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Original article

KNEE OSTEOARTHRITIS TREATED WITH MESENCHYMAL STEM CELLS ARTHROSCOPY AND PHYSIOTHERAPY: EVALUATION WITH WHOQOL

Badalli Fitim[1], Ahmetaj Donjete[2], Atay Evren Fehmi[1], Xhoxhaj Veron [3]

[1]Ortomedica Hospital in Prizren, Kosovo
[2]AAB College, Prishtina, Kosovo
[3]Veroni Physiotherapy Clinic, Prizren, Kosovo
e-mail: badallifitim25@gmail.com

Abstract

Introduction: Osteoarthritis (OA), a degenerative joint disease, affects the quality of life (QoL). Although there are various therapy options, no existing therapy fully restores cartilage tissue. Mesenchymal stem cells (MSC) arthroscopy has emerged as a promising treatment. Impact of MSC arthroscopy with physiotherapy on patients' QoL requires further study.

Aim: This study examined the effects of MSC arthroscopy, combined with an eight-week standard physiotherapy regimen, on QoL in knee OA patients, with a focus on gender- and age-related differences.

Material and methods: This mono-centric clinical study involved 35 knee OA patients (aged 45-65, both genders) treated with MSC arthroscopy and physiotherapy. QoL was assessed pre- and post-treatment using the World Health Organization Quality of Life Brief Version (WHOQOL-BREF), focusing on physical health, psychological health, social health and environmental health domains. Additionally, the influence of age and gender on treatment efficacy was analyzed to understand demographic impacts on therapeutic response.

Results: The average WHOQOL-BREF score after the treatment in male patients presented better condition compared to the female in individual domains and for WHOQOL-BREF total. The physical health domain showed the greatest improvement followed by the psychological health domain. Younger age was associated with better outcomes in QoL.

Conclusion: The results of the study show MSC arthroscopy therapy in combination with physiotherapy for managing knee OA a promising treatment approach showing significant improvement in QoL. However, further research is needed to understand long-term effects and optimize the treatment of patients with diverse demographic backgrounds.

Keywords: OA, MSC, WHOQOL-BREF, QoL

Introduction

Knee osteoarthritis (OA) is a common degenerative joint disorder, with its prevalence increasing with age, making it a significant public health concern for the aging population[1,2]. Since the mid-20th century, the prevalence of OA has increased two-fold, and studies expect further increase in the future[3].

There are many risk factors contributing to OA incidence and development, including aging, since its prevalence increases with age, and gender, with females exhibiting a higher prevalence than males[4]. Other contributing factors include obesity, genetic background, ethnicity, and mechanical factors like joint structure, past injuries, and physical activity levels[5,6]. The joints, muscles, and tendons of patients with knee OA are damaged, which leads to joint pain, stiffness and swelling, all of which contribute to decreased mobility and reduced quality of life[7-9].

There are various treatment approaches for OA and the primary objective is to improve mobility and decrease pain[10,11].

The National Institute for Health and Care Excellence (NICE) highlights the importance of a holistic approach in the evaluation and treatment, to provide comprehensive and patient-centered care[12]. Therefore, combining different treatment approaches is considered an effective strategy in treatment of knee OA. Studies have demonstrated that physical exercise significantly reduces pain and improves physical function in OA patients[13-15]. Physical exercise is a preferred treatment option due to its advantages such as low cost, minimal side effects, and easy to administer. It is not only used as an individual therapy but also as part of a rehabilitation process after joint replacement or arthroscopic surgeries.

In recent years, regenerative medicine has gained attention as a potential alternative, with mesenchymal stem cells (MSC) therapy emerging as a promising treatment option for cartilage repair and symptom management in knee OA. MSC have many unique advantages, including differentiation into chondrocytes and regulation of inflammation[16]. Intra-articular injection of MSC has been shown to improve joint function, decrease pain, and prevent further progression [17]. However, despite numerous studies presenting the advantages of MSC therapy, results are variable across studies. The primary sources of variability include differences in MSC dosage, cell origin, and processing techniques, and therefore, standardization remains as a key challenge in this field[18].

Despite advancements in OA treatment, the effects of MSC, arthroscopy, and physiotherapy on health-related QoL in knee OA patients are still not fully understood. Additionally, there is limited information of the effect of demographic factors, such as age and gender, on therapy outcomes.

The World Health Organization Quality of Life Brief Version (WHOQOL-BREF) questionnaire is designed to evaluate physical, psychological, social, and environmental domains of QoL[19]. Evaluating WHOQOL-BREF scores before and after MSC arthroscopy, particularly when combined with standard physiotherapy, provides critical information on patients' experience and the effectiveness of this treatment modality.

