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Use of intra-articular hyaluronic acid in knee osteoarthritis or osteoarthritis

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct research and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.
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INTRODUCTION

With an estimated worldwide prevalence of 3%, osteoarthritis (OA) is among the most frequent problems in elderly clinical practice. For a long time, it was considered a disease that only involved wear and tear of the articular cartilage, but today, with the advances in the understanding of the disease, the understanding is that the pathophysiological changes involve the joints as a whole (cartilage, bone, synovial membrane, ligaments, adipose tissue, and meniscus), as well as pain processing nerve pathways. Changes may arise due to internal (obesity) and external mechanical loads, joint misalignment (genu varus and genu valgus), metabolic, and genetic factors. Excessive load on the bone can result in spinal cord injuries with microfractures, necrosis, fibrosis, and adipocytes, all suggestive of damage and remodeling in the injured area. Synovitis is commonly observed, and it plays an important role in joint destruction. Factors with pro-inflammatory cytokines (interleukin-6 [IL6]), monocyte chemoattractant protein, vascular endothelial growth factor, protein, and monokine induced by interferon γ are responsible for the progressive destruction due to the stimulation of degradation enzymes, and the growth factors stimulate the production of matrix for remodeling but end up promoting the formation of osteophytosis, thus contributing to subchondral sclerosis. Cytokines are not only the drivers of joint destruction but also potential targets for intervention to modify disease progression. Cartilage, as the only tissue without vascular, nervous, or lymphatic supply, has properties that condition its low intrinsic repair capacity, making repair difficult[1].

The treatment of knee OA begins with clear and consistent information about the history of the disease to patients, clarifying the benefits of exercise, weight loss, and physiotherapy, which are behaviors that have well-established benefits to reduce pain, in addition to anti-inflammatory drugs, administered topically or orally, which are the backbone of pharmacological treatment. Intra-articular (IA) corticosteroid injections provide temporary relief. Hyaluronic acid (HA) injection is also frequently offered, although evidence of its benefit remains controversial[1].

With the discovery of HA in bovine vitreous humor in 1934, it began to play an important role in the repair of wounds and skin damage. Thus, the use of HA in the form of IA injections in patients with OA of the knee, called viscosupplementation, was the first indication for clinical use in orthopedics and traumatology, with the aim of treating joint cartilage injuries by having a lubricating effect, mechanical and biochemical, with the expected result of partial relief of painful symptoms and improvement in function. The effect is not immediate but long-term. Currently, the use of HA is widespread and frequent, but without clear evidence of benefit and with the risk of potential harm[1].

The objective of this study was to evaluate the clinical efficacy and adverse effects of treatment with HA for anterior knee pain caused by grade II and III OA, as it causes discomfort and an inability to perform daily activities. Assessments will be short- and medium-term, measuring different scores.

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METHODOLOGY

In the methodology, we will express the clinical question, the structured question (PICO), eligibility criteria of the studies, consulted information sources, search strategies used, critical evaluation method (risk of bias), quality of evidence, data to be extracted, measures to be used to express results, and the method of analysis.

Clinical question

Is the use of HA in IA application for the treatment of knee OA efficacy and safe?

Structured question

- P (population): Patients with osteoarthritis or osteoarthrosis of the knee
- I (intervention): High or low molecular weight hyaluronic acid
- C (comparison): Placebo or sham or steroid or usual care
- O (outcome): Clinical improvement (overall – pain – stiffness – gait)

Sources of information consulted and search strategies

The searches they were performed in the Medline database (PubMed), with the next terms: (Osteoarthritis OR Osteoarthritides OR Osteoarthrosis OR Osteoarthroses) AND Knee AND (Viscosupplements OR Viscosupplement OR Visco Supplements OR Viscosupplementation OR Viscosupplementations OR Hyaluronic Acid OR Hyaluronate Sodium) AND Random*.

