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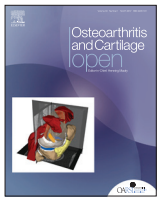

Review

The effects of exercise and intra-articular injections versus exercise alone for the treatment of knee osteoarthritis: A scoping review of the evidence

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ABSTRACT

Objective: Current treatment for knee Osteoarthritis (OA) includes exercise and intra-articular injections with corticosteroid (CS), hyaluronic acid (HA), etc., which address OA-related pain and functional limitation. While these interventions can be given together, little is known about the efficacy of a multi-modal approach. The purpose of this scoping review is to examine studies that compare combining exercise and intra-articular knee injections to exercise alone for the management of knee OA.

Methods: A search was performed using PubMed, CINAHL, and Clinicaltrials.gov with MeSH terms "knee osteoarthritis" AND "exercise" AND "injections". Abstracts were screened to meet inclusion criteria of both intervention groups including exercise and one group receiving an injection for treatment of knee OA. Full text articles were screened to meet inclusion criteria and rated using the Pedro Scale.

Results: 11 studies that met inclusion criteria. The included studies utilized CS, hyaluronic acid (HA), and Bone Marrow Concentrate (BMC), botulinum toxin A, or a combination of dextrose and lidocaine injections. Most studies included supervised exercise interventions with all studies including strengthening of the quadriceps. CS and exercise compared to exercise alone showed similar improvements in pain. The HA injection studies yielded mixed results with two studies finding HA and exercise was not superior than exercise alone while two other studies found that HA and exercise were superior.

Conclusion: There was a paucity of literature investigating multimodal approaches. Most of the included studies did not find superior effects of adding a knee injection to exercise compared to exercise alone for knee OA.

1. Introduction

Knee osteoarthritis (OA) is a common disease and a leading cause of global disability [1,2]. As there is no cure for knee OA, treatment focuses on the management of symptoms [3], which include pain, muscle weakness, functional limitation, and disability with activities of daily living (ADLs) [3]. Both intra-articular injections and exercise are recommended treatments for the management of knee OA to address the symptoms of OA [4,5]. Intra-articular corticosteroid (CS) is strongly recommended and a commonly utilized injection for the management of knee OA [5]. CS injections are recommended for use when patients are experiencing acute pain or an OA related flare in symptoms [6]. Exercise is also highly recommended by both Osteoarthritis Research Society International (OARSI) and American College of Rheumatology (ACR) throughout the continuum of care from initial diagnosis to before joint replacement [4,5].

At present, there is a lack of clinical guidance regarding using a multimodal approach to manage the symptoms of knee OA, i.e., prescribing both intra-articular injections and exercise at the same. This is a major gap as both are feasible to be prescribed at the same time. For example, physicians can perform an intra-articular CS injection then recommend starting physical therapy for supervised exercise for adults with knee OA. However, many health professionals are unsure if there are unique benefits to prescribing both injections and exercise at the same time. We are particularly interested in examining if adding an intra-articular injection to exercise was superior to exercise alone in adults with knee OA given that an injection is not as readily accessible as exercise. Hence, we conducted a scoping review of evidence regarding the combination of exercise and knee injections versus exercise alone for the management of knee OA.

2. Methods

Studies of randomized control trials that included an injection to the knee and exercise among adults with knee OA were considered for this scoping review. We restricted our search by only including articles that

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involved exercise for both groups and with at least one group receiving an injection as part of the intervention. We did not exclude studies based on the content of the knee injection, e.g., corticosteroid (CS), hyaluronic acid (HA), and Bone Marrow Concentrate (BMC) could be included. We included studies that used any type of exercise, e.g., strength training or aerobic exercise, which could be supervised or unsupervised. We performed our search using PubMed, CINAHL, and ClinicalTrials.gov using the MeSH terms "knee osteoarthritis" AND "exercise" AND "injections". Study quality was assessed by two reviewers independently using the Pedro Scale [7]. Cohen's D effect sizes were calculated for studies with published group means and measures of variation (standard deviation or 95% confidence intervals). The mean difference and pooled standard deviation were used to calculated effect size between control and intervention groups.

3. Results

3.1. Study characteristics

The literature search yielded 434 abstracts, of which 115 were randomized control trials that met search criteria. Of these 115 studies, 44 were excluded for not including exercise as part of the intervention for both groups. Other studies were excluded for not including an intra-articular knee injection as an intervention or not assessing knee OA specifically (see Fig. 1). This resulted in 11 studies being included. Of note, four of the corticosteroid studies [8–11] included were secondary analyses using the same participants from a parent trial [12]. The Pedro Scale scores of the studies are listed in Table 1. Scores of six or more are considered "good" to excellent studies, while scores of less than four are considered "poor" and scores of four to five are considered "fair" [13].