Moreover, demographic factors such as gender and age in addition to chronic diseases, affect treatment efficacy. Understanding the variations is important to optimize treatment protocols.

This study analyzed WHOQOL-BREF scores in knee OA patients to evaluate the effects of MSC arthroscopy in combination with an eight-weeks physiotherapy regimen.

The aim of this study was to compare the QoL using WHOQOL-BREF of patients with knee OA before and after treatment with MSC arthroscopy combined with an eight-week standard physiotherapy based on gender and age.

Material and methods

This was a prospective mono-centric clinical study conducted in the Ortomedica Hospital in Prizren, Kosovo during the period March-December 2024. The study elaborated the QoL of 35

patients with a third-degree knee OA treated with MSC arthroscopy combined with eight-weeks of standard physiotherapy.

Before surgery, MSC were collected from patients under sterile conditions and processed using centrifugation at 5000 rpm for 10 minutes during the surgical procedure. Following the surgery, the isolated MSC were administered into the operated knee. Post-surgery, each patient underwent a three-phase physiotherapy rehabilitation program. In the first phase, knee exercises and positions that could trigger pain were avoided, focusing instead on patella mobilizations and isometric exercises combined with passive exercises to maintain knee extension. The second phase aimed to achieve full knee extension through active and active-assisted exercises to enhance muscle strength. During the third phase, the rehabilitation included strengthening and stretching exercises, as well as stationary cycling, balance training, treadmill walking, and running.

We used WHOQOL-BREF to assess the QoL of patients across 4 health domains with 24 different domain aspects. A total of 26 questions were elaborated (7 - physical health; 6 - psychological health; 3 - social relationships, and 8 - environmental health). Thus, a patient's physical, psychological, social, and environmental state of health were assessed separately. The response to each question was given on 5-point Likert scale rated from 1 to 5 and then transformed linearly to a scale of 0-100 where 0 points represent the worst while 100 points represent the best possible state of health with regard to the respective domain. All study participants were asked to answer the questionnaire. To assess the internal consistency of the four health domains, a reliability analysis was performed on the answers received.

This study was conducted in accordance with the principles of the Helsinki Declaration of 1975, revised in 2000. Informed consent was obtained from all participants prior to study enrolment. The Council of the Kosovo Medical Chamber and the Scientific Board of Ortomedica Hospital, Prizren, Kosovo approved the implementation of the study.

Statistical analysis

The quantitative parameters were analyzed using measures of central tendency (mean, median, range), and dispersion measures (standard deviation). Categorical data were presented as counts and percentages. In order to understand the internal consistency of the WHOQOL-BREF questions, the reliability analysis of the received answers was analyzed by calculating the Cronbach's alpha coefficient. Association between gender and diagnosed chronic disease were checked using the Fisher exact test. The Shapiro-Wilk W test was used to determine the normality of frequency distribution of age. The Mann Whitney U test was used to compare differences between genders related to age. The Wilcoxon signed-rank test and Sign test were used for analysis of two dependent quantitative not normally distributed parameters (comparison of answers score before/ after treatment). Spearman's rang order correlation was used as a measure of the strength and direction of association between age and WHOQOL-BREF domain and total score after treatment. Data obtained in the study were processed in the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). A two-sided analysis with a significance level of $p<0.05$ was used to determine the statistical significance.

Results

Study group characteristics

The study sample analyzed 35 patients with knee OA treated with MSC combined with eight-weeks of standard physiotherapy. There were 14(40%) male and 21(60%) female patients,

with male/ female ratio of 0.67:1. The average age of patients in the study group was 54.97±7.39 years with median IQR=53(47-63). The average age of male patients was 49.07±4.99 years with median IQR=47.5(46-51) and of female 58.90±6.01 years with median IQR=61(55-63). About 75% of male and female patients were younger than 51 and 63 years, respectively. Female patients in the study group were significantly older compared to male (Z=-3.788; p=0.0001).

The presence of other chronic diseases besides third-degree knee OA was reported by 4(28.57%) male and 10(47.62%) female patients, with no significant association between gender and diagnosed chronic diseases (p=0.259).

