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SYSTEMATIC REVIEW

A Systematic Review of Intra-Articular Hyaluronic Acid, Corticosteroids, and Platelet Rich Plasma Injections on Gait Biomechanics in Knee Osteoarthritis

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ABSTRACT

The purpose of this systematic review was to assess the consequences of injections of corticosteroid (CS), hyaluronic acid (HA), and platelet-rich plasma (PRP) on gait metrics in patients with osteoarthritis (OA). We examined through the Cochrane library, SCOPUS, Web of Science, and PubMed to find pertinent publications that evaluated the effects of CS, HA, and PRP injections on gait parameters in patients with OA of the knee. Utilizing the Physiotherapy Evidence Database (PEDro) scale, quality evaluation was put into practice. A total of 15 publications with 11 randomized control trials based studies describing results for 1160 participants were published. The combined data for velocity showed a significant change with HA injection (SMD: 0.28 95% CI 0.04 to 0.53). In comparison to the control group, the HA injection group's stride length was longer, however the disparity was not statistically significant (SMD: 0.16 95% CI -0.09 to 0.4). No statistically significant differences were observed between the HA and control groups for the other variables. Results demonstrated a significant increase in knee range of motion after CS injection compared to placebo control (MD= 1.70 95% CI -0.03° to 3.37°) and without intervention. There is insufficient data to conclude that PRP and CS have a greater therapeutic advantage than one another in terms of participants' gait. Nonetheless, no intervention is supported by the available data, and HA is still thought to be more effective than a placebo. To find out how well therapeutic injections affect patients with knee OA's function and gait, more research is needed.

Keywords: Corticosteroid, Hyaluronic Acid, Knee injury, Osteoarthritis, Platelet Rich Plasma.

INTRODUCTION

Knee osteoarthritis (OA), a degenerative joint disease, is one of the most common musculoskeletal disorders, affecting about 20% of individuals over the age of 45 and it is thought to be the main factor contributing to older individuals' disabilities.[1,2] According to the Global Burden of Disease 2010 study, people living with knee OA are estimated to increase considerably.[3] Knee OA is a disease characterized by cartilage erosion, synovial inflammation, soft tissue fibrosis, and osteophytes. Severe conditions of this disease have an essential effect on the patient´s life, functional activities, and gait variables.[4]

A comparison of patients with knee OA with healthy people has shown the difference in gait kinetics and kinematics. Patients with knee OA exhibited lower knee and ankle joint moments, reduced ground reaction forces, greater knee flexion at heel strike, and reduced knee extensor force and walking velocity compared to healthy subjects.[5,6] Since the limitation of full flexion and painful walking are the common symptoms of this disease, Therefore patients with knee OA attempt to adopt a gait pattern to unload the affected structures during walking.[7] According to a study there is a correlation between the severity of OA and gait, and patients with OA develop ways to maintain their step length and gait velocity. Despite their walking velocity, patients with more severe OA often exhibit increased joint stiffness as a defense against the effect of external forces. On the other hand, patients with knee OA are subject to high overload. Therefore, these patients

reduce their speed to reduce the loading and pain in this way.[8]

There are several options for the treatment of knee OA. Rehabilitation is widely recommended in primary care settings for managing OA. Rehabilitation is even considered the core treatment of OA and is recommended for all patients biomechanical therapies, weight management, exercise therapy, strength training, and self-management and education, and a physically active lifestyle are all common components of OA rehabilitation.[9] Intra-articular (IA) injection has been widely used to treat knee osteoarthritis. Platelet-rich plasma (PRP), Hyaluronic acid (HA), and corticosteroid (CS) are the most commonly used in these patients. Several systematic and meta-analytic studies have been conducted on the effects of these three injections or knee OA, each of which has reported significant effects of HA, CS, and PRP separately.[10-14] However, the efficacy of injections on gait parameters such as kinetic, kinematic and range of motion is not well known. Therefore this review aims to conduct the first systematic review that investigates the effect of three types of knee injections (PRP, HA, and CS) on gait parameters in patients with knee OA.

METHODS

Our systematic review followed the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement, and the protocol of this systematic review has been registered in PROSPERO registration number: CRD42016051797.

Data Sources and Search Strategy

We searched PubMed, SCOPUS, Web of Sciences, Cochrane library, and Google Scholar from 2000 to 9 June 2017 by using different combinations of free text and MeSH terms (via MEDLINE) related to the topics of PRP, HA, CS, gait and knee Osteoarthritis. We reviewed through the references of the articles that were included and reviews to find possible further research that our computerized search did not turn up. Furthermore, ProQuest database was searched to find potentially related unpublished research and gray literature (theses, dissertations, conference papers, and research reports). Only English-language studies were retrieved.

Eligibility Criteria

We initiated our search with criteria for inclusion in place. We used randomized controlled trials (RCTs) or randomized controlled trials and pilot RCTs, and clinical trials (CT) without proper randomization or concurrent controlled group were included. Other study designs, as well as review articles, were excluded. Studies of patients with knee pain with a diagnosis of knee OA in both sexes (male and/or female) were included. We included studies that compared knee intra-articular injections (including; PRP, HA, and CS) together or with the placebo control group. Outcomes of interest were gait parameters, spatiotemporal parameters including velocity, stride length, stride width, and cadence; kinetic and kinematic parameters such as knee range of motion (ROM), angles, and ground reaction force (GRF), torque, etc. Studies of patients with OA with a history of total knee joint replacement and injections were examined as an adjuvant to surgery and were excluded. Furthermore, we excluded the studies that compare injections with physiotherapy or surgery interventions. Those studies where gait parameters were not measured as a primary endpoint were not included in this review.