A summary of included studies is in Table 1. Age criteria ranged from having no minimum [14,15] to requiring participants to be at least 50 years of age [16,17]. All included studies required a radiographic diagnosis of knee OA. Seven studies also required the presence of knee pain or pain with walking. The studies generally excluded participants with a recent knee injection, surgery to the affected side, and/or the presence of severe knee OA, i.e., KL = 4.

The duration of studies ranged from eight weeks up to one year, with 8 studies lasting between three to nine months. The most common follow up times were 3- and 6-months. The frequency of follow up range from once every four weeks to a single follow up measure one year later [14].

The only study included in this analysis which followed a triple-blind approach was the CS injection parent study [12]. Some studies made no mention of the blinding process utilized [16,18]. Three studies reports using a single blind approach [14,15,17] while another reports blinding randomization until time of enrollment only [18].

Of the seven studies, not including the secondary analyses of the CS injection parent trial, three studies did not perform a power analysis (Table 2) [14,15,19]. The CS injection parent study was powered to 91% to detect a 10 point change difference between groups in the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale [12]. Two studies mentioned both the power analysis and estimated effect size; one study had 80% power to detect an effect size of 0.4[16] and the other study had 90% power to detect an effect size of 0.7 [18]. One study only mentioned that all tests were powered to 80% [17].

3.2. Injection type and frequency

The agents used in injections included CS, HA, BMC, botulinum toxin, and a combination of dextrose and lidocaine. Comparison groups received the same injection as the intervention either at the same time in a cross-over design, saline and lidocaine, dextrose, or no injection. The number of injections ranged from one to five (Table 3).

3.3. Exercise interventions and adherence

Most of the studies included strengthening exercises of the lower extremity, such as isometric quadriceps strengthening, straight leg raises,

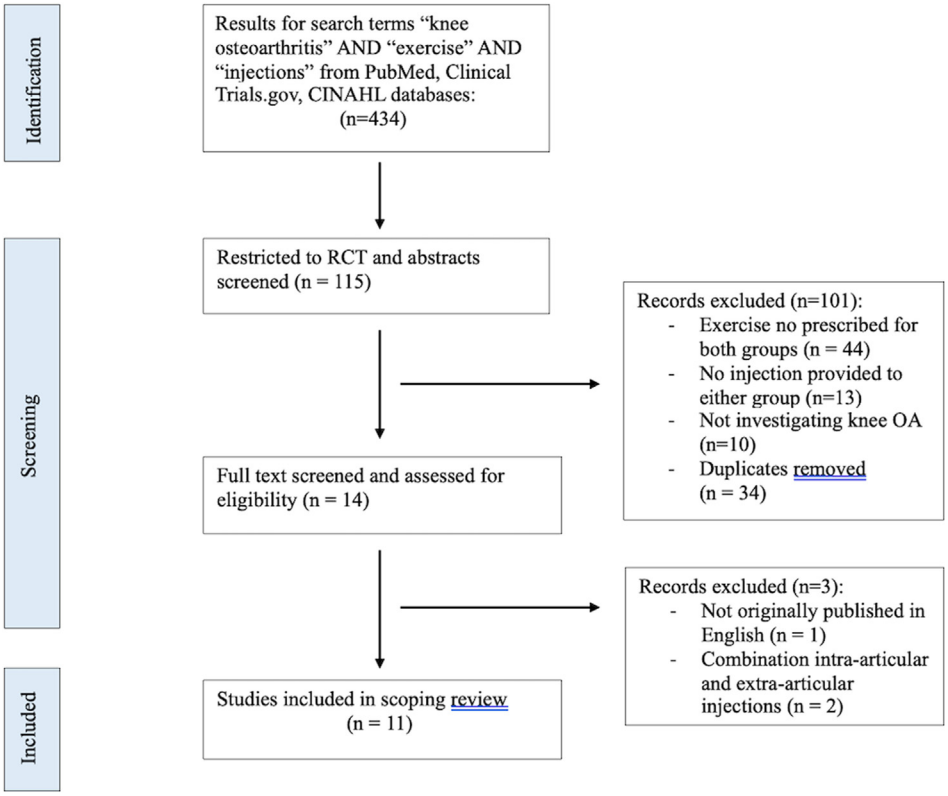

Fig. 1. Consort diagram of study inclusion.

Table 1
Overview of included articles.

