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Clinical Outcomes Comparison in Administration of Secretome vs Hyaluronic Acid in Patients with Knee Osteoarthritis Kellgren-Lawrence Grade I-III

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ABSTRACT

Background: The prevalence of OA in Indonesia is predicted to reach more than 20% of the population aged over 60 years in 2050, with a high risk of disability. So far, early treatment of osteoarthritis in the form of administering hyaluronic acid has not been completely satisfactory and tends to be progressive until ending in more invasive operative therapy. This study aimed to compare the clinical outcomes between secretome injection and hyaluronic acid in patients with Kellgren-Lawrence grade I-III knee osteoarthritis.

Subjects and Method: This was a single-blind experimental study. This study was conducted in the orthopedic polyclinic at General Hospital Prof. Dr. I.G.N.G. Ngoerah Bali. A total sample of 36 knee osteoarthritis patients was selected using permuted block sampling with randomization. The sample was divided into two groups, (1) secretome (intervention group) and (2) hyaluronic acid (control group). The independent variables were secretome injection and hyaluronic acid injection. The dependent variable was pain. Pain was measured using Western Ontario and McMaster University (WOMAC), Knee Osteoarthritis Outcome Score (KOOS), Visual Analog Score (VAS), and Patient-Reported Outcome Measure (PROM).

Results: Based on gender, there are more women than men and the right foot is more affected at 58.3%. Functional score parameters in each secretome and hyluronic acid group were compared between the 3rd and 6th months of follow-up. Pain in the hyaluronic acid group was lower than in the secretome group.

Conclusion: Hyaluronic acid has better effect in pain reduction than secretome. Further studies could explore the underlying mechanisms and potential long-term effects to better understand these differences in pain outcomes.

Keywords: hyaluronic acid, knee, osteoarthritis, secretome

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BACKGROUND

Osteoarthritis (OA) is the most common chronic articular disease, characterized by articular cartilage degeneration and persistent pain that causes disability, loss of limb function, decreased quality of life, and economic burden for the family. (Jang et al., 2021a) About 25 % of patients with symptoms of osteoarthritis cannot return to activities in daily life. (Hunter and Bierma-Zeinstra, 2019a) The global incidence of OA is estimated at 20% with an OA incidence of 16-29% in Asia, Africa and Middle Eastern countries. (Cui et al., 2020a) In Indonesia, the prevalence of OA is reported to reach 65% at ages over 61 years, and continues to increase with increasing age and obesity. (Rachmat, et al., 2021) In 2050, it is estimated that It will be found that more than 20% of the population is over 60 years old, of which around 20% of cases will end up experiencing functional impairment, and a third will experience severe disability.

Knee OA therapy generally includes non-operative and operative therapy. The American College of Rheumatology (ACR) in 2012 recommended administering intra-articular injections of hyaluronic acid (HA) in osteoarthritis patients. (Hochberg et al., 2012) Hyaluronic acid contains high molecular weight glucosamine, which is produced by chondrocytes, synoviocytes, and fibroblasts. Hyaluronic acid plays a role in biomechanics, lubrication and visco-elasticity of joint synovial fluid which is found to be decreased in osteoarthritis. So far, HA injection is quite widely used and has effectiveness such as improving joint function, relieving pain, and reducing the dose of analgesia which is quite good. (Ayhan, 2014; Koiri et al., 2018) In addition to commonly used therapies, there is now increasing interest in the use of autologous biologics, namely: mesenchymal stem cell (MSC) secretome, for regenerative medicine applications, especially in musculoskeletal conditions such as knee osteoarthritis (Gupta, 2022). Throughout its development, the MSC secretome is a collection of MSC-derived bioactive factors (including soluble proteins, nucleic acids, lipids, and extra-cellular vesicles) which have begun to be widely developed and become increasingly popular in research worldwide.

Secretome successfully demonstrated therapeutic effects similar to the positive effects observed after MSC transplantation. Some of the advantages of the secretome include: that it can bypass some of the weaknesses of cell-based therapy, such as unwanted differentiation and the potential for activation of an allogeneic immune response. The therapeutic effect of the MSC secretome depends on its ability to reach target cells and deliver genetic material, growth factors, and immunomodulators. (Amodeo et al., 2021; Teixeira et al., 2013).