Internal consistency

No missing data on WHOQOL-BREF questions were found in all four domains. The values obtained for the Cronbach's Alpha coefficient before and after treatment were 0.911 *vs*. 0.921 for physical health (Items-7), 0.891 *vs*. 0.899 for psychological health (Items-6), 0.864 *vs*. 0.871 for social relationships (Items-3) and 0.878 *vs*. 0.873 for environmental health (Items-8), respectively. The Cronbach's Alpha coefficient indicated high consistency i.e., reliability of received answers for all four WHOQOL-BREF domains.

Comparison of treatment effect

Significant improvement of QoL after treatment was found for WHOQOL-BREF total score and for all four domains (physical health, psychological health, social health and environmental health) for both genders and for the study sample as a whole. The QoL average score after treatment in male patients was better compared to female patients in both overall scores and individual WHOQOL-BREF domains. Also, men in relation to women had bigger improvement (after/before difference) in QoL for each of the four domains as well as for the total WHOQOL-BREF (Table 1).

Patients had the biggest average improvement of the QoL (after/before difference) in the physical health domain for 48.67±12.37%, followed by psychological health domain for 43.81± 15.70%. The QoL had the slightest average improvement in the environmental health for 15.90±9.44%, followed by the social health for 20.24±12.17% (Table 1).

The greatest improvement in QoL after treatment for both genders was observed in the domain of physical health, males had an average of 88.77±11.79% and females an average of 72.28 ±12.11%. Half of male and female patients in the sample had QoL physical health ≥91.1% *vs*. ≥71.4%, respectively. Additionally, compared to the other domains, patients reported worst QoL after treatment related to the environmental health, which was 62.51±14.55% for male and 57.59±13.08 for female patients. Related to this domain, half of male and female patients had QoL scores <59.4% *vs*. <56.2%, respectively (Table 1).

The average total QoL of the study patients after treatment was 71.57±12.89% with half of them with QoL ≥74.18% and quarter of them with QoL >79.6%. For male patients, the average total QoL after treatment was 79.26±11.41% with min/max of 58.4/94.1% and half of them with QoL ≥78.6, and for females it was 66.45±11.35 with min/max of 50.9/93.2 and half of them with QoL ≥65.8% (Table 1).

Table 1. Comparison of WHOQOL-BREF scores of patients with knee osteoarthritis before and after treatment with MSC arthroscopy combined with physiotherapy by gender

WHOQOL-BREF domains		Patients with third-degree knee osteoarthritis					p
		N	Mean± SD	Min / Max	Median (IQR)	Difference	
QoL Physical health (%)							
male	**before**	14	37.75±14.27	17.8/60.7	35.7(25-50)	51.02±12.48	Z=(3.192); p=0.001*
	after	21	88.77±11.79	60.7/100	91.1(82.1-100)		
female	**before**	14	25.17±15.95	3.5/60.7	25(10.7-35.7)	47.11±12.35	Z=(3.939); p=0.0001*
	after	21	72.28±12.11	50/100	71.4(64.3-82.1)		
total	**before**	14	30.20±16.33	3.5/60.71	28.6(17.9-42.9)	48.67±12.37	Z=(5.163); p=0.0001*
	after	21	78.88±14.37	50/100	82.1(71.4-89.3)		
QoL Psychological health (%)							
male	**before**	14	37.20±15.37	12.5/66.6	33.3(29.2-50)	47.02±18.01	Z=(3.301); p=0.001*
	after	21	84.23±11.22	62.5/100	87.5(79.2-91.7)		
female	**before**	14	26.39±15.94	0/66.6	25(12.5-33.3)	41.67±14.01	Z=(3.830); p=0.0001*
	after	21	68.05±12.80	50/100	66.7(54.7-75)		
total	**before**	14	30.71±16.39	0/66.6	29.2(16.7-41.7)	43.81±15.70	Z=(5.163); p=0.0001*
	after	21	74.53±14.46	50/100	75(62.5-87.5)		
QoL Social health (%)							
male	**before**	14	58.33±14.98	33.3/91.6	58.3(50-66.7)	23.21±13.15	Z=(3.312); p=0.001*
	after	21	81.55±12.73	58.3/100	83.3(75-91.7)		
female	**before**	14	49.60±13.81	33.3/83.3	50(41.7-58.3)	18.25±11.37	Z=(4.017); p=0.0001*
	after	21	67.86±13.76	41.7/91.7	66.7(58.3-75)		
total	**before**	14	53.09±14.72	33.3/91.7	50(41.7-58.3)	20.24±12.17	Z=(5.031); p=0.0001*
	after	21	73.33±14.82	41.7/100	75(58.3-91.7)		
QoL Environmental health (%)							
male	**before**	14	46.43±8.57	34.4/65.6	45.3(40.6-53.1)	16.08±8.82	Z=(3.297); p=0.001*
	after	21	62.51±14.55	40.6/84.4	59.4(56.1-75)		
female	**before**	14	41.82±8.97	28.1/59.4	37.5(34.5-5)	15.77±10.04	Z=(4.020); p=0.0001*
	after	21	57.59±13.08	28.2/ 81.2	56.2(50-68.7)		
total	**before**	14	43.66±8.98	28.1/ 65.6	40.6(37.5-53.1)	15.90±9.44	Z=(5.006); p=0.0001*
	after	21	59.56±13.69	28.2/ 84.4	56.4(50-68.7)		
QoL Total (%)							
male	**before**	14	44.93±10.97	30.3/61.9	44.7(35.2-52.9)	34.33±11.51	Z=(3.296); p=0.001*
	after	21	79.26±11.41	58.4/94.1	78.6(74.7-91.1)		
female	**before**	14	35.74±11.11	21.7/61.8	35.2(27.4-37.8)	30.70±8.68	Z=(4.015); p=0.0001*
	after	21	66.45±11.35	50.9/93.2	65.8(56.2-75.2)		
total	**before**	14	39.42±11.11	21.7/61.8	35.2(27.4-37.8)	32.15±9.91	Z=(5.159); p=0.0001*
	after	21	71.57±12.89	50.9/94.0	74.2(60-79.6)		