Review Details	Averaged Pedro Scale Score	Participants inclusion criteria	Sample Size	Groups	Primary Outcomes	Main Conclusions	Blinding	Follow-up times
Henriksen et al.[a] RCT JAMA Intern Med	10	age ≥40 years, tibiofemoral OA according to the ACR-criteria, clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index (BMI) ≤ 35 kg/m2.	N = 100	- Control: saline + lidocaine - Intervention: corticosteriod	KOOS Pain subscale, Secondary outcomes remaining KOOS subscales and objective measures of physical function and inflammation.	CS injections before exercise intervention had no added benefit, further research required to determine optimal combinations	participant, care provider, and outcome assessor blinded	baseline, 2 weeks, 14 weeks, 26 weeks
Soriano-Maldonado et al.[a] RCT PLoS ONE	10	age ≥40 years, tibiofemoral OA according to the ACR-criteria, clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index (BMI) ≤ 35 kg/m2.	N = 100	- Control: saline + lidocaine - Intervention: corticosteriod	KOOS pain subscale; measures of pressure pain sensitivity (pressure pain threshold [PPT] and temporal summation [TS]),	No added benefit of CS injection before exercise intervention	participant, care provider, and outcome assessor blinded	before, 14 weeks, 26 weeks
Nielsen et al.[a] RCT Osteoarthritis and Cartilage	9.5	age ≥40 years, tibiofemoral OA according to the ACR-criteria, clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index (BMI) ≤ 35 kg/m2.	N = 100	- Control: saline + lidocaine - Intervention: corticosteriod	patient-reported pain; change in BML	Little support for a relationship between CS injections and BML volume	participant, care provider, and outcome assessor blinded	baseline, 14 week, 26 week
Henricsdotter et al.[a] RCT Osteoarthritis and Cartilage	10	age ≥40 years, tibiofemoral OA according to the ACR-criteria, clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index (BMI) ≤ 35 kg/m2.	N = 99	- Control: saline + lidocaine - Intervention: corticosteriod	changes US-assessed synovial size, Doppler activity presence in the synovial membrane, and numbers of US-detected Baker's cysts	CS injection prior to exercise not superior to placebo injection prior to exercise	participant-, care provider-, outcome assessor blind	baseline, 14 week, 26 week
Riis et al.[a] RCT Osteoarthritis Cartilage	9	age ≥40 years, tibiofemoral OA according to the ACR-criteria, clinical signs of localized knee inflammation, knee pain during walking (>4 on a 0–10 point scale), and a body mass index (BMI) ≤ 35 kg/m2.	N = 91	- Control: saline + lidocaine - Intervention: corticosteriod	PROMs using the KOOS, Synovitis	Does not support use of CS injections over placebo injection prior to exercise.	participant-, care provider-, outcome assessor blinded	at baseline, week 14 (primary time point) and week 26 (follow-up).
Bao et al. RCT Journal of Rehabilitation Medicine	7.5	mentally intact, radiographic OA severity KL-grade 2 or above, and pain on visual analogue scale score ≥6 after walking a distance of 100 m continuously on level ground	N = 60	- Control: saline -Intervention 1:botulinum toxin A - 1 injection -Intervention 2:hyaluronate - 1x/wk for 5 weeks	WOMAC, visual analogue scale (VAS) pain scale, and SF-36	Botox-A or HA injections used in combination with therapeutic exercise were shown to reduce pain and improve function in individuals with knee OA.	single blind	baseline, 4 week, 8 week
Huang et al. RCT Arthritis and Rheumatism	8.5	bilateral knee OA Altman grade II	N = 140	- Control:warm up exercises -Intervention 1: isokinetic exercise -Intervention 2: isokinetic exercise + pulsed US -Intervention 3: isokinetic exercise + pulsed US + intraarticular hyaluronan therapy	Knee ROM, VAS, Lequesne's index, ambulation speed, peak muscle torque knee flex/ext	A combination of modalities should be used for the treatment of knee OA	assessor blinding	before treatment, after treatment, 1 year follow up

(*continued on next page*)

Table 1 (*continued*)