So far, OA treatment is still not completely satisfactory, so it is more common for OA patients to end up with operative therapy. (Gigis et al., 2016; Wang et al., 2022) Along with the development of regenerative therapy, the secretome has become a product of scientific development which is expected to be able to answer this gap. This study was specifically carried out to compare the effectiveness of Secretome therapy and the more commonly used HA in OA patients. (Delgado et al., 2018; Ramkumar et al., 2015; Roos and Toksvig-Larsen, 2003; Samma et al., 2021)

SUBJECTS AND METHOD

1. Study Design

This was a single blind randomized controlled study.

2. Population and Sample

The population in this study were all orthopedic patients at the orthopedic

polyclinic at General Hospital Prof. Dr. I.G.N.G. Ngoerah Bali and took samples from a group of patients diagnosed with grade I-III KL knee OA. The total sample size in this study was 36 patients consisting of 2 treatment groups, namely 18 patients in the intervention group (Secretome) and 18 patients in the control group (Hyaluronic Acid "HA"). The sample for this study was taken from a population that met the inclusion and exclusion criteria set by the researchers in this study. The sample in this study came from a population of patients diagnosed with grade I-III KL knee OA at Prof. Dr. Hospital. I.G.N.G. Ngoerah, Denpasar Bali. Inclusion criteria include: age at least 45 years, knee pain for ≈ 4 months, confirmed OA with Kellgren Lawrence I-III classification by radio-graphic examination of the knee in a standing position. Exclusion criteria include: suffering from Osteoarthritis with Kellgren Lawrence IV classification, joint disorders caused by malignancy or infection, severe coagulation disorders, history of Rheumatoid Arthritis, use of NSAIDs within the last week, autoimmune disorders, patients who have undergone total knee replacement surgery, The patient cannot speak Indonesian. Drop out criteria include: the patient suffers from serious illness, the patient dies, the patient does not return for follow-up. The sample distribution technique in this study used a randomized permuted block sampling method.

3. Study Variables

The dependent variables were the knee joint function and pain. The independent variables were secretome injection and HA injection.

4. Operational Definition of Variables

Osteoarthritis is a chronic arthritis disease that is characterized by progressive damage to joint cartilage, resulting in the base of the bones located in the underlying layer rubbing against each other and causing symptoms such as pain, stiffness, and movement disorders with grade I-III KL as proven by reading results knee radiograph by a radiologist.

A secretome is a number of cytoprotective factors produced by MSC with paracrine effects in the processes of differentiation, matrix synthesis, angiogenesis, tissue repair, immune modulation, chondrogenic potential, and regeneration. The amount of secretome injection given is 0.2 mL/kg of the patient's body weight (Műzes and Sipos, 2022)

Hyaluronic acid (sodium hyaluronic acid, low molecular weight) is a glycolsaminoglycan compound that is found in many tissues and body fluids, especially cartilage and synovial fluid. Hyaluronic acid is administered intra-articularly to knees with osteoarthritis. Hyaluronic acid is given as one injection, at a dose of 20-25 mg (1 vial contains 20 mg in a 2 mL dosage) in adults. (Abate et al., 2017).

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is an index used to measure functional impairment and pain associated with OA of the knee. The parameter used is WOMAC numerical scoring.

Visual Analog Scale (VAS) is a tool used to measure the intensity of pain experienced by patients on a scale of 1-10. Vas parameters will be grouped into 3 categories, namely: light (VAS 1-3), medium (VAS 4-6), and heavy (7-10).

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a knee-specific questionnaire instrument, developed to assess patients' opinions about their knees and related problems. The KOOS has five separate scores with subscales: Pain, Other symptoms, Function in daily living (ADL), Function in Sports and Recreation (Sports/Rec), and knee-related Quality of

Life (QOL). The parameter used is the numeric KOOS score.

Patient-reported outcome Measure (PROM) is a measurement tool that patients use to provide information about aspects of their health status that are relevant to their quality of life including symptoms, function, and physical, mental, and social health. The parameter used is the numerical number of PROM scores.

5. Study Instruments

The amount of secretome injection given is 0.2 mL/kg of the patient's body weight. Hyaluronic acid is administered intra-articularly to knees with osteoarthritis. Hyaluronic acid is given as one injection, at a dose of 20-25 mg (1 vial contains 20 mg in a 2 mL dosage) in adults.

