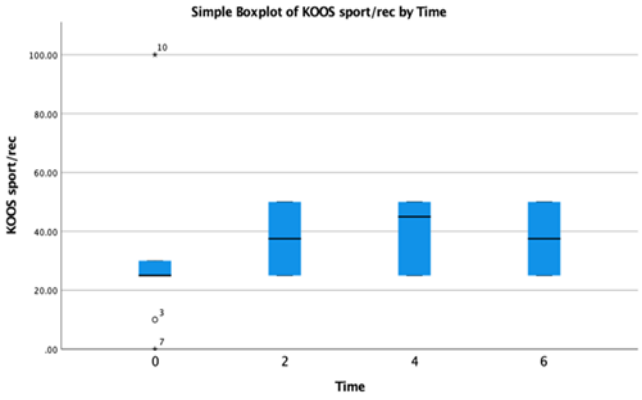

Figure 4. KOOS Sport and Recreation

The results of the functional score statistical analysis carried out on the KOOS quality of life (QOL) score, based on the results of the Shapiro-Wilk normality test, showed that all data were not normally distributed. Then, continuing with the Friedman test, no significant differences were found p = 0.121 (p > 0.05) in all months of examination. Because there were no significant differences in the results of the analysis, the data was not subjected to a post-hoc test.

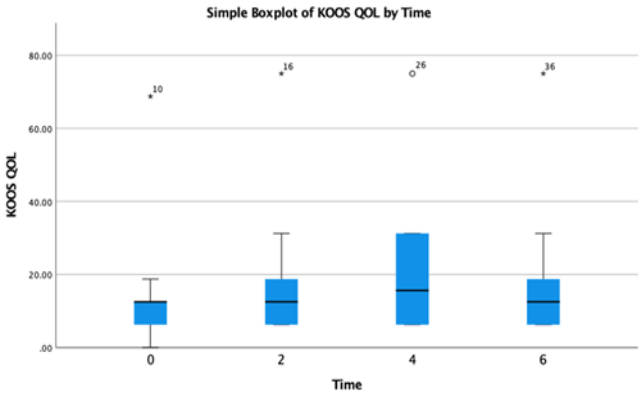

Figure 5. KOOS Quality of Life (QOL)

The results of statistical analysis of functional scores carried out on the WOMAC score, based on the results of the Shapiro-Wilk normality test, showed that all data were normally distributed (p < 0.05). Then, continuing with the ANOVA test, significant differences were obtained p=0.001 (p < 0.05) in all months of examination. Likewise, using the Post-hoc Bonferroni test, statistically significant differences were found p=0.007 (p < 0.05) at months 2, 4 and 6 compared to month 0 (before treatment). Meanwhile, there was no significant difference between the 2nd and 4th months, then the 4th and 6th months.

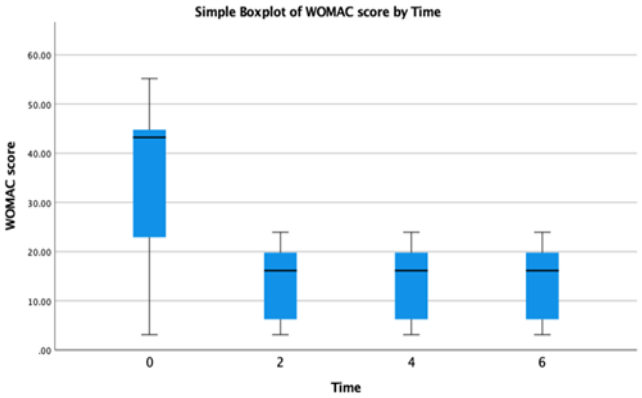

Figure 6. WOMAC Score

The results of statistical analysis of functional scores carried out on KSS scores, based on the results of the Shapiro-Wilk normality test, showed that not all data was normally distributed. Then, continuing with the Friedman test, significant differences were found p= 0.001 (p < 0.05) in all months of examination. Likewise, using the Post-hoc Wilcoxon test, statistically significant differences were found p = 0.007 (p < 0.05) at months 2, 4 and 6 compared to month 0 (before treatment). The highest score was obtained at month 4. Meanwhile, there was no significant difference between months 2 and 4 (p=0.317), then months 4 and 6 (p=0.317).