Review Details	Averaged Pedro Scale Score	Participants inclusion criteria	Sample Size	Groups	Primary Outcomes	Main Conclusions	Blinding	Follow-up times
Rezasoltani et al. RCT Int J Rehabil Res	5.5	age ≥50 years, OA documented through assessment of patients' medical record, interview, physical examination, and confirmatory radiography of the knee. Knee deformity, tenderness, crepitus, effusion, and decreased range of motion were noticed.	N = 120	- Control:superficial heat, transcutaneous electrical nerve stimulation and pulsed ultrasound - Intervention 1:single intra-articular injection of botulinum neurotoxin type A -intervention 2: three injections of hyaluronic acid -intervention 3: 20% dextrose	knee pain in visual analog scale; secondary outcome KOOS	Does not support use of HA injections in combination with exercise for knee OA management		1 wk, 4 wk, 3 month
Centeno et al. RCT J Transl Med	6	Men or women aged 18–70, diagnosis of knee osteoarthritis Kellgren–Lawrence (KL) classification of grade II or III OA severity	N = 48	- Control: exercise -Intervention 1: BMC -Intervention 2: cross over	Knee Society Score (KSS), Pain Visual Analogue Scale, SF-12, and Lower Extremity Activity Scale (LEAS).	The use of BMC and BMC + exercise was superior to exercise alone in management of knee OA symptoms	enrollment randomization envelopes blinded until time of enrollment by study coordinator	baseline and at 6-weeks, 3, 6, 12 and 24 months
Saccomanno et al. RCT Knee Surgery, Sports Traumatology, Arthroscopy	7.5	men and women older than 18 in good health other than knee OA; moderate OA	N = 165	- Control: HA injections -Intervention: HA injections + exercise	WOMAC; secondary outcome active range of movement (AROM)	Combination of HA injections and exercise programs were superior to either intervention alone for pain relief		before and 1, 3 and 6 months
Stitik et al. RCT Archives of Physical Medicine and Rehabilitation	8	men and women 50 or older with diagnosis of knee OA meeting ACR criteria and KL grade 2–3 by x-ray; participants taking pain medication had to report knee pain of 30–90 mm on the 100 mm VAS, participants not taking pain medication had to report pain of 40–90 mm on the 100 mm VAS pain scale	N = 60	- Control: 3 HA injections -Intervention 1: 3 HA injections + exercise -Intervention 2: 5 HA injections	VAS pain; secondary outcomes: WOMAC total, WOMAC pain, WOMAC function, WOMAC stiffness	The use of HA injections in combination with exercise was superior to HA injectiosn alone	single-blind	baseline, injection visits, 1, 3, 6, 9, and 12 months[a]

[a] Studies are CS injection parent study and secondary analyses.

and knee extension utilizing weights or resistance bands (Table 3). The CS injection parent study included a warm-up using cycle ergometer followed by an eight-exercise circuit program including: abdominal activation exercises, bridges, clamshells, terminal knee extensions, lunges, leg press, step ups with band, and functional exercise such as walking or stair climbing [12]. This study had progressions for each exercise included and could include the use of bands, weights, or unstable surfaces. Calf stretching and/or range of motion exercises were included in three studies [16–18].

Eight studies provided supervised exercise programs in either group [8–12,15] or individual format [14]. One study provided participants with a home exercise program with ability to review exercises at follow-up visits [17]. One study provided a home exercise program with progression of exercises after 6 weeks [19]. One study [18] did not specify if the supervised exercise sessions were delivered in group or individual format while another study [16] did not specify if the individual session was supervised or unsupervised.

Five studies made no mention of how they monitored adherence to the exercise portion of the intervention [14–16,18,19]. Five studies took attendance of sessions to try to promote adherence by encouraging participants to attend a minimum number of sessions [8–12]. One study used an exercise log to track completion of exercises [17]. Overall, there was no consistent method of ensuring completion of the exercise intervention.

3.4. Study outcomes

The primary outcomes of the studies in this review were not consistent. The most commonly used outcomes were the Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms (WOMAC) [15,17,18], KOOS pain subsection [8,12], and the pain visual analogue scale (VAS) [14–18]. Other measures included range of motion [11,14], other KOOS subscales [12,16], pain pressure threshold [8], changes in US imaging including synovial size [10], bone marrow lesion [9], and baker cyst size [10]. Other outcomes are included in Table 1. The corticosteroid randomized control trial (RCT) and secondary analyses reports one adverse event in the intervention group and three total adverse events in the control group [8]. [–] [12] Two studies reported no adverse events [15,18]. The BMC study [19] reported no serious adverse events, although 16 participants reported pain after the treatment, one patient reported swelling along with knee pain after treatment, and 17 reported recurrent knee pain after the injection [19]. Two studies did not specifically report adverse events, however Huang et al. noted that 9 out of 12 participants withdrew from the study due to

Table 2
Primary outcome effect measures for included studies.