Hyaluronic acid is given 1 injection every 1 week for 4 weeks, at a dose of 20-25 mg (1 vial contains 20 mg in 2 mL preparation) in adults. The follow-up evaluation had been done in 0,3,6 months to measure the functional and pain outcomes. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is an index used to measure functional impairment and pain associated with OA of the knee. Visual Analog Scale (VAS) is a tool used to measure the intensity of pain experienced by patients on a scale of 1-10. Vas parameters will be grouped into 3 categories, namely: light (VAS 1-3), medium (VAS 4-6), and heavy (7-10).

Knee Injury and Osteoarthritis Outcome Score (KOOS) is a questionnaire instrument specifically used in the knee, which was developed to assess patients' opinions about their knees and related problems. The KOOS has five separate scores with subscales: Pain, Other symptoms, Function in daily living (ADL), Function in Sports and Recreation (Sports/Rec), and knee-related Quality of Life (QOL). The parameter used is the numeric KOOS score.

Patient-reported outcome Measure (PROM) is a measurement tool that patients use to provide information about aspects of their health status that are relevant to their quality of life including symptoms, function, and physical, mental, and social health. The parameter used is the numerical number of PROM scores.

6. Data analysis

Man Withney test and Wilcoxon test were carried out on the functional outcomes to determine the differences in the outcomes of administering secretome and hyaluronic acid at 3 and 6 months after the procedure.

7. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Research Ethics Committee at General Hospital Prof. Dr. IGNG Ngoerah Denpasar, No. 79/II/HREC/2017, on February 16, 2017.

RESULTS

1. Sample Characteristics

The mean age is 63.61 years (Mean= 63.61; SD= 7.50), with the youngest was 47 years old and the oldest was 79 years old.

2. Bivariate analysis

Interpret the results of the mean difference in outcomes between groups at any follow-up stage.

Table 1. Sample characteristics (n=36)

Characteristic	n (%)
Gender	
Male	12 (33.3)
Female	24 (66.7)

Characteristic	n (%)
Affected Knee	
Right	21 (58.3)
Left	15 (41.7)
Occupation	
Entrepreneur	15 (41.7)
Employee	9 (25.0)
Retired	8 (22.2)
Others	4 (11.1)
Chief Complain	
Pain	30 (83.3)
Stiffness	4 (11.1)
Deformity	2 (5.6)
Systemic Disease	
Yes	10 (27.9)
No	26 (72.2)

Table 2. Mean difference in study outcomes between groups

Functional Outcome		Groups	Mean	SD	p
VAS	Baseline	Secretome	59.44	14.43	0.203*
		Hyaluronic acid	64.16	14.67	
	3 months	Secretome	29.44	14.43	<0.001*
		Hyaluronic acid	51.11	14.40	
	6 months	Secretome	12.78	10.60	<0.001*
		Hyaluronic acid	38.61	16.52	
WOMAC	Baseline	Secretome	57.78	3.42	0.175*
		Hyaluronic acid	61.00	8.08	
	3 months	Secretome	39.17	4.41	<0.001*
		Hyaluronic acid	51.00	8.08	
	6 months	Secretome	33.16	4.32	<0.001*
		Hyaluronic acid	44.00	8.08	
KOOS	Baseline	Secretome	35.74	2.79	0,008*
		Hyaluronic acid	34.08	2.74	
	3 months	Secretome	55.74	2.79	<0.001*
		Hyaluronic acid	49.08	2.74	
	6 months	Secretome	75.74	2.79	<0.001*
		Hyaluronic acid	59.08	2.74	
PROM	Baseline	Secretome	16.21	5.45	0.271*
		Hyaluronic acid	16.45	1.98	
	3 months	Secretome	21.98	3.73	0.281*
		Hyaluronic acid	21.44	1.96	
	6 months	Secretome	26.34	2.82	0.261*
		Hyaluronic acid	26.33	2.10	

Note: *Mann-Whitney test; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; KOOS: Knee injury and Osteoarthritis Outcome Score; PROM: Patient Reported Outcome Measures

DISCUSSION

1. Relationship between Visual Analogue Score (VAS) and Secretome Administration versus HA

This analysis is intended to provide a more in-depth picture of the effectiveness and relative impact of the two therapies on symptom severity at certain levels of osteoarthritis. This study shows a significant relationship between the severity of knee osteoarthritis symptoms in Grade I-III, as assessed via VAS, and the response to secretome administration. Results showed a significant improvement in VAS scores after administration of secretome, indicating a positive effect on improving symptoms at mild to moderate levels of severity. In contrast, the response to the use of HA also showed a significant increase in VAS scores. This indicates that HA is effective in relieving symptoms in patients with Grade I-II knee osteoarthritis, in line with previous literature supporting the use of HA as an intra-articular therapy.