Eligibility criteria

PICO components; randomized clinical trials (RCTs); no period restriction; languages English, Spanish, and Portuguese; full text or abstract with the necessary data; outcomes expressed in absolute number of events or mean/median with variation.

Exclusion criteria

Observational and noncomparative studies, in vitro and/or animal studies, case series or case reports, narrative or systematic reviews, and guidelines.

Risk of bias and quality of evidence

For RCTs, the following risks of bias will be evaluated: focal question, randomization, blinded allocation, double blinding, losses, analysis by intention to treat (ITT), definition of outcomes, sample calculation, early interruption, and prognostic characteristics.

Extracted data

Author, year of publication, study design, characteristics and number of patients, intervention, comparison, and outcomes (clinical improvement and adverse effects). Each study was described individually in a qualitative analysis of the evidence. Evaluation of seven outcomes (adverse and clinical events) with priority for categorical outcomes and/or averages (SD). Subgroup analysis: HA versus CORTICOID and HA versus SALINE SOLUTION (SS). Outcomes – overall WOMAC – pain WOMAC – functional WOMAC – overall KSS – overall VAS. Measured with continuous variables (final mean or mean difference with standard deviation) and dichotomous variables.

Outcome measures

For categorical variables, we will use absolute numbers, percentages, absolute risk, reduction or increase in risk, number needed to treat or number of harm (NNH), and 95% confidence interval (95%CI). For continuous variables, we will use means or the difference of means with a standard deviation.

Expression of results

If it is possible to aggregate the results of one or more included studies regarding one or more common outcomes, a meta-analysis will be performed [RevMan 5.4 software (Cochrane)].

Evidence quality analysis

Comparisons were demonstrated in the risk difference and 95%CI. The inconsistency of effects across interventions was assessed using I^2. The random effects model was used if $I^2>50\%$ and the fixed effects model if $I^2\leq50\%$. To access possible publication biases, Egger's test (funnel plot) was analyzed for asymmetry. The certainty of the evidence was assessed using the GRADEpro guideline development tool and rated as high, moderate, low, or very low.

RESULTS

The results presented will be: study recovery and selection diagram (Figure 1), study characteristics (Tables 1A, B), risk of bias (Tables 2A, B), results (Tables 3A, B), analysis by outcomes (Figures 2–12), quality of evidence (Tables 4 and 5), and synthesis of evidence.

A total of 680 studies were retrieved, of which, meeting the eligibility criteria, 27 studies were selected[2-28], of which 17 were comparisons against saline solution (Table 1A)[2-18] and 10 comparisons against steroids (Table 1B)[19-28]. The main reasons for exclusion were orphan studies and outcomes, technical comparisons, and lack of comparisons.