Study	Study Outcome	Control Group Mean (SD/SE/95% CI)	Control Group Sample Size (n)	Experimental Group Mean (SD/SE/95% CI)	Experimental Group Sample Size (n)	P-value	Effect Size
Henriksen et al.[a] RCT JAMA Intern Med	Change from Baseline to 14 weeks in KOOS Pain subscale	Placebo mean (SD): 55.2 (16.0)	n = 50	CS mean (SD): 53.3 (11.4)	n = 50	0.64	−0.14
Soriano-Maldonado et al.[a] RCT PLoS ONE	Pressure pain sensitivity (pressure pain threshold [PPT] at 14-week followup	Placebo mean (SE): PPT 0.6 (0.8)	n = 49	CS mean (SE): PPT 0.0 (0.8)	n = 50	0.63	−0.11
	Temporal summation [TS]) at 14-week followup	Placebo mean (SE): TS -3764 (1196)	n = 48	CS mean (SE): TS -4150	n = 48	0.82	−0.05
Nielsen et al.[a] RCT Osteoarthritis and Cartilage	Change in BML volume (%) at follow-up	Placebo mean (95% CI): 26 week 1.6 (-1.0, 4.1)	n = 50	CS mean (95% CI): 26 week 0.8 (−1.7, 3.3)	n = 50	0.65	−0.09
Henricsdotter et al.[a] RCT Osteoarthritis and Cartilage	Changes in synovial membrane thickness at 26-week followup	Placebo changes from baseline mean (SE):26 week −2.1 (0.9)	n = 50	CS changes from baseline mean (SE): 26 week −2.9 (1.0)	n = 49	0.56	−0.12
Riis et al.[a] RCT Osteoarthritis Cartilage	Changes in DCE-MRI variable ME x Nvoxel (measures of synovitis)	Placebo changes from baseline mean (95% CI): 26 week −3.27 (−16.76, 10.22)	n = 50	CS changes from baseline mean (95% CI): 26 weeks −3.83 (−17.47, 9.82)	n = 50	0.95	−0.01
Bao et al. RCT Journal of Rehabilitation Medicine	WOMAC Pain	Control mean (SD):8 weeks WOMAC Pain 56.5 (3.47)	n = 20	BoNT-A mean (SD): 8 weeks WOMAC Pain 26.3 (5.08)	n = 20	<0.01	−6.94
	WOMAC Pain	Control mean (SD): 8 weeks WOMAC Pain 56.5 (3.47)	n = 20	HA mean (SD): 8 weeks WOMAC Pain 48.3 (8.07)	n = 20	<0.05	−1.32
Huang et al. RCT Arthritis and Rheumatism	Knee Range of Motion (ROM) at follow-up	Control mean ± SD: Follow-up 98° ± 17°	n = 70	Isokinetic strengthening + pulse US ROM mean ± SD: Follow-up 118° ± 14°	n = 70	<0.05	1.28
	Knee Range of Motion (ROM) at follow-up	Control mean ± SD: Follow-up 98° ± 17°	n = 70	Isokinetic strengthening + pulsed US + HA ROM mean ± SD:Follow-up 124° ± 18°	n = 70	<0.05	1.49
	Knee Range of Motion (ROM) at follow-up	Control mean ± SD: Follow-up 98° ± 17°	n = 70	Isokinetic Strengthening ROM mean ± SD: Follow-up 110° ± 14°	n = 70	<0.05	0.77
Rezasoltani et al. RCT Int J Rehabil Res	VAS pain	Data Only Published in Figure Format, No Numeric Values Provided					
Centeno et al. RCT J Transl Med	Knee Society Score (KSS) Function	Control (Exercise Therapy) mean change score at 3 months: KSS-function score 7.5	n = 22	BMC + Exercise mean change score at 3 months: KSS-function score 2.3	n = 26	0.17	Unable to be calculated
Saccomanno et al. RCT Knee Surgery, Sports Traumatology, Arthroscopy	WOMAC Pain	HA mean ± SD 6-month followup: WOMAC Pain 181.5 ± 98	n = 55	Exercise-based Rehab mean ± SD 6-month followup: WOMAC Pain 161.6 ± 90.2	n = 55	Not significant, no p-value reported	−0.21
	WOMAC Function	HA mean ± SD 6-month followup: Function 691.4 ± 363.9	n = 55	Exercise-based Rehab mean ± SD 6-month followup: Function 618.5 ± 310.5	n = 55	Not significant, no p-value reported	−0.22
	WOMAC Pain	HA mean ± SD 6-month followup: WOMAC Pain 181.5 ± 98	n = 55	HA + exercise-based rehab mean ± SD 6-month followup: WOMAC Pain 173.3 ± 101.6	n = 55	Not significant, no p-value reported	−0.08
	WOMAC Function	HA mean ± SD 6-month followup: Function 691.4 ± 363.11	n = 55	HA + exercise-based rehab mean ± SD 6-month followup: Function 643.5 ± 336.7	n = 55	Not significant, no p-value reported	−0.14
Stitik et al. RCT Archives of Physical Medicine and Rehabilitation	Improvement in VAS pain after 50-foot walk at week 2	Data Only Published in Figure Format, No Numeric Values Provided[a]					

[a] Studies are CS injection parent study and secondary analyses.

Table 3
Summary of interventions.