A study conducted by Kim et al. involving 209 knee OA patients found that MSC treatment significantly improved VAS, IKDC, and Lysholm scores compared to HA treatment. VAS scores decreased at 1 month, increased slightly at 3 months, and increased significantly at 3 months to 1 year after injection. IKDC and Lysholm scores improved up to 3 months but worsened thereafter. MSC treatment showed better VAS, IKDC, and Lysholm scores at 1-year post-treatment, although early clinical improvement was superior in the HA group. (Kim et al., 2020)

This is in line with research conducted by Partan et al. (2023) which stated that the Secretome group and Hyaluronic Acid group showed a decrease in average pain scores over a duration of 12 weeks. In the Secretome Group, knee OA scores decreased significantly, as measured by VAS −4 (Mean= 4.06; SD= 1.48). This reduction was identified to be greater than the reduction observed in the hyaluronic acid group, which achieved a mean pain reduction indicated by a VAS of −3 (Mean= 2.60; SD= 1.24).

In a direct comparison between secretome administration and HA use, findings showed that both provided significant improvements in reducing symptom severity. However, changes in VAS scores may differ between the two groups, raising questions regarding the relative superiority of each therapy.

2. Correlation of WOMAC, KOOS and PROM Scores on Secretome Administration versus HA

The study results provide significant insight into the effectiveness of both treatments in treating symptoms and improving knee function at mild to moderate levels of severity. These findings demonstrated that both the secretome and HA provided significant improvements in WOMAC, KOOS, and PROM functional scores. This indicates the positive effect of both types of treatment in improving the quality of life of knee OA patients with Kelgren Lawrence Grade I-III.

A study conducted by Partan on 30 subjects found that the secretome group showed better improvement in functional scores in knees with OA compared to the HA group. The therapy was most effective after the third injection, and the group showed a decrease in Matrix metalloproteinase-3 (MMP-3) ratio and an increase in Transforming growth factor beta 1 (TGF-β1) compared with the HA group. Intra-articular secretome injection showed superior clinical improvement, biomarker changes, and no side effects compared with HA in a 5-week interval. In the Secretome Group, knee OA scores decreased significantly, as measured by WOMAC −41 (95% CI, mean ± SD −41.06 ±

24.02). This reduction was identified to be greater than the reduction observed in the hyaluronic acid group, which achieved a mean WOMAC reduction of −21 (mean= −21.13; SD= 14.07). Statistical analysis revealed a significant difference in the mean reduction in pain scores (measured by VAS and WOMAC) before and after treatment between secretome and hyaluronic acid ($p < 0.05$).

Ding et al. (2020) investigated, in a systematic review and network meta-analysis, the efficacy and safety of intra-articular secretome therapy in knee OA. They reported clinical improvement at 12-month follow-up in KOOS and pain reduction (pain VAS). However, the disease modifying effect was not significant. Similar findings were reported by Tan et al. (2021) have reported in a systematic review and meta-analysis of intra-articular MSC injections without additional therapy that single secretome application in sympto-matic knee OA resulted in good clinical outcomes with a reduction in pain and knee function.

Based on a meta-analysis conducted by Shoukrie et al., six studies reported WOMAC, baseline evaluation, and follow-up in a cohort, including 160 patients. Three studies were tracked for 12 years, one trial was monitored for 24 months, one study had a follow-up period of 48 weeks, and for six months, one trial was followed. ($P < 0.05$). Additionally, compared with the HA group, significantly more people experienced a 50% improvement in WOMAC, and after 12 months, the Secretome group experienced a 70% improvement rate, indicating that more patients experienced improvement. Six months after injection, a single injection of Secretome resulted in a 55 percent reduction in the WOMAC total score, the WOMAC pain score by 59 percent, the WOMAC stiffness score by 54 percent, and the WOMAC stiffness score by 54 percent. WOMAC physical function score. According to research in previous studies, clinical results improved six months after secretome injection. (Shoukrie et al., 2022)