Study Selection and Risk of Bias Assessment

Following the process of eliminating duplicates using the reference manager software Endnote, research titles and abstracts were obtained in order to pinpoint studies that would satisfy the inclusion requirements. Subsequently, an additional search was carried out utilizing every discovered keyword across the complete text of those papers that may qualify. Two authors (FB and FM) conducted the final study selection by checking the full texts separately. A third author (AA) was available for any uncertainty between reviewers. Studies with the following in the title or abstract were eligible: (1) Participants were subjects with knee OA, (2) The intervention included PRP, HA, and CS intra-articular injections, (3) The outcome measures included gait parameters, and (4) study designs included RCT and Cts. The study selection process is summarized in a PRISMA flow diagram (Figure 1).

After final study selection, the full text of eligible studies was assessed for risk of bias assessment. We had a protocol deviation for quality assessment of included studies from Downs and Black checklist to the Physiotherapy Evidence Database (PEDro) scale according to the reviewer's comments on our study protocol. The PEDro Scale total is a 10, with the item "specified eligibility criteria" not scored.[15]

A score of 7-10 on the total PEDro scale was considered high quality, medium quality was considered for scores of 4-6, and studies that scored less than four were considered low quality. Two review team members conducted this process independently (FB and FM). Any discordance was resolved by consensus in each phase. The third person (AA) is used to resolve the discrepancy when necessary.

Data Extraction

For each study selected for inclusion, two team members independently extracted data. Data items included overall study characteristics (including first author, year of publication, study design, and the number of participants), characteristics of participants (age, gender, and knee severity), intervention and comparison group characteristics (type of injection and follow up time), outcome measures and key results. Outcomes are presented separately for studies with several outcome measurements during the follow-up time. Means and standard deviations (SD) for each gait variable were obtained. Our primary outcome was walking speed, and secondary outcomes were step length, step width, cadence, knee range of motion, knee angles, forces, and knee moment during walking.

RESULTS

The review identified 15 studies that evaluated the effects of knee injections (HA, CS, and PRP) on the spatiotemporal, kinetic, and kinematic parameters during walking. We initially identified 1290 studies and 1146 studies were excluded on the basis of their title and keywords. After a further screening to evaluate the relevance of the abstract and the aim of each study and 44 studies were retrieved (Figure 1). Eleven studies involved RCTs and 4 studies involved clinical trials. The effects HA injection on gait parameters in subjects with knee OA was assessed in 13 articles that included in this study. Two studies with RCT design compares effects of HA and CS and one study evaluated the comparison of PRP and CS on gait of individuals with knee OA. In a single trial, the effects of PRP and HA on gait metrics in participants with knee OA were compared.[16]