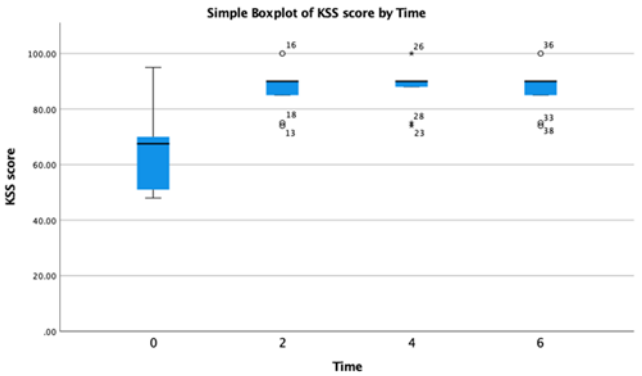

Figure 7. KSS Score

MRI EVALUATION

Radiological data collection was carried out during the research stages, namely data before the action was carried out in the form of a two-projection x-ray of the knee and a full leg standing x ray. Then a magnetic resonance imaging (MRI) of the knee without contrast with a CartiGram measurement was performed.

Initial radiological data collection before treatment was carried out on all research samples before the injection was carried out. The radiological images showed OA knee Kellgrance-Lawrence grade II in two patients and OA knee Kellgrance-Lawrence grade III in eight patients. MRI results also showed cartilage damage according to radiological readings. There was no difference in the x-ray results 6 months after injection. The results of MRI examinations on patients were carried out using T2 mapping sequence CartiGram on a 1.5-tesla MRI machine (GE Healthcare, USA). The patient underwent MRI twice, namely at 0 months before and 6 months after treatment.

MRI examination was performed using the T2 mapping sequence CartiGram. A region of interest (ROI) measuring 3 mm x 3 mm was placed on cartilage assessed as damaged in three compartments of the knee: the patellofemoral, medial, and lateral compartments (one ROI per compartment, for a total of three ROIs). The mean T2 value from these three ROIs was calculated and compared before and after the action. Results can be seen in Table 2 and Table 3.

In this study, differences in intensity and quality of ligaments were assessed in all ROI using CartiGram. Before carrying out the difference test, a normality test was carried out using the Shapiro-Wilk test. From these results it is known that all data are normally distributed ($p \geq 0.05$) except for the overall pre- and post-intervention ROI data. Next, the difference test on the entire ROI was carried out using the non-parametric Wilcoxon test while the data on each ROI was carried out using the Paired T-test.

The results of the CartiGram test are presented in Table 2. These results showed that there were no statistically significant differences in the overall ROI and each ROI between pre- and post-intervention. However, at post-intervention there was a decrease of 0.059 in overall ROI, 0.503 in ROI 1, 1.102 in ROI 2, and 0.778 in ROI 3 compared to pre-intervention.

Table 2. CartiGram MRI the difference between ROI

	Pre-Intervention	Post-Intervension	Mean. Diff.	P-value
All ROI	47.564 (12.938)	47.505 (12.814)	0.059	0.959
ROI 1	47.372 (11.830)	46.869 (12.757)	0.503	0.799
ROI 2	48.740 (12.774)	47.638 (14.099)	1.102	0.629
ROI 3	47.683 (14.163)	46.905 (14.163)	0.778	0.744

Table 3. CartiGram pre and post-treatment result in each sample

No	Sample	Pre	Post
1	SK-01	52,26	46,41
2	SK-02	63,62	59,98
3	SK-03	36,62	31,38
4	SK-05	48,92	41,84
5	SK-06	67,02	64,49
6	SK-07	35,77	28,59
7	SK-08	40,27	36,80
8	SK-09	38,29	36,51
9	SK-10	64,79	63,26
10	SK-11	45,04	44,50