Comparison between the secretome and HA shows that both have a positive effect on improving knee function. However, further analysis needs to be carried out to determine whether there are significant differences in the level of improvement provided by each therapy. Special attention also needs to be paid to the duration of the effects of both treatments

In Conclusion, this research is one of the studies that proves that administering Secretome has different clinical outcomes compared to administering AH in patients with grade I-III KL knee OA. In the future, it is hoped that this research can become a basis for development to increase knowledge about the importance of the role of administering Secretome. in knee OA conditions. However, to support the results of this research, further research is still needed using larger samples and longer follow-up times to obtain more accurate results.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCE

Abate M, Vanni D, Pantalone A, Salini V (2017). Hyaluronic acid in knee osteoarthritis: preliminary results using a four months administration schedule. Int J Rheumatic Dis. 20(2): 199–202. https://doi.org/10.1111/1756-185x.12572.

Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E (2016) Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. Am J Sports Med. 44(8): 2158–2165. https://doi.org/10.1177/0363546515609599.

Amo C del, Perez-Valle A, Atilano L, Andia I (2022). Unraveling the signaling secretome of platelet-rich plasma: Towards a better understanding of its therapeutic potential in knee osteoarthritis. J Clin Med. 11(3): 473. https://doi.org/10.3390/jcm11030473.

Amodeo G, Niada S, Moschetti G, Franchi S, Savadori P, Brini AT, Sacerdote P (2021). Secretome of human adipose-derived mesenchymal stem cell relieves pain and neuroinflammation independently of the route of administration in experimental osteoarthritis. Brain Behav Immun. 94: 29-40. https://doi.org/10.1016/j.bbi.2021.03.011.

Anitua E, Sánchez M, Orive G, Andia I (2007). The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 28(31): 4551-60. https://doi.org/10.1016/j.biomaterials.2007.06.037.

Antony J, McGuinness K, O'Connor NE, Moran K (2016). Quantifying radiographic knee osteoarthritis severity using deep convolutional neural networks. In: 2016 23rd International Conference on Pattern Recognition (ICPR), December 2016: 1195–1200.

Ayhan E, Kesmezacar H, Akgun I (2014) Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthoped. 5(3): 351-361. https://doi.org/10.5312/wjo.v5.i3.351

Bousnaki M, Bakopoulou A, Kritis A, Koidis P (2020). The efficacy of stem cells secretome application in osteoarthritis: A systematic review of in vivo studies. Stem Cell Rev Rep. 16(6): 1222-1241. https://doi.org/10.1007/-s12015-020-09980-x.

Charlesworth J, Fitzpatrick J, Perera NKP, Orchard J (2019). Osteoarthritis- a systematic review of long-term safety implications for osteoarthritis of the knee. BMC Musculoskelet Disord. 20(1): 151. https://doi.org/10.1186/s12891-019-2525-0.

Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H (2020a). Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 29–30. https://doi.org/10.1016/j.eclinm.2020.100587.

D'arrigo D, Roffi A, Cucchiarini M, Moretti M, Candrian C, Filardo G (2019). Secretome and Extracellular Vesicles as New Biological Therapies for Knee Osteoarthritis: A Systematic Review. J Clin Med. 8(11): 1867. https://doi.org-/10.3390/jcm8111867.

Delgado DA, Lambert BS, Boutris N, et al. (2018). Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. J Am Acad Orthop Surg Glob Res Rev. 2(3): e088. https://doi.org/10.5435/jaaosglobal-d-17-00088.

Gigis I, Fotiadis E, Nenopoulos A, et al. (2016). Comparison of two different molecular weight intra-articular injections of hyaluronic acid for the treatment of knee osteoarthritis. Hippokratia. 20(1): 26–31. https://pmc.ncbi.nlm.nih.gov/articles/PMC5074393/.

Gupta A (2022). Autologous adipose tissue vs. platelet-rich plasma for treatment of knee osteoarthritis. Biomedicines. 10(10):2527. https://doi.org/10.3390/biomedicines10102527.

Gupta RC, Lall R, Srivastava A, Sinha A (2019). Hyaluronic acid: Molecular mechanisms and therapeutic trajectory. Front Vet Sci. 6:192. https://doi.org/10.3389/fvets.2019.00192.