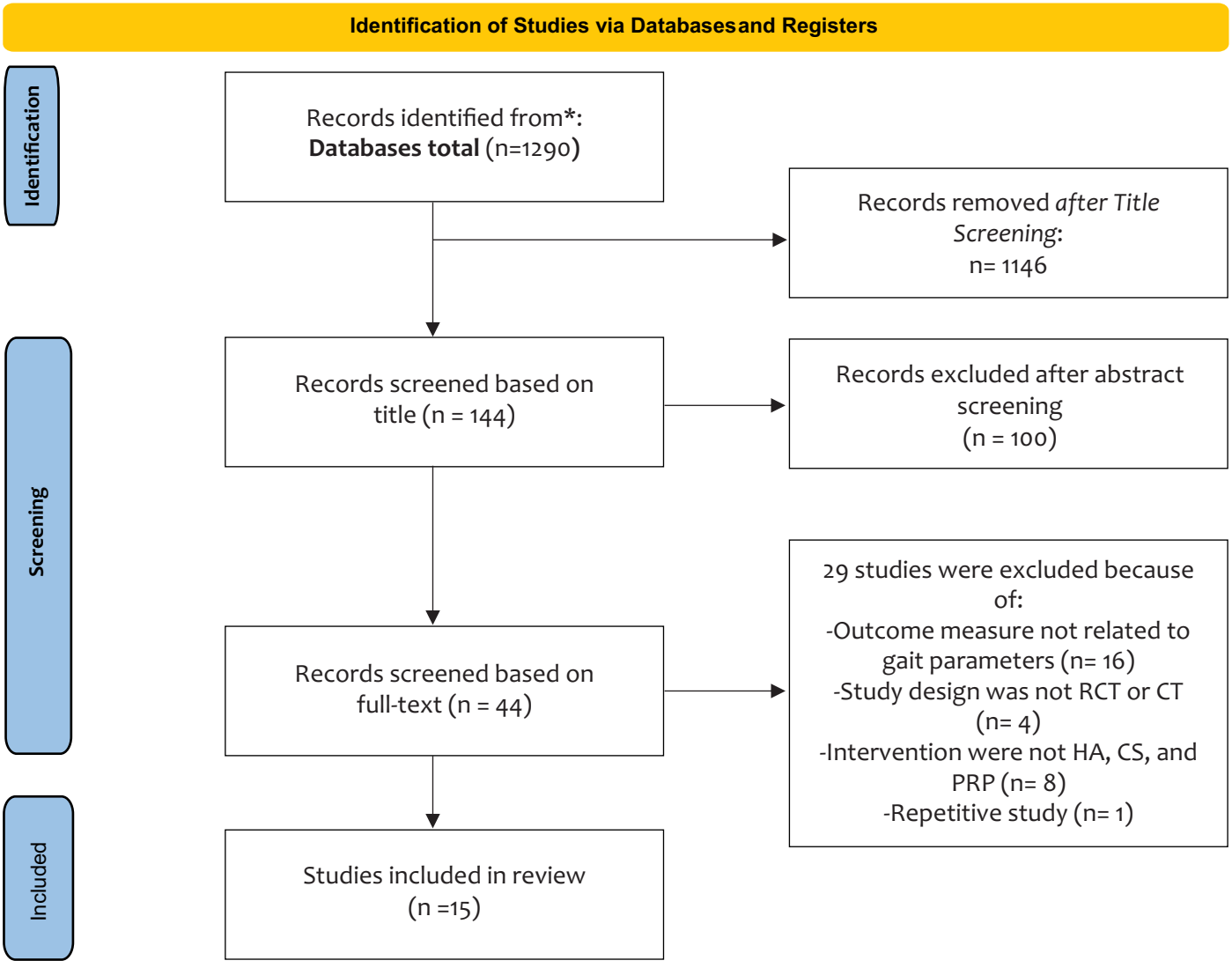

Figure 1: The flow diagram of study selection process based on PRISMA guideline

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Quality Assessment of Included Studies

The total score of PED roand study demographics is reported in Table 1 for each study. Of the 15 interventional studies included in this review, eight studies were scored as high quality.[16-23] Three studies were scored as medium quality,[24-26] and four studies had low quality score.

Study Participants

A total of 1160 participants were examined, and follow-up time was recorded for the selected studies. The mean age for included participants was 63.83 years (Min: 53 years and Max: 73 years).

Outcomes

Spatial-Temporal Gait Characteristics

Time-distance variables were reported in nine studies and included velocity (m/s), cadence (steps/min), strides length (meter), strides time, single support time, and double support time (second). There was an increase in velocity during walking with HA in six studies[19,26-30] that evaluated the effect of HA, and two studies' demonstrated a significant increase in velocity. Tang *et al*, found significant difference between HA group in comparison with control group for velocity after 6 month; (MD= 0.11 m/s, 95% CI 0.01 to 0.21 m/s). Pooled SMD for studies that assessed the effect of HA on velocity was (0.28 m/s, 95% CI 0.04 to 0.53).[30]

Five studies evaluated stride length.[26-30] All studies examined the effects of HA injection, and one study compared the effect of HA and CS injections. Two studies demonstrated a significant increase in stride length during walking with HA injection.[26,30] The remaining studies did not report meaningful change after intra-articular injections. Pooled SMD for studies that assessed the effect of HA on stride length was (0.16 m, 95% CI -0.09 to 0.4).

The effect of HA injection on stride time was investigated in three studies. There were no significant changes after HA injection in single-limb support time[27,31] and double support time, Huang *et al*., showed that both groups (HA and Placebo groups) consumed a reduction in time on the 50-foot walking test. But this difference was not significant for both groups.[20]

There was a trend for increasing cadence[30] with HA compared to control after six months (MD= 16.6 step/min, 95% CI 7.06 to 26.14 step/min). Skwara *et al*., in one study, compared the effect of HA injection and CS. Results showed no significant differences in walking speed before and after HA and CS injections and also no significant differences between the two groups.[28] The results for time-distance parameters are provided in table 2.

Kinetic Parameters

Two studies evaluated the effect of injections on vertical force.[28,29] One study compared the effects of both injections (HA and CS) on the vertical force. They reported no significant difference between HA and CS injections.[28] However, an increase in vertical force after the injection of HA was reported in one study (MD= 0.03, 95% CI -0.01 to 0.06).[29] Lester *et al*. considered the effects of HA on-ground impact and found no significant changes after injection (MD= -0.01N, 95% CI -0.13 to 0.11N).[27] Also, Miltner *et al*, reported that knee flexion and extension torques increased after injection of HA (MD flexion= 6.94Nm 95% CI -6.07 to 19.95 Nm, MD extension =5.78 Nm 95% CI -11.91 to 23.47 Nm).[31]

Three studies evaluated the effect of HA injection on knee moments.[26,28,29] Yavuzer *et al*. indicated that knee extensor (MD= -0.12N/kg 95% CI -0.25N/kg to 0.01N/kg) and adductor moments (MD= -0.04N/kg 95% CI -0.12N/kg to 0.04N/kg) decreased after HA injection in patients with knee OA.[29] Skwara *et al*., which analyzed the effect of HA compared to CS showed no significant differences after HA and CS injections.[28] The results for kinetic parameters are provided in table 3.

Two articles compared the effects of CS with HA,[17,28] one study compared the effects of CS with PRP,[25] and one study compared the effects of HA with PRP.[16] Two studies demonstrated a significant increase in knee ROM after CS injection compared to placebo control (MD= 1.70 95% CI -0.03° to 3.37°) and without intervention.[17,23] The only research showed a significant increase in knee ROM in the stance phase of gait after HA injection (MD= 6° 95% CI 2.22° to 9.78°). However, there were no significant differences between HA and CS injection groups after six months in knee ROM.[17,28] The other studies showed no significant difference in knee ROMs.[26,17,22,23,25,27] The results for kinematic parameters are provided in table 4.