Study	Injection Type	Dosage of Injection	Exercise type	Format (individual/ group and supervised/ unsupervised)	Monitor adherence	Duration
Henriksen et al.[a]	CS	CS-1ml methylprednisolone (40 mg depo-medrol, pfizer) dissolved in 4 ml lidocaine (10 mg/ml)	bike ergometer, circuit training (strength and coordination trunk, hip, knees)	group, supervised	tracked class attendance	12 weeks
Henricsdotter et al.[a]	CS	CS-1ml methylprednisolone (40 mg depo-medrol, pfizer) dissolved in 4 ml lidocaine (10 mg/ml)	bike ergometer, circuit training (strength and coordination trunk, hip, knees)	group, supervised	tracked class attendance	12 weeks
Soriano-Maldonado et al.[a]	CS	CS-1ml methylprednisolone (40 mg depo-medrol, pfizer) dissolved in 4 ml lidocaine (10 mg/ml)	bike ergometer, circuit training (strength and coordination trunk, hip, knees)	group, supervised	tracked class attendance	12 weeks
Nielsen et al.[a]	CS	CS-1ml methylprednisolone (40 mg depo-medrol, pfizer) dissolved in 4 ml lidocaine (10 mg/ml	bike ergometer, circuit training (strength and coordination trunk, hip, knees)	group, supervised	tracked class attendance	12 weeks
Riis et al.[a]	CS	CS-1ml methylprednisolone (40 mg depo-medrol, pfizer) dissolved in 4 ml lidocaine (10 mg/ml)	bike ergometer, circuit training (strength and coordination trunk, hip, knees)	group, supervised	tracked class attendance	12 weeks
Bao et al.	Botox A or HA	Botox A injection - 100 U BoNT-A (Botox, allergan inc.) diluted with 2.5 ml preservative free 0.9% saline; HA injection- sodium hyaluronate (ARTZ) unspecified dosage	strength, balance, walking	group, supervised	not mentioned	8 weeks
Saccomanno et al.	HA	Orthovisc 2 ml injection with concentration of 15 mg/ml	isometric and isotonic exercises for the quadriceps and other muscles based on compartment, proprioceptive training, and stretching	supervised; does not mention if individual or group sessions	not mentioned	1 month
Huang et al.	HA	2 ml (hyalgan 20 mg in 2 ml of phosphate buffer)	stationary bike, isokinetic exercise	individual, supervised	not mentioned	8 weeks
Rezasoltani et al.	Botox A, HA, or Dextrose	HA injection - 2 ml of HA; botulinum neurotoxin A injection - 250 units dysport equivalent to 100 units of botox A diluted with 5 ml of saline; dextrose injection- 8 ml 20% dextrose plus 2 ml of 2% lidocaine	isometric exercise for the quadriceps and stretches	individual, does not specify if supervised	not mentioned	3 months
Centeno et al.	BMC	pre-treatment injection of dextrose 2–5 cc of 12.5% dextrose and 0.125% ropivacaine in saline; BMC injection 5–7 ml solution of 75% BMC, 12.5% PRP and 12.5% PL; post-treatment injection - 3 ml of 25% PRP, 25% of PL, 25% of compounded 400 ng/ml dose of hyrocortisone, and 25% of 40 μg/ml doxycycline	Functional strength and resistance exercises, balance training, and aerobic activity; mobility included if indicated	individual, unsupervised	exercises updated at 6 week follow up but no mention of measured adherence	not specified
Stitik et al.	HA	Hyalgan 20 mg in 2 mL given as either 3 weekly or 5 weekly injections	Quadriceps exericse and wall slides	individual unsupervised	exercise diary	not specified

[a] Studies are CS injection parent study and secondary analyses.

Table 4
Overview of CS studies.

Author	Study Design	Control group	Intervention	Outcomes	Results
Henriksen et al.	RCT	saline + lidocaine	corticosteriod	Pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire Secondary outcomes included the remaining KOOS subscales and objective measures of physical function and inflammation.	CS injections before exercise intervention had no added benefit, further research required to determine optimal combinations
Soriano-Maldonado et al.	RCT - sub-study	saline + lidocaine	corticosteriod	pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire; measures of pressure pain sensitivity (pressure pain threshold [PPT] and temporal summation [TS]),	No added benefit of CS injection before exercise intervention
Nielsen et al.	RCT - sub-study	saline + lidocaine	corticosteriod	patient-reported pain; change in BML	Little support for a relationship between CS injections and BML volume
Henricsdotter et al.	RCT - sub-study	saline + lidocaine	corticosteriod	changes from baseline in US-assessed synovial size, Doppler activity presence in the synovial membrane, and numbers of US-detected Baker's cysts	CS injection prior to exercise not superior to placebo injection prior to exercise
Riis et al.	RCT - sub-study	saline + lidocaine	corticosteriod	PROMs were assessed using the KOOS, Synovitis on conventional non-contrast-enhanced, conventional contrast-enhanced (CE) and dynamic contrast-enhanced (DCE) MRI	Does not support use of CS injections over placebo injection prior to exercise.

knee pain [14,16]. No studies included any measures of physical activity or changes in physical activity following the intervention.