Hafez AR, Alenazi AM, Kachanathu SJ, Alroumi AM, Mohamed ES (2014). Knee osteoarthritis: A review of literature. Phys Med Rehabil Int. 1(5): 8. https://austinpublishinggroup.com/physical-medicine/fulltext/pmr-v1-id-1021.php.

He Y, Li Z, Alexander PG, Ocasio-Nieves BD, Yocum L, Lin H, Tuan RS (2020). Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. Biology. 9(8): 194. https://doi.org/10.3390/biology9080194.

Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, et al. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care & Research 64(4): 465–474. https://doi.org/10.1002/acr.21596.

Hunter DJ and Bierma-Zeinstra S (2019a). Osteoarthritis. Lancet. 393(10182): 1745-1759. https://doi.org/10.1016/s0140-6736(19)30417-9.

Iijima H, Isho T, Kuroki H, et al. (2018). Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. NPJ Regen Med. 3(1): 15. https://doi.org/10.1038/s41536-018-0041-8.

Jang S, Lee K, Ju JH (2021). Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci. 22(5):2619. https://doi.org/10.3390/ijms22052619.

Kim YS, Suh DS, Tak DH, Chung PK, Kwon YB, Kim TY, Koh YG (2020). Comparative matched-pair cohort analysis of the short-term clinical outcomes of mesenchymal stem cells versus hyaluronic acid treatments through intra-articular injections for knee osteoarthritis. J Exp Orthop. 7(1):90. https://doi.org/10.1186/s40634-020-00310-1.

Kohn MD, Sassoon AA, Fernando ND (2016). Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 474(8): 1886–1893. https://doi.org/10.1007/s11999-016-4732-4.

Koiri SP, Yang Y, Kui H (2018). Hyaluronic acid in the treatment of knee osteoarthritis: Review. Yangtze Medicine. 02(02): 62–72. https://doi.org/10.4236/ym.2018.22007.

Lopa S, Colombini A, Moretti M, de Girolamo L (2019). Injective mesenchymal stem cell-based treatments for knee osteoarthritis: from mechanisms of action to current clinical evidences. Knee Surg Sports Traumatol Arthrosc. 27(6): 2003-2020. https://doi.org/10.1007/s00167-018-5118-9.

Maheu E, Zaim M, Appelboom T, Jeka S, Trc T, Berenbaum F, Maasalu K, et al. (2011). Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F20 in symptomatic osteoarthritis of the knee (KOA). Results of a non inferiority, prospective, randomized, controlled trial. Clin Exp Rheumatol. 29(3): 527–35. https://pubmed.ncbi.nlm.nih.gov/21722501/.

Migliore A (2015). Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab. 12(1): 31-3. https://doi.org/10.11138/ccmbm/2015.12.1.031.

Miller LE, Bhattacharyya S, Parrish WR, Fredericson M, Bisson B, Altman RD (2021). Safety of intra-articular hyaluronic acid for knee osteo-arthritis: Systematic review and meta-analysis of randomized trials involving more than 8,000 patients. Cartilage. 13(1): 351S-363S. https://doi.org/10.1177/1947603519888783.

Műzes G, Sipos F (2022). Mesenchymal stem cell-derived secretome: A potential therapeutic option for autoimmune and immune-mediated inflammatory diseases. Cells. 11(15): 2300. https://doi.org/10.3390/cells11152300.

Nabavizadeh SS, Talaei-Khozani T, Zarei M, Zare S, Hosseinabadi OK, Tanideh N, Daneshi S (2021). Attenuation of osteoarthritis progression via a combination of intra-articular injection of synovial membrane-derived MSCs (SMMSCs), platelet rich plasma (PRP) and conditioned medium (Secretome). J Orthop Surg Res. https://doi.org/10.1186/s13018-021-02851-2.

Partan RU, Putra KM, Kusuma NF, Darma S, Reagan M, Muthia P, Radiandina AS, et al. (2023). Umbilical cord mesenchymal stem cell secretome improves clinical outcomes and changes biomarkers in knee osteoarthritis. J Clin Med. 12(22):7138. https://doi.org/10.3390/jcm12227138.