DISCUSSION

We systematically reviewed studies to identify, evaluate, and summarize the current evidence for the effects of HA, CS, and PRP injections on the gait of subjects with knee OA. According to the data of this study, few studies were available on the effects of PRP and CS injections. Due to a lack of information, most of the results were related to HA injections. The main finding of this systematic review was that the HA injection has a significant effect on the speed of walking, but for other gait parameters, there was no significant effect of knee injections in patients with knee OA.

Table 1: Major characteristics of included studies

Author/ year	Baseline -Sample Size	Age: Mean (SD)	OA Severity (Kellgren-Lawrence grade)	Study Design	Intervention(s)			Follow up Time	Variables	Total PEDro Score
					HA	CS	PRP			
Tammachote. et al./2016 [17]	HA (n = 50) CS (n = 49)	62.6 (7.1) 61.0 (6.2)	I to IV	Double-Blind, RCT	✓	✓		2weeks 3 months 6 months	Knee angle	8
Forogh et al./2016 [25]	PRP (n=24) CS (n=24)	59.1 (7.3) 61.1 (6.7)	II, III	Double-blind RCT		✓	✓	2 months 6 months	Active and passive ROM	6
Tang et al./2015[26]	HA (n=25) Healthy (n=15)	65.0 (8.3) 64.7 (7.3)	I, II	Clinical trial	✓			1week , 3 months 6 months	Walking speed Step length Knee moment	3
Filardo et al. /2015 [16]	PRP (n = 94) HA (n = 89)	53.3 (13.2) 57.5 (11.8)	I, II, III	RCT	✓		✓	2 Months 6 Months 12 Months	Knee ROM	7
DeCaria et al./2012 [19]	HA (n = 15) Placebo control (n = 15)	71.9 (6.8) 72.3 (5.4)	II, III	RCT	✓			4 weeks 3 months 3 6months	Gait velocity	8
Huang et al./2011[20]	HA (n = 100) Placebo control (n = 100)	65.9 (8.1) 64.2 (8.4)	II, III	RCT	✓			1 week 5 weeks 13 weeks 25 weeks	50-foot walking time	8
Decaria et al./2011 [18]	HA (n = 15) placebo control (n = 15)	71.9 (6.8) 72.9 (5.5)	mild to moderate (according to the American College of Rheumatolog)	RCT	✓			3months 6 months	double support time stride time	8
Lester et al./2010 [27]	HA (n= 53 ,25 M, 28 F)	61.8 (8.9)	Not known	Clinical trial	✓			Before/ After 3 Weeks	Single & double limb support time Ground impact Velocity Cadence Step length	3
Skwara et al./2009 [28]	HA (n=30) CS (n=30)	60.9 (10.4) 61.8 (10.5)	II, III	RCT	✓	✓		12 weeks	Stride length Gait Velocity Knee ROM Knee moment Vertical force	5

Table 1: Major characteristics of included studies (Cont . .)

Petrella et al./2006 [22]	HA (n = 53) Placebo control (n = 53)	63.9 (9.3) 62.4 (10.3)	I, II, III	RCT	✓		6 Weeks	Knee ROM	8
Yavuzer et al/2005 [29]	HA (n = 12)	63.2 (4.4)	I ,II		✓		Before/ After 4 Weeks	Stride length Gait Velocity Stride time Knee moment Vertical force	3
Tang et al./2004 [30]	HA (n = 15) Control (n = 15)	61.3 (10.2) 63.5 (11.3)	II, (according to halfback Grade)		✓		1week 3 Months 6 Months	GRF Gait velocitycadence Step length Stride time (s) Single & double limb support	5
Raynauldet al./2003 [23]	CS (n = 34) HA (n = 34)	63.1 (9.1) 63.3 (9.0)	II, III	RCT		✓	12 months 24 months	50-foot walking time, Knee ROM	8
Petrella et al./2002 [21]	HA (n= 25) NSAIDs + HA (n=29) NSAIDs+ Salin (n=26) Placebo Control (n=28)	67.3 (8.9) 65 (9.7) 66.3 (8.8) 62.6 (9.5)	I, II, III	RCT	✓		4 Weeks	SPW test (self-paced walking test)	8
Miltner,/ 2002 [31]	HA Group (n=12) Control (n=13)	67.0	II, III	RCT	✓		1 week	Flexion torque Extension torque	3

RCT: Randomized Controlled Trial, HA: Hyaluronic Acid, CS: Corticosteroid, PRP: Platelet Rich Plasma, M: Male, F: Female

Table 2: Summary of time-distance characteristics for control and intervention group(s)