Difference = After - Before treatment SD - standard deviation; IQR - Interquartile range, *significant for $p<0.05$

Table 2. Frequencies of WHOQOL – BREF therapeutic effect change in two time points in patients with knee osteoarthritis treated with MSC arthroscopy combined with physiotherapy

Parameters	WHOQOL - BREF domains		Social health
	Physical health	Psychological health	
p - value	0.0001*	0.0001*	0.0001*
	A< B-0	A<B-0	A<B-0
Determined	A>B-35	A>B-35	A>B-35
change	A=B-0	A=B-0	A=B-0
	N=35	N=35	N=35
Parameters	**Environmental health**	**Total QoL**	
p - value	0.0001*	0.0001*	
	A<B-1	A<B-0	
Determined	A>B-33	A>B-35	
change	A=B-1	A=B-0	
	N=35	N=35	

A - After, B - Before, *significant for p<0,05

All patients in each of the four WHOQOL-BREF domains and in total score experienced QoL improvement after treatment, except in the environmental health domain, where 1 patient reported worse QoL after treatment, and another one showed no change in the environmental health before/after treatment (Table 2).

There was a significant negative correlation between the age of patients with knee OA after treatment with MSC arthroscopy combined with eight-weeks of standard physiotherapy and WHOQOL-BREF domain and total scores. We found: a) significant negative moderate correlation between the age and the social health for $R_{(35)}$=-0.509; p=0.0017; b) significant negative weak correlation between the age and the environmental health for $R_{(35)}$=-0.309; p=0.0203; c) significant negative moderate correlation between the age and the physical health for $R_{(35)}$=-0.753; p=0.00001; d) significant negative moderate correlation between the age and the psychosocial health for $R_{(35)}$=-0.674; p=0.00001; and e) significant negative moderate correlation between the age and the total WHOQOL-BREF score for $R_{(35)}$=-0.628; p=0.00005. Better QoL after treatment across all WHOQOL-BREF domains and the total score significantly correlated with younger age of patients (Figure 1).

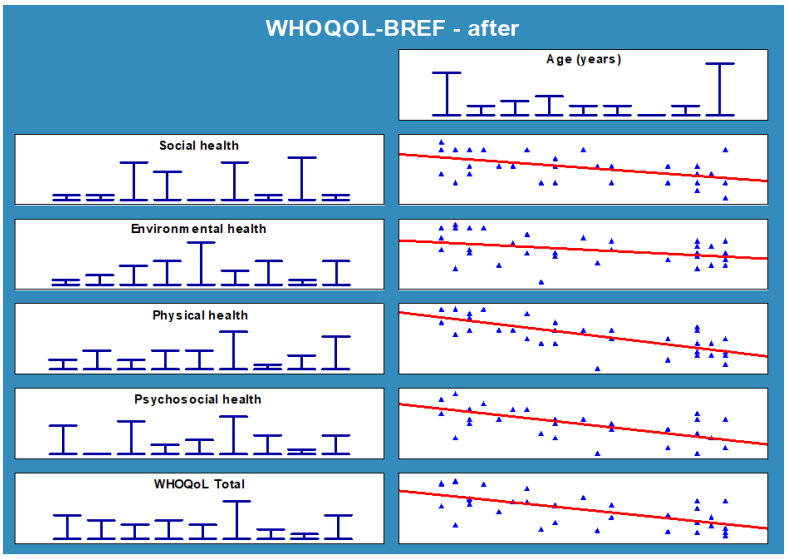

Fig. 1. Correlation between WHOQOL - BREF domains and total scores and age of patients with knee osteoarthritis after treatment with MSC arthroscopy combined with physiotherapy