DISCUSSION

Conditioned media injection in knee osteoarthritis has been studied as a potential treatment option. The secretome is a collection of bioactive molecules secreted by stem cells that have therapeutic effects. A study conducted on rats showed that intra-articular injection of a combination of synovial membrane-derived MSCs (SMMSCs), platelet-rich plasma (PRP), and conditioned medium (secretome) attenuated osteoarthritis progression[15]. Another study compared the healing properties of intra-articular injection of human dental pulp stem cells and cell-free-secretome on induced knee osteoarthritis in male rats[16]. A randomized, double-blind, placebo-controlled trial protocol was designed to evaluate the efficacy of intra-articular injection of allogeneic platelet-rich plasma for knee osteoarthritis combined with hematologic blood dyscrasias with platelet dysfunction[17]. In addition, a study on laboratory rabbits showed that intraarticular and intramuscular injection of chondroitin sulfate reduces the intensity of the degenerative-dystrophic process due to the impact on inflammatory and the activation of anabolic mechanisms[18]. These studies suggest that secretome injection may have potential as a treatment option for knee osteoarthritis, but further research is needed to further determine its efficacy and

safety in humans. In this study, the translational clinal study injected secretome from conditioned media of UC-MSCs to knee OA. The results showed overall positive results in functional scores. This result is consistent with the previous study that secretome showed anticatabolic, immunomodulatory, and regenerative properties in vitro studies[19]. Moreover, in vivo studies confirmed that secretomes showed effective in functional in the terms of pain improvement and morphological changes[19]. In this study, we make this biological approach as a candidate for human translatability. The result also showed functional and morphological improvement as seen on functional scoring and MRI T2 mapping sequences (CartiGram). In this study, the functional score increased immediately after treatment to 4 months after treatment. Then decreasing in 6 months after treatment. This result is consistent with many previous MSCs intraarticular injections in knee OA studies claim that intraarticular injections of MSCs alleviate knee pain in the short term[20]. However, this study showed an improvement in cartilage integrity only based on MRI T2 Mapping sequence (CartiGram) without significantly difference statistic. To the best of our knowledge, there were no studies that had investigated the relationship between intraarticular secretome injection and knee MRI. However, intraarticular injection of MSCs show increase degree of cartilage repair defect on MRI at 2 years follow up[21]. At 6 months follow up, MSCs injection showed a slight increase in thickness of some part tibial and femoral articular cartilages on MRI findings[22]. This suggests that a longer intervention evaluation period is required for this type of variable. Limitation of this study is the absence of a control group for comparison and randomization process. This study also lacks of the number of respondents. However, this study showed the promising result that secretomes injection could become regenerative therapy for knee OA. In addition, further research comparing MSCs secretomes with a placebo (control) is required as well as a standard protocol for intraarticular injections before advising intraarticular MSCs secretome injections as a routine therapy.

CONCLUSION

This study found that there was an increase in functional and a decrease in pain felt by patients during post-injection compared to before injection up to 4 months and 6 months. Based on the results of analysis using CartiGram, there was an increase in cartilage integrity. However, these results warrant cautious interpretation, given that the result did not reach statistical significance. It is necessary to carry out further clinical trial research with a larger number of samples and longer period of evaluation to obtain more representative data regarding improvements in cartilage quality as assessed using MRI T2 mapping sequence CartiGram analysis.

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CONFLICT OF INTEREST

The authors hereby declare that no conflict of interest.

REFERENCES

1. Aspden RM, Saunders FR. Osteoarthritis as an organ disease: From the cradle to the grave. *Eur Cell Mater*. 2019;37:74-87.

2. Raman S, FitzGerald U, Murphy JM. Interplay of inflammatory mediators with epigenetics and cartilage modifications in osteoarthritis. *Front Bioeng Biotechnol*. 2018;6:22.

3. Ahmad IW, Diah Rahmawati LD, Wardhana TH. Demographic Profile, Clinical and Analysis of Osteoarthritis Patients in Surabaya. *Biomol Heal Sci J*. 2018;1(1):34-39.

4. Koentjoro SL. Hubungan antara Indeks Masa tubuh (IMT) dengan Derajat Osteoartritis Lutut Menurut Kellgren dan Lawrence. Semarang: Fakultas Kedokteran Universitas Diponegoro. 2010.

5. Perhimpunan Reumatologi Indonesia. *Rekomendasi IRA Untuk Diagnosis Dan Penatalaksanaan Osteoartritis*. Jakarta: Divisi Reumatologi Departemen Ilmu Penyakit Dalam FKUI/RSCM. 2014: 1-3p.