			Control Group		Intervention(s)			
Variables	**Study**	**Follow-up Time**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean Diff (95% CI)**	**Significant Change***
Velocity(m/s)	Tang et al./2015	1 week 3 month 6 month	0.47 (0.18)	25	HA: 0.58 (0.17) HA: 0.59 (0.24) HA: 0.59 (0.24)	25	0.11 (0.01 to 0.21) 0.12 (0.01 to 0.24) 0.12 (0.01 to 0.24)	↑ ↑ ↑
	DeCaria et al./2012	6 months	NR	15	NR	15	0.12 (-0.18 to 0.20)	
	Tang et al./2004	1week 3 months 6 months	0.50 (0.11)	15	HA: 0.62 (0.10) HA: 0.63 (0.16) HA: 0.61 (0.16)	15	0.12 (0.04to 0.20) 0.13 (0.03 to 0.23) 0.11 (0.01 to 0.21)	↑ ↑ ↑
	Yavuzer et al./2005	4 Weeks	0.81 (0.2)	12	HA: 0.82 (0.2)	12	0.01 (-0.16 to 0.18)	-
	Lester et al./2010	3 Weeks	0.64 (0.12)	53	HA: 0.66 (0.2)	53	0.02 (-0.04 to 0.08)	-
	Skwara et al./2009	12 weeks	1.16 (0.17) 1.15 (0.20)	24 26	HA: 1.19 (0.18) CS: 1.13 (0.18)	24 26	0.03 (-0.07to 0.13) -0.02 (-0.13to 0.09)	-
Single Support (%GC)	Tang et al./2004	1week 3 months 6 months	37.5 (3.5)	15	HA: 36.6 (2.5) HA: 36.2 (3.2) HA: 37.1 (3.0)	15	-0.9 (-3.17 to 21.37) -1.3 (-3.81 to 1.21) -0.4 (-2.84 to 2.04)	- - -
Single Support Time (s)	Lester et al./2010	3 weeks	0.39 (0.03)	53	HA: 0.40 (0.03)	53	0.01 (-0.011 to 0.014)	-
Double Support Time(s)	Lester et al./2010	3 weeks	0.16 (0.035)	53	HA: 0.17 (0.03)	53	0.01 (0.0 to 0. 02)	↑
Double Support (%GC)	Tang et al./2004	1week 3 months 6 months	24.4 (2.6)	15	HA:26.8 (4.7) HA:27.4 (5.3) HA: 25.8 (4.3)	15	2.4(-0.44 to 5.24) 3 (- 0.12 to 6.12) 1. 4 (-1.26 to 4.06)	- - -

Table 2: Summary of time-distance characteristics for control and intervention group(s) (Cont. .)

SPW Time (s)	Petrella et al./2002	4 weeks	70.56 (14.79)	28	HA: 77.23 (19.9)	25	6.67 (-2.07 to 15.41)	-
Cadence (steps/min)	Tang et al./2004	1week	96.1 (11.0)	15	HA: 108.8 (10.1)	15	12.7(4.8 to 20.6)	↑
		3 months			HA: 110.7 (12.0)		14.6 (5.99 to 23.21)	↑
		6 months			HA: 112.7 (14.3)		16.6 (7.06 to 26.14)	↑
	Lester et al./2010	3 weeks	103.94 (9.37)		HA: 106.15 (11.34)	53	2.21 (-1.80 to 6.22)	-
Stride Length (m)	Tang et al./2015	1 week	0.60 (0.20)	25	HA: 0.69 (0.09)	25	0.09 (0.001 to 0.18)	↑
		3 month			HA: 0.66 (0.23)		0.06 (-0.06 to 0.18)	-
		6 month			HA: 0.65 (0.26)		0.05 (-0.08 to 0.18)	-
	Tang et al./200	1week	0.60 (0.10)	15	HA: 0.69 (0.09)	15	0.09 (0.02 to 0.16)	↑
		3 months			HA: 0.67 (0.1)		0.07 (0.0 to 0.14)	↑
		6 months			HA : 0.67 (0.1)		0.07 (0.0 to 0.13)	↑
	Skwara et al./2009	12 weeks	0.63 (0.06)	24	HA: 0.64 (0.06)	24	0.01 (-0.03 to 0.05)	-
			0.63 (0.09)	26	CS: 0.64 (0.08)	26	0.01 (-0.04 to 0.06)	
	Yavuzeret al./2005	3 weeks	0.97 (0.1)	12	HA: 0.98 (0.2)	12	0.01 (-0.12 to 0.14)	-
	Lester et al./2010	3 weeks	1.24 (0.2)	53	HA: 1.25 (0.29)	53	0.01 (-0.09 to 0.11)	-
Stride Time (s)	Tang et al./2004	1week	1.25 (0.17)	15	HA: 1.12 (0.11)	15	-0.13 (-0.24 to -0.02)	↓
		3 months			HA: 1.07 (0.13)		-0.18 (-0.29 to -0.07)	↓
		6 months			HA: 1.07 (0.15)		-0.18 (-0.30 to -0.06)	↓
	Yavuzeret al./2005	3weeks	1.23 (0.2)	12	HA: 1.20 (0.1)	12	-0.03 (-0.16 to 0.10)	-
	Decaria, J/ 2011	6 months	2.6 (0.8%)	15	HA: 2.10 (0.5%)	15	-0.5 (-1.0 to 0.00)	-

* A hyphen (-) denotes no change from baseline or across groups, an up arrow (↑) denotes a substantial rise in the intervention group relative to the control, and a down arrow (↓) indicates a significant reduction in the intervention group.