Discussion

OA is one of the most prevalent degenerative joint diseases which significantly affects patients' QoL by limiting function and causing pain. To this date, there is no existing treatment option which can fully restore the cartilage tissue. However, as regenerative medicine started to gain attention recently, MSC arthroscopy emerged as a promising treatment option considering the unique features that MSC hold such as self-renewal capabilities, differentiation potential, and immunomodulatory properties[20,21].

In this study, WHOQOL-BREF scores of 35 knee OA patients were analyzed. The results were compared between males and females and across different age groups after treatment with MSC arthroscopy combined with an eight-weeks standard physiotherapy program.

The gender distribution in the cohort study was relatively balanced, with 40% male and 60% female patients. The average age was 54.97 years, which is clinically relevant considering OA prevalence increases with aging.

The results of the WHOQOL-BREF score both overall and across all four domains (physical health, psychological health, social health, and environmental health) showed significant increase after MSC arthroscopy treatment combined with an eight-weeks standard physiotherapy program. According to the literature, these findings are consistent with previous clinical studies examining the efficacy of MSC in knee OA. A study by Freitag *et al.,* investigated the effect of adipose-derived MSC for knee OA treatment, where patients received either one or two injections. The results of the study showed that both treatment groups had significant improvements in function and pain without reporting any serious adverse effects[22]. Additionally, another study comparing the efficacy of umbilical cord-derived MSC to hyaluronic acid showed that patients who received umbilical cord-derived MSC showed more improvement compared to patients who received hyaluronic acid[23]. Although MSC provides improvement in the condition, it is not known yet which biomolecules are responsible for this effect. A meta-analysis including 19 publications and 584 patients was conducted to present the findings regarding MSC effect on OA[24]. It was concluded that significant improvements were observed in patients with knee OA after MSC

therapy. However, the included studies had certain limitations regarding small cohort sizes, short follow-up periods after treatment, and more importantly significant variations in MSC sources and treatment protocols, which affect the generalizability and comparability of the findings.

In this study, the post-treatment QoL scores were found higher in males compared to females both in overall scores and in individual domains. However, these results are not enough to conclude that the treatment is more effective in male patients. Factors such as such as the cohort size and, more importantly, the significant age difference between male and female participants, where females were older, need to be considered when interpreting these findings. Nevertheless, this trend is also shown in another study examining the efficacy of total knee arthroplasty showing less improvement in female patients in the first year following surgery[25]. Although significant improvements were observed in both male and female patients in both total score and in individual health domains, when the results are analyzed regarding the age of the patients, negative correlation was observed between age and improvement after treatment. These results showed that younger patients experienced better improvements in response to treatment compared to older patients.

These findings suggest that factors such as age and biological differences may affect treatment outcomes.

In this study, the greatest average improvement across individual health domains was observed in the physical health domain for both male and female patients, with an average of 88.77±11.79% and 72.28±12.11%, respectively after treatment. The second most significant improvement was observed in psychological health domain, with an average of 84.23±11.22 for males and 68.05±12.80 for females after treatment. Although studies show higher OA prevalence and pain intensity in females, there is lack of information on the comparison of treatment efficacy between males and females[26].

Although the results of this study are consistent with the literature, showing improvement in QoL after MSC arthroscopy and suggesting MSC arthroscopy as a promising treatment option, there is still lack of information in the literature regarding relation of the treatment efficacy and factors such as MSC source, processing methods, and optimal dosage[27-30].

This study demonstrates that MSC arthroscopy combined with a standard eight-week physiotherapy regimen, emerges as a potential treatment option for knee OA and it leads to improvements in QoL across physical health, psychological health, social health, and environmental health domains. While the treatment effects were more pronounced in males compared to females and in younger patients compared to older patients, all participants experienced a significant improvement overall. These findings highlight the need for further research to optimize this treatment approach and improve its effectiveness across diverse patient populations.

Conflict of interest statement. The authors declare no conflict of interest.

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