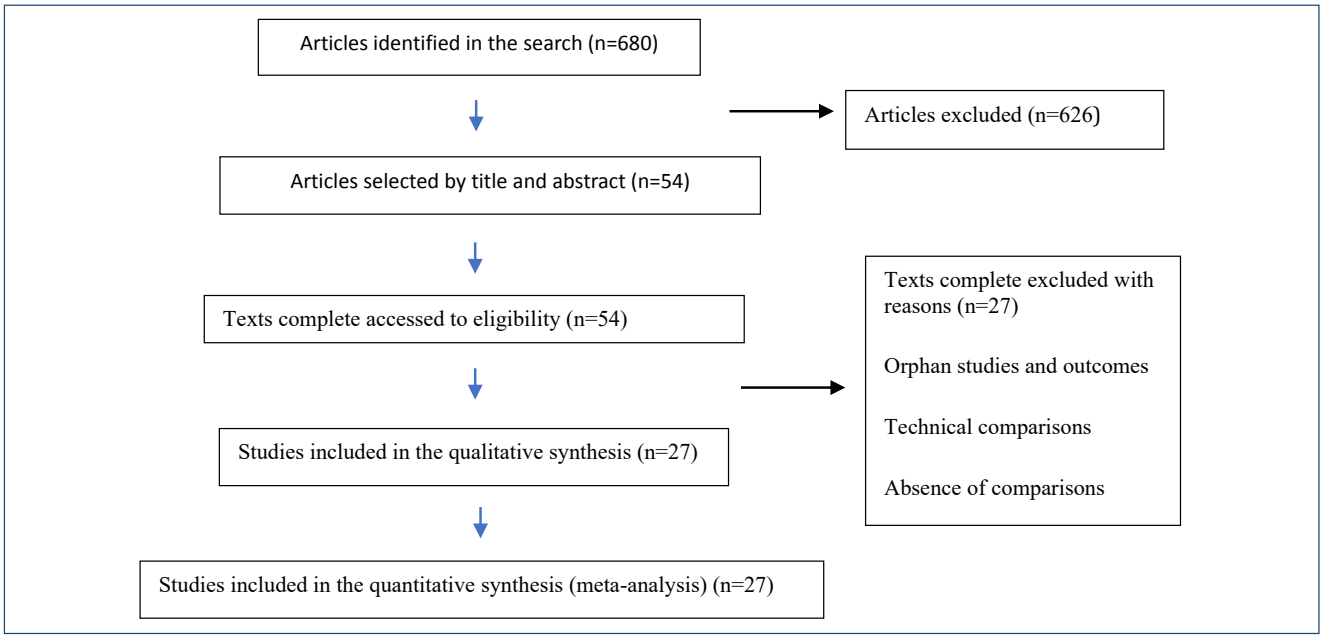

Figure 1. Flowchart of selected works.

Table 1A. Description of studies comparing hyaluronic acid with saline solution (n=17).

Author/year	Patients number		Outcomes measured - Instrument		Adverse effects reported	Molecular weight	Injection number	Follow-up weeks
	Hyaluronic Acid	Saline Solution	Pain	Function				
Altman RD 2004	173	174	WOMAC	WOMAC	Yes	High	1	24
Altman RD 2009	293	295	WOMAC	WOMAC	Yes	High	3	26
Arden N 2013	108	110	WOMAC	WOMAC	Yes	Intermediate	1	6
Baltzer AWA 2008	135	107	WOMAC	VAS	Yes	High	3	26
Brandt KD 2001	114	112	WOMAC		Yes	Intermediate	3	16
Chevalier X 2010	124	129	WOMAC	WOMAC	Yes	High	1	26
Day R 2004	116	124	WOMAC		Yes	High	5	18
Dougados M 1993	55	55	VAS	Lequesne index	Yes	High	4	52
Hangody L 2018	150	69	WOMAC	WOMAC	Yes	Intermediate	1	2
Henderson EB 1994	45	46	VAS	VAS	Yes	High	4	5
Huang TL 2011	98	100	Pain on walking (VAS)	WOMAC	Yes	Low	5	25
Huskisson EC1999	50	50	Pain on walking (VAS)	Lequesne index	Yes	High	5	24
Karlsson J 2002	88	66	VAS	Lequesne index	Yes	High	3	52
Migliore A 2021	347	345	VAS	Lequesne index	Yes	Low/high	1	24
Petterson SC 2019	184	185	WOMAC	WOMAC	Yes	High	1	26
Pham T 2004	131	85	Global pain (VAS)	Lequesne index	No	Intermediate	3	52
Strand V 2012	251	128	WOMAC		Yes	Intermediate	1	1

Table 1B. Description of studies comparing hyaluronic acid with steroids (n=10).