3.5. Results of exercise + CS

One parent study and four secondary papers examined the combination of corticosteroid injections and exercise versus exercise alone [8–12]. (Table 4). There were no between-group differences in any of these studies, which included the KOOS pain subscale [12]; pain sensitivity (calculated using visual analog scale scores) [8], synovitis [11], or synovial hypertrophy [9]; and no reduction in doppler activity or Baker's cyst presence [10]. Ultrasound doppler activity indirectly measures increased perfusion through movements of erythrocytes in the synovial membrane [10]. It is noteworthy that KOOS pain did improve within each group, and that changes in synovitis were correlated with improvements in KOOS pain, KOOS activities of daily living (ADL) subscale, and Health Related Quality of Life (HRQoL) [11]. However, the secondary analyses of the CS injection study were not powered for their respective primary outcomes [8–12]. The effect sizes for the CS injection studies were small and ranged from −0.14 to −0.01.

3.6. Results of exercise + HA

Two studies found that HA injections either delivered alone or in combination with exercise were no better than exercise alone over 3 months [16] and 6 months [18]. In contrast, two studies reported that HA and exercise were superior in all study outcomes compared to exercise + saline over 8 weeks [15] and exercise alone over 12 months [14]. One study found that HA and exercise was superior to HA alone in improving self-reported pain [17]. Two HA studies had large calculated effect sizes of −1.32 [15] and 1.49 [14]. One HA study had small calculated effect sizes [18] and effect sizes for two studies were unable to be calculated [16,17].

3.6.1. Results of exercise + other types of injections

An injection of botulinum toxin type A and exercise were reported to be superior for WOMAC subscales, VAS pain, and HRQoL compared to a saline injection and exercise over 8 weeks [15]. This study had calculated effect size −6.94 for WOMAC pain at 8 weeks [15].

One trial randomized participants into a bone marrow concentrate (BMC) group or a home exercise program at baseline which was progressed at a 6-week follow up visit by a physical therapist [19]. At three months, participants in the BMC group had greater improvement in the lower extremity activity scale and the knee score subscale of the knee society score of assessment and function. Pain VAS, SF-12 physical and mental subscales, and knee range of motion were not different between groups [19].

4. Discussion

We found little evidence for multimodal treatment of knee OA. Namely, there were only 11 studies that met our study criteria of adding an intra-articular knee injection to prescribed exercise. Among the studies included the addition of an intra-articular injection to exercise was in general not superior to exercise alone. For example, there were no differences in outcome measures such as pain sensitivity and synovitis between the groups receiving a CS injection in addition to exercise compared with a placebo injection with exercise [8–12]. However, we are unable to conclude if adding intra-articular injections to exercise is effective given the paucity of studies in this area.

Similarly, only four of seven studies, not including the CS injection secondary analyses, conducted power analyses. Six of the eleven included studies, including the CS injection secondary analyses, had small effect sizes [8–12,18]. None of those studies reached statistical significance between group differences for any outcome which could be due to small sample sizes [8–12,18]. Two studies had medium to large calculated effect sizes with both studies finding significant improvements in the outcome of interest for combination therapies [14,15]. There were two studies where effect sizes could not be calculated [16,17].

There are few studies looking at the combined effect of exercise and corticosteroid injections despite the widespread use of CS injection and recommendations for use. The one CS injection study and secondary analyses presented did not find differences between the groups receiving CS injections and exercise and a placebo injection and exercise. This could be due to the relatively short-term effects of CS injections on pain similar to the analgesic component of the placebo injection. This could potentially indicate that performing the exercise component of the treatment is more beneficial than the pain relief on outcomes, since both CS and placebo injections would provide some short-term pain relief. Similarly, CS injections are utilized for the management of pain associated with knee OA [6], which does not improve muscle strength and could explain why there is no difference in pain and functional outcomes at the intermediate and long-term follow-ups compared to exercise alone. Additionally, the modest observed effect sizes for the CS injection studies, which had small sample sizes, may indicate that the studies were underpowered. However, since all data on CS injections and exercise come from one study with secondary analyses no conclusions can be drawn on the effectiveness of this combination of treatments.