CS: Corticosteroid, HA: Hyaluronic Acid, PRP: Platelet-Rich Plasma,N: Number of Participants, NR: Not Reported

Table 3: Summary of Kinetic characteristics for control and intervention roup(s)

				Control Group		Intervention(s)			
Variables		**Study**	**Follow-up Time**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean Diff (95% CI)**	**Significant Change***
Knee Abduction Moment (Nm/kg BW)	**Max1**	Skwara et al./2009	12 Weeks	0.45±0.23 0.41±0.23	HA:24	HA: 0.46±0.22 CS: 0.38±0.21	CS:26	HA: 0.01 (-0.11to 0.14) CS: -0.0 (-0.15 to 0.10)	-
	Max2			0.35±0. 23 0.28±0.17		HA: 0.37±0.23 CS: 0.31±0.17		HA: 0.02 (-0.10 to 0.15) CS: 0.02 (-0.07 to 0.12)	-
Knee Flexion Moment (Nm/kg BW)		Tang et al./2015	1 week 3 months 6 months	0.59±0.22	25	HA: 0.52±0.22 HA: 0.44±0.26 HA: 0.49±0.14	25	-0.07 (-0.2 to 0.06) -0.15 (-0.29 to -0.01) -0.1 (-0.23 to 0.0)	- ↓ ↓
Knee Adductor Moment (N/kg)		Yavuzeret al./2005	4 Weeks	0.45±0.1	12	HA: 0.41±0.1	12	-0.04 (-0.12 to 0.04)	↓
Knee Extensor Moment (N/kg)		Yavuzeret al./2005	4 Weeks	0.26±0.2	12	HA: 0.14±0.1	12	-0.12 (-0.25 to 0.0)	↓
		Tang et al./2015	1 week 3months 6months	0.04±0.18	25	-0.08±0.14 -0.15±0.14 -0.09±0.18	25	0.12 (0.03 to 0.21) 0.19 (0.1 to 0.28) 0.13 (0.03 to 0.23)	↓ ↓ ↓
Vertical Force Maximum 1 (BW)		Yavuzeret al./2005	4 Weeks	0.85±0.04	12	HA: 0.88±0.05	12	0.03 (0.01to0.06)	↑
		Skwara et al./2009	12 Weeks	1.05±0.08 1.07±0.10	HA:24	HA: 1.06±0.10 CS: 1.07±0.08	CS:26	HA: 0.01 (-0.04to 0.05) CS: 0.0 (-0.04 to 0.06)	-
Vertical Force Minimum (BW)		Skwara et al./2009	12 Weeks	0.8.±0.76 0.81±0.78	HA:24	HA: 0.79±0.75 CS: 0.80±0.77	CS:26	HA: -0.13 (-0.06 to 0.03) CS: -0.01 (-0.06 to0.0 4)	-
Vertical Force Maximum 2 (BW)		Skwara et al./2009	12 Weeks	1.07±0.59 1.07±0.79	HA:26	HA: 1.08±0.58 CS: 1.07±0.8	CS:24	HA: 0.01 (-0.02 to 0.04) CE: -0.0 (-0.04 to 0.046)	-
Ground Impact (g)		Lester et al./2010	3 weeks	1.12±0.32	53	HA: 1.11±0.28	53	-0.01 (-0.13 to 0.11)	-
Flexion Torque(Nm) Extension		Miltneret al,/ 2002	1 week	27.11±14.02 42.05±21.30	13	HA: 34.05±17.37 HA: 47.83±21.43	12	6.94 (-6.07 to 19.95) 5.78 (-11.91 to 23.47)	- -

* A hyphen (-) denotes no change from baseline or across groups, an up arrow (↑) denotes a substantial rise in the intervention group relative to the control, and a down arrow (↓) indicates a significant reduction in the intervention group.

CS: Corticosteroid, HA: Hyaluronic Acid, PRP: Platelet-Rich Plasma, F: Flexion, E: Extension, N: Number of Participants

Table 4: Summary of Kinematic characteristics for control and intervention group(s)

Variables	Study	Follow-up Time	Mean (SD)	n	Mean (SD)	n	Mean Differences (95% CI)	Significant Change*
Knee range of motion	Tammachote, et al./2016	2weeks	CS (F): 125 (12.0) CS (E): 0.5 (2.1) HA (F): 126 (10.0) HA (E): 0.3 (2.1)	HA: 50	CS (F): 130 (10) CS (E): 0.1 (0.7) HA (F): 129 (10.0) HA (E): 0.2 (1.4)	CS: 49	CS (F): 5 (0.59 to 9.43) CS (E): -0.4 (-1.03 to 0.23) HA (F): 3 (-0.97 to 6.97) HA (E): -0.1 (-0.81 to 0.61)	- - - -
		3 months			CS (F): 132 (9.0) CS (E): 0.2 (1.0) HA (F): 131 (10.0) HA (E): 0.2 (1.4)		CS (F): 6.6 (2.36 to 10.84) CS (E): -0.3(-0.96 to 0.36) HA (F): 5 (1.03 to 8.97) HA (E): -0.1 (-0.81 to 0.61)	- - ↑ -
		6 months			CS (F): 133 (9.0) CS (E): 0.2 (1.0) HA (F): 132 (9.0) HA (E): 0.2 (1.4)		CE F: 8 (3.75 to 12.25) CE E:-0.3 (-0.96 to 0.36) HA (F): 6 (2.22 to 9.78) HA (E): -0.1 (-0.81 to 0.61)	↑ - ↑ -
	Forogh, et al 2016	2 months	Active PRP: 98.6 (13.9) Active CS: 95.6 (11.1) Passive PRP: 114.9 (13.3) Passive CS: 108.5 (9.8)	PRP: 23	Active PRP: 103.2 (12.2) Active CS: 99.4 (11.3) Passive PRP: 115.8 (13.1) Passive CS: 119.8 (47.3)	CS: 16	Active PRP: 4.16 (-3.17 to 12.37) Active CS: 3.8 (-4.29 to 11.89) Passive PRP: 0.9 (-6.94 to 8.74) Passive CS: 11.3 (-13.36 to 35.96)	-
		6 months			Active PRP: 103.8 (12.5) Active CS: 97.6 (10.9) Passive PRP: 114.6 (11.3) Passive CS: 106.1 (9.8)		Active PRP: 5.2 (-2.66 to 13.06) Active CE: 2 (-5.94 to 9.94) Passive PRP: -0.3 (-7.63 to 7.03) Passive CE: -2.4 (-9.48 to 4.68)	-
	Filardo et al. /2015	2 Months	PRP: 129.6 (12.2) HA: 128.2 (12.2)	PRP: 94	PRP: 130.6 (11.8) HA: 129.0 (10.9)	HA: 89	PRP: 1 (-2.45 to 4.45) HA: 0.8 (-2.62 to 4.22)	-
		6 Months			PRP: 130.3 (10.7) HA: 128.0 (11.4)		PRP: 0.7 (-2.60 to 4.0) HA: -0.2 (-3.96 to 3.29)	-
		12 Months			PRP: 130.2 (11.1) HA: 127.4 (12.0)		PRP: 0.6 (-2.76 to 3.96) HA: -0.8 (-4.38 to 2.78)	-
	Raynauld et al./2003	1 year 2 years	CS: 126.9 (12.2) Saline: 129.9 (14.1)	33	CS: NR Saline-control: NR	33	CS-control: 1.70 (-0.00 to 3.37)	-
				33	CS: NR Saline-control: NR	33	CS-control: 1.43 (-0.56 to 3.42)	-