6. Bousnaki M, Bakopoulou A, Kritis A, et al. The Efficacy of Stem Cells Secretome Application in Osteoarthritis: A Systematic Review of In Vivo Studies. *Stem Cell Rev Rep*. 2020;16(6):1222-1241.

7. Feng JE, Novikov D, Anoushiravani AA, et al. Total knee arthroplasty: Improving outcomes with a multidisciplinary approach. *J Multidiscip Healthc*. 2018;11:63-73.

8. Lee WY wai, Wang B. Cartilage repair by mesenchymal stem cells: Clinical trial update and perspectives. *J Orthop Translat*. 2017;9:76-88.

9. McKinney JM, Doan TN, Wang L, et al. Therapeutic efficacy of intra-articular delivery of encapsulated human mesenchymal stem cells on early stage osteoarthritis. *Eur Cell Mater*. 2019;37:42-59.
10. Colombini A, Perucca Orfei C, Kouroupis D, et al. Mesenchymal stem cells in the treatment of articular cartilage degeneration: New biological insights for an old-timer cell. *Cytotherapy*. 2019;21(12):1179-1197.
11. Arrigoni C, D'Arrigo D, Rossella V, et al. Umbilical Cord MSCs and Their Secretome in the Therapy of Arthritic Diseases: A Research and Industrial Perspective. *Cells*. 2020;9(6):1343.
12. Soetjahjo B, Hidayat M, Sujuti H, et al.. Immunohistochemistry Evaluation of TGF-β1, SOX-9, Type II Collagen and Aggrecan in Cartilage Lesions Treated with Conditioned Medium of Umbilical Cord Mesencyhmal Stem Cells in Wistar Mice (Rattus novergicus). *J Trop Life Sci*. 2018;8(1):21-27.
13. Rastogi AK, Davis KW, Ross A, et al. Fundamentals of joint injection. AJR *Am J Roentgenol*. 2016;207(3):484-94.
14. Sun SF, Hsu CW, Lin HS, et al. Comparison of Single Intra-Articular Injection of Novel Hyaluronan (HYA-JOINT Plus) with Synvisc-one for knee osteoarthritis: A randomized, controlled, double-blind trial of efficacy and safety. *J Bone Joint Surg Am.* 2017;99(6):462-471.
15. Nabavizadeh SS, Talaei-Khozani T, Zarei M, et al. Attenuation of osteoarthritis progression through intra-articular injection of a combination of synovial membrane-derived MSCs (SMMSCs), platelet-rich plasma (PRP) and conditioned medium (secretome). J Orthop Surg Res. 2022;17(1):102.
16. Nowzari F, Zare M, Tanideh N, et al. Comparing the healing properties of intra-articular injection of human dental pulp stem cells and cell-free-secretome on induced knee osteoarthritis in male rats. Tissue Cell. 2023;82:102055.
17. Zhu X, Zhao L, Liu A, et al. Efficacy of intra-articular injection of allogeneic platelet-rich plasma for knee osteoarthritis combined with hematologic blood dyscrasias with platelet dysfunction: protocol of a randomized, double-blind, placebo-controlled trial. BMC Musculoskelet Disord. 2022; 23(1):1095.
18. Nosivets D. Macroscopic Changes in the Knee Joint with Intraarticular and Intramuscular Administration of Chondroitin Sulfate on the Background of Experimental Osteoarthritis. Ukr J Med Biol Sports. 2022;7(2):67-73.
19. D'Arrigo D, Roffi A, Cucchiarini M, et al. Secretome and Extracellular Vesicles as New Biological Therapies for Knee Osteoarthritis: A Systematic Review. J Clin Med. 2019;8(11):1867.
20. Rodríguez-Merchán EC. Intraarticular Injections of Mesenchymal Stem Cells in Knee Osteoarthritis: A Review of Their Current Molecular Mechanisms of Action and Their Efficacy. Int J Mol Sci. 2022;23(23):14953.
21. Koh YG, Kwon OR, Kim YS, et al. Adipose-Derived Mesenchymal Stem Cells with Microfracture Versus Microfracture Alone: 2-Year Follow-up of a Prospective Randomized Trial. Arthroscopy. 2016;32(1):97-109.
22. Sadri B, Hassanzadeh M, Bagherifard A, et al. Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial. Stem Cell Res Ther. 2023; 14(1): 162.