Rachmat N, Janmo Minulyo A, Zubaidi A (2021). An overview of the quality of life of knee osteoarthritis patients at the surakarta orthopedic hospital. Jurnal Keterapian Fisik. 6(1): 38–48. https://doi.org/10.37341/jkf.v0i0.271

Ramkumar PN, Harris JD, Noble PC (2015) Patient-reported outcome measures after total knee arthroplasty. Bone Joint Res. 4(7): 120–127. https://doi.org/10.1302/2046-3758.47.2000380.

Roos EM, Toksvig-Larsen S (2003). Health and quality of life outcomes knee injury and osteoarthritis outcome score (KOOS)-validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes. 1: 17. https://doi.org/10.1186/1477-7525-1-17.

Saccomano SJ (2018). Osteoarthritis treatment. The Nurse Practitioner 43(9): 49–55. https://doi.org/10.1097/01.npr.0000544281.05010.86.

Salaffi F, Carotti M, Stancati A, Grassi W (2003). Radiographic assessment of osteoarthritis: Analysis of disease progression. Aging Clin Exp Res. 15(5): 391–404. https://doi.org/10.1007/bf03327360.

Samma L, Rasjad C, Prihantono, Seweng A, Haryasena, Latief J, Bausat A, et al. (2021). Correlation between body mass index (BMI), visual analogue scale (VAS) score and knee osteoarthritis grading. Medicina Clínica Práctica. 4(1): 100228. https://doi.org/10.1016/j.mcpsp.2021.100228.

Santilli V (2016). Hyaluronic acid in the management of osteoarthritis: injec-

tion therapies innovations. Clin Cases Miner Bone Metab. 13(2):131–134. https://doi.org/10.11138/ccmbm/2016.13.2.131.

Schelbergen RF, van Dalen S, ter Huurne M, Roth J, Vogl T, Noël D, Jorgensen C, et al. (2014). Treatment efficacy of adipose-derived stem cells in experimental osteoarthritis is driven by high synovial activation and reflected by S100A8/A9 serum levels. Osteoarthritis Cartilage 22(8): 1158–1166. https://doi.org/10.1016/j.joca.2014.05.022.

Sharma L (2021) Osteoarthritis of the Knee. N England J Med. 384(1): 51–59. https://doi.org/10.1056/nejmcp1903768.

Shimizu H, Shimoura K, Iijima H, Suzuki Y, Aoyama T (2022). Functional manifestations of early knee osteoarthritis: a systematic review and meta-analysis. Clinical Rheumatology 41(9): 2625–2634. https://doi.org/10.1007/s10067-022-06150-x.

Shoukrie SI, Venugopal S, Dhanoa RK, et al. (2022). Safety and efficacy of injecting mesenchymal stem cells into a human knee joint to treat osteoarthritis: A systematic review. Cureus. 14(5): e24823. https://doi.org/10.7759/cureus.24823.

Sopiyudin Dahlan (2009). Besar sampel dan cara pengambilan sampel dalam penelitian kedokteran dan kesehatan. Jakarta: Salemba Medika.

Tamer TM (2013). Hyaluronan and synovial joint: function, distribution and healing. Interdisciplinary Toxicology 6(3): 111–125. https://pubmed.ncbi.nlm.nih.gov/24678248/.

Teixeira FG, Carvalho MM, Sousa N, Salgado AJ (2013). Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration?. Cell Mol Life Sci. 70(20): 3871–3882. https://doi.org/10.1007/s00018-013-1290-8.

Wang YC, Lee CL, Chen YJ, Tien YC, Lin SY, Chen CH, Chou PPH, Huang HT (2022) Comparing the efficacy of intra-articular single platelet-rich plasma (PRP) versus novel cross-linked hyaluronic acid for early-stage knee osteoarthritis: A prospective, double-blind, randomized controlled trial. Medicina (Kaunas). 58(8): 1028. https://doi.org/10.3390/medicina58081028.

Wasterlain AS, Braun HJ, Harris AHS, Kim HJ, Dragoo JL (2012). The systemic effects of platelet-rich plasma injection. Am J Sports Med. 41(1): 186-93. https://doi.org/10.1177/0363546512466383.

Zhang H, Zhang K, Zhang X, Zhu Z, Yan S, Sun T, Guo A, et al. (2015) Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. Arthritis Research & Therapy 17(1): 51. https://doi.org/10.1186/s13075-015-0557-x.