Table 4: Summary of Kinematic characteristics for control and intervention group(s) (Cont. .)

Knee Range of Motion in Stance (°)	Skwara et al./2009	12 weeks	HA: 12.5 (4.40) CS: 13.8 (5.62)	HA: 24	HA: 14.10 (5.56) CS: 14.15 (5.09)	CS: 26	HA: 1.57 (-1. 34 to 4.48) CS: 0.34 (-2.65 to 3.33)	- -
Knee range of motion in swing	Skwara et al./2009	12 weeks	HA: 55.3 (6.70) CS: 5 (7.78)	HA: 24	HA: 55.56 (5.70) CS: 53.06 (7.03)	CS: 26	HA: 0.2 (-3.27 to 3.67) CS: 0.06 (-4.25 to 4.37)	- -
Pre swing angle (°)	Lester et al./2010	3 weeks	43.83 (20.82)	53	HA: 42.31 (19.80)	53	-1.52 (-9.35 to 6.31)	-
Mid Stance Knee Flexion (°)	Skwara et al./2009	12 weeks	16.82 (6.80) 18.80 (5.19)	HA: 24	HA: 18.20 (5.74) CS: 19.24 (5.71)	CS: 26	HA: 1.38 (-2.13 to 4.89) CS: 0.44 (-2.73 to 3.61)	-
Flexion Rom	Petrella et al./2006	12 Weeks	2.0 (11.9)	53	HA: 0.8 (10.8)	53	-1.2 (-5.58 to 3.18)	-

***** A hyphen (-) denotes no change from baseline or across groups, an up arrow (↑) denotes a substantial rise in the intervention group relative to the control, and a down arrow (↓) indicates a significant reduction in the intervention group.

CS: Corticosteroid, HA: Hyaluronic Acid, PRP: Platelet-Rich Plasma, F: Flexion, E: Extension, N: Number of Participant

Effect of Knee Injections on Spatial-Temporal Parameters

Walking speed, step length, and cadence usually decrease in subjects with knee OA. Patients with knee OA tend to walk slower than normal people.[32] It seems that speed reduction in subjects with knee OA can be a strategy to reduce the loads at the knee joint. Furthermore, knee pain causes reducation of the speed of walking in patients with knee OA.[33] The present review showed that walking speed increased after HA injection.[19,26-29,32] Since changes in gait speed of 0.1 to 0.2 m/s are considered minimum important clinically significant difference;[34] this systematic review demonstrated a weighted mean difference (WMD) of 0.05 with HA injection compared to controls that shows injections are not practically effective in improving gait speed. Cadence was increased after HA; this increase would be higher in longer follow-up.[30] It seems patients may walk faster with more cadences after pain reduction. .

Stride length was increased significantly in two studies with HA injection.[26,30] This increase is beneficial because it increases the stability of these individuals. Most patients with knee OA were elderly subjects, and increasing velocity and stride length was effective in doing activity, daily living, and functions. However, the quantitative analysis showed that injections did not have any clinical effects on stride length (SMD <0.2, WMD= 0.02). Most of the studies did not report significant changes with or without injections on stride length.[27-29]

Patients with knee OA often spend more time taking one step,[35] and this time was decreased after the injection of HA.[18,29,32] It assumes an increase of cadence and velocity can be reasons for decreasing stride time. However, some studies did not show significant differences in stride time.[18,29] One of the possible reasons for this inconsistency is due to different follow-up times and severity of pain and knee degeneration in included patients. Patients who were evaluated in these studies had grades II and III, according to Kellgren, and may be changed in gait are not necessarily apparent in these subjects.