Similarly, there are very few studies investigating the effects of combining other types of injections with exercise. The HA studies included in this analysis found conflicting evidence regarding whether the use of HA injections with exercise is beneficial. The two studies utilizing 5 total injections support the use of HA injections [14,15] while the studies using 3 total injections did not support HA's use [16,17,19]. These contradictory findings could be the result of the varying concentrations and dosages of different brands of HA injections. Similarly, there are not enough studies to determine if the use of botulinum toxin type A, dextrose, or BMC injections combined with exercise are beneficial [15,16,19]. Though the study of botulinum toxin type A, dextrose, and BMC used in combination with exercise showed some positive results, no conclusions on effectiveness can be drawn based on this review [15,16,19].

The exercise interventions utilized in the studies were poorly described and most studies failed to monitor adherence to the interventions. The dosage of each exercise is especially important to consider when looking at outcomes of the intervention. If exercises are not dosed properly or progressed regularly then it is likely there is little benefit of performing these exercises. Also, since adherence was not well monitored it is unclear if participants completed the exercises as prescribed. The exercise type prescribed varied widely with some studies including balance training or endurance training along with strengthening while others focused on strengthening exercises alone [8–12,14–19]. One exception to this was that the included studies all prescribed quadricep muscle strengthening in the form of isometrics, concentric and isotonic knee extension, and isotonic exercises. Another major difference was the form of delivery of these interventions with many studies provided the exercise interventions in supervised group sessions. Only two studies utilized individual unsupervised exercises [17,19] as the intervention and another study which did not specify supervision level of the sessions [16]. The supervised interventions required patients to attend three to five sessions per week for anywhere from four to twelve weeks thus feasibility of attendance should be considered. Additionally, the corticosteroid study and secondary analysis tracked attendance of sessions requiring participants attend a minimum number of sessions while the other studies made no mention of adherence to interventions. The individual unsupervised exercise interventions would have benefitted the most from measures of adherence to ensure participants completed the exercises per protocol.

The studies included in this review utilized a range of outcome measures for analysis. OMERACT-OARSI core domain sets to be included in randomized control trials for knee osteoarthritis include quality of life, pain, physical function, joint structure, adverse events including

mortality, and patient global assessment [20]. The KOOS WOMAC, and measures of knee pain were the most utilized outcome measures. However, no studies included in this review included all six of the core domains. All studies included a measure of pain and physical function, while no studies mention use of patient global assessment of their target joint [8–12,14–19]. Measures of physical activity level were also not included as outcomes in any of the studies. We find it noteworthy that none of the studies commented or measured if there was an overall increased physical activity level of participants within or between groups. The included studies did not describe baseline levels of physical activity when recruiting their samples, which could have had implications on the effectiveness of the exercise intervention in managing pain levels.

Future clinical trials should be blinded to the patient, physician, and assessors to decrease risk of bias within data collection and statistical analysis. This type of blinding only occurred in the CS injection study [12]. Future studies should include outcome measures on physical activity level. Future studies should also include measures of adherence to determine if participants are completing the exercise interventions to make conclusions on the effectiveness of the interventions. The OARSI recommendations for core outcomes includes adherence as an important contextual factor [20]. There is a need for increased research into this area to provide the most beneficial treatment to individuals with knee OA. Future studies should seek to better understand the possible synergistic effects of these two interventions, the most beneficial combinations, as well as the order in which these interventions should be provided.

Limitations of this review include the small number of studies included. There were only 11 studies meeting the inclusion criteria for this review, of these four were secondary analyses of a parent study. Only five of the included studies investigated CS injections, with 4 being secondary analyses, while the other six investigated other types of intra-articular injections. This further limits the number of studies from which conclusions can be drawn on a certain type of injection. Additionally, the screening of articles for inclusion in this review was conducted by one reviewer with confirmation of eligibility of the final 11 studies completed by two individual reviewers.

5. Conclusion

This review highlights the gap in literature pertaining to the combination of two recommended treatments in the management of knee OA. There is a paucity of trials looking into possible synergistic effects of intra-articular injection and exercise for knee OA, while clinically many patients receive both treatments. For instance, CS injections are highly recommended for the treatment of OA, and we only found one study examining the combined effects of CS injections and exercise compared to exercise alone. Additionally, the exercise portion of the interventions were highly variable and patient adherence was not well monitored which may have implications on the effectiveness of the interventions and long-term outcomes. There is a need for future trials to systematically investigate the effects of adding an intra-articular injection to a standardized exercise program for adults with knee OA.

Author contributions

Sydney Liles, PT, DPT, MS: First author, main contributor to conception, draft of the article, and critical revision of the article for important intellectual content; final approval of the version to be published.

Brad Bley, DO, FAAP, RMSK, CSCS: Second author, substantial contributions to critical revision of the article, and final approval of the version to be published.

Daniel K White MSPT, ScD, MSc: Last author, substantial contributions to the design of the work, critical revision of the article, and final approval of the version to be published.

Conflicts of interest

The authors have no conflicts of interest with regard to this work.

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