Effect of Knee Injections on Kinetic

The results of studies showed that the intra-articular injections were effective in decreasing joint loading and vertical force vector. The data demonstrated that the primary causes of the increased stress at the knee joints in OA are greater adductor and extensor moments.[36,37] To absorb the knee stress during weight loading, regulated knee flexion is also important. Consequently, increased knee joint loading will result from compromised quadriceps function and knee joint moments. Degenerative joint illnesses may cause an increase in knee angle, which raises the plane lever arm and raises knee moments.[26] Patients with knee OA effort to decrease internal knee extensor moments to reduce knee joint loading. In addition, the maximum knee adduction moment is higher in these patients than in healthy subjects when walking. The studies showed that intra-articular injections decreased the adductor and extensor moments of the knee joint.[26,29] This study showed that HA injection reduces force. At the same time, the difference was not statistically significant. A possible reason for this trivial change can be a reduction of co-contraction of the lower extremity muscles and, following reduction of pain, decreased the adductor and extensor moments of the knee and, as a result, decreased the ground reaction force and joint loading.[38] Additionally, the outcomes demonstrated that patients walked with more extended knees after intra-articular injections to reduce discomfort. Consequently, a little extension moment can be applied by the extensor muscles.[26] Likewise, patients with medial knee OA may benefit from interventions focusing on reducing the magnitude of the lever arm and, as a result, reducing the force on the medial compartment of the knee. Based on the chronic nature of OA and the need for long-term care, exercise therapy or some knee braces, such as applying valgus bracing to reduce knee adduction moment may have more effects on the kinetic parameters than knee injections.[39]

Effect of Knee Injections on Kinematic

Often, patients with knee OA have a reduced ROM, which causes functional limitations in these individuals.[26] Deterioration of joint ROM is one of the significant outcomes of OA. Also, a decreased knee extension and flexion were reported compared to the healthy older subjects.[40] Intra articular injections have been shown to improve the stiffness and joint pain; thus, a dynamic range of knee flexion after injections can reflect the efficacy of treatment.[17] Unlike the opinion of some studies that considered intra-articular injections ineffective in the ROM,[16,25] the result of some studies showed an increase in knee ROM after treatment with injections.[17,23] It seems that reduction of pain and stiffness can have a positive effect on knee ROM. Based on limited studies, there was no difference in HA and CS injection effectiveness compared to placebo and no intervention in knee ROM.[17,23]

This systematic study included studies where most of the participants in these studies are elderly. The reduction of the step length, velocity, and alterations of gait parameters in these patients can be due to the

aging process and cannot be related to arthritis alone. These changes in older people can be an approach to adapt to changes in these individuals' sensory-motor systems. Of course, some changes in walking parameters in older adults could be a mechanism for having a safer gait pattern to prevent fall.[41]

Study Limitations and Suggestion for Further Research

The present review has some limitations that need to be considered when interpreting the findings of this study. Quantitative analysis was performed just for velocity and stride length. Because of incomparable data and the small number of same studies, quantitative analysis was not done for other outcome measures. Also, methodological limitations were recognized during the risk of bias assessment of included studies. No studies attempted to blind those assessing the outcome measures. Random allocation concealment was not considered in all clinical trials between different interventions, which may cause performance bias. Interventions directed through needles, such as intra-articular injections, would show a more significant placebo effect. A previous review showed that the placebo effect is mainly significant in the treatment of knee OA.[42] Therefore, blinding participants is critical to minimize the bias during performing trials.

Furthermore, there are different PRP protocols, molecular weight differences, and the number of injections in various HA products. This manuscript's data is too heterogeneous concerning age and OA grading that treatment effects can be determined. In addition, the study groups are heterogeneous regarding the level of involvement and injection dosage. Most studies did not separate and classify the result of a different group of knee OA, and combined results of study participants were reported. It caused difficulty in determining the efficiency of injections in subjects with different OA grades.

Another limitation is that non-English language studies were not included in this review; it can cause some selection bias that may affect the interpretation of the results of this review. According to our result, we also predict some negative results bias that has precluded publication of these studies. Because of limited studies that investigated the effect of CS and especially PRP, superiority over each other's on gait variables of subjects with knee OA was not determined. On the other hand, according to the knowledge, there was no similar systematic review on this topic to compare our results. The previous systematic review showed that knee injections and physiotherapy agents have equally effective in improving pain, knee function, and quality of life in subjects with knee OA.[39] As knee OA correlates with knee malalignment,[43] authors, suggest conducting high-quality trials to assess the effect of conservative treatments such as knee braces and exercise therapy on gait outcomes. These interventions could have different clinical results in subjects with knee OA.

CONCLUSION

In conclusion, this systematic review suggests relative improvement in velocity and cadence and a reduction of stride length with HA injection. However, these changes were not clinically significant. Knee adductor and extensor moments were decreased after HA injections. However, Because of limited studies that investigated the effect of CS and especially PRP, superiority over each other's on gait variables of subjects with knee OA was not determined. Nonetheless, it is still believed that HA improves gait parameter more than a placebo does and no intervention is based on present evidence. We should keep in mind that the larger number of studies that have been conducted, as well as the widespread use of HA, may have an impact on the results of our study. Because most OA literature presents non-stratified cohorts in non-blinded treatment, further high-quality studies such as double-blinded RCTs are required to determine the efficacy of therapeutic injections on the function and walk of subjects with knee OA.

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