Author/year	Patients number		Outcomes measured - Instrument		Adverse effects reported	Molecular weight	Injection number	Follow-up weeks
	Hyaluronic acid	Saline solution	Pain	Function				
Askari A 2016	71	69	WOMAC	VAS	No	High	1	12
Bisicchia S 2016	75	75	WOMAC		No	High	2	26 and 52
Caborn D 2004	113	102	WOMAC / VAS	WOMAC	No	High	3	26
Maia PAV 2019	16	12	WOMAC	WOMAC	No	High	1	24
Shimizu M 2010	32	29	VAS		No	High	5	24
Skwara A 2009	30	30	VAS	Lequesne index	No	Intermediate	1	12
Tammachote N 2016	50	49	VAS	WOMAC	Yes	High	1	24
Tasciotaoglu F 2003	28	27	VAS	Lequesne index	Yes	High	3	26
Housman L 2014	129	132	WOMAC		Yes	High	1	26
Leighton R 2014	221	221	WOMAC		Yes	Intermediate	1	26

Table 2A. Overall risk of bias in studies comparing HA and saline AI.

Author/year	Randomization	Allocation	Double blind	Evaluator blindness	Losses	Prognostic	Outcomes	Intention to treat	Sample	Interruption
Baltzer AWA 2008										
Chevalier X 2010										
Day R 2004										
Dougados M 1993										
Pham T 2004										
Huskisson EC 1999										
Karlsson J 2002										
Migliore A 2021										
Altman RD 2004										
Altman RD 2009										
Petterson SC 2019										
Brandt KD 2001										
Hangody L 2018										
Huang TL 2011										
Arden NK 2014										
Henderson EB 1994										
Strand V 2012										
Subtitle	Low bias risk				Without information			High bias risk		

Characteristics of the included studies

A total of 5,917 patients with OA or knee osteoarthrosis who underwent IA injection of HA (n=3,101) compared to saline solution (n=2,816) were studied and followed for a period between 8 and 52 weeks. Molecular weight ranged from high to intermediate, and the outcomes measured were pain and functional (WOMAC, Lequesne index, KSS, and VAS) (Table 1A).

A total of 1,677 patients with OA or osteoarthrosis of the knee who underwent IA injection of HA (n=847) compared to steroids (n=830) were studied and followed for a period between

Table 2B. Overall risk of bias in studies comparing HA and steroid AI.

Author/Year	Randomization	Allocation	Double blind	Evaluator blindness	Losses	Prognostic	Outcomes	Intention to treat	Sample	Interruption
Askari A 2016										
Maia PAV 2019										
Caborn D 2004										
Tammachote N 2016										
Skwara A 2009										
Bisicchia S 2016										
Shimizu M 2010										
Tasciotaoglu F 2003										
Housman L 2014										
Leighton R 2014										
Subtitle	Low bias risk				Without information			High bias risk		

12 and 52 weeks. Molecular weight ranged from high to intermediate, and the outcomes measured were pain and functional (WOMAC, Fansne index, KSS, and VAS) (Table 1B).

Risk of bias

The overall risk of bias in studies comparing HA and saline solution AI is high, with most of this risk concentrated in the lack of blinding, losses, and analysis by ITT (Table 2A).

The overall risk of bias in studies comparing HA and steroid AI is high, with most of this risk concentrated in the lack of blinding, losses, and analysis by ITT (Table 2B).

Results of the quantitative analysis by comparison and by outcomes (meta-analysis)

Comparison between HA IA (IA-HA) and saline solution IA (IA-SS) (Figures 2–8)

In this comparison and analysis, it was possible to aggregate the results of 17 studies in relation to seven outcomes: overall WOMAC for pain, pain at rest (VAS), functional index (Lequesne), WOMAC (functional), WOMAC (pain), pain (VAS) walking, and adverse events (Table 3A).

Overall WOMAC for pain at 18 to 26 weeks – IA-HA versus IA-SS (Figure 2)

In pain assessment using the global WOMAC score (Figure 2), comparing IA-HA (n=375) and IA-SS (n=360), three studies were included[2-4]. The analysis identified a benefit of HA with a mean score reduction of -0.16 [95%CI -0.23, -0.10][2-4]. The quality of evidence is very low (Table 4).

Pain at rest (VAS) – IA-HA versus IA-SS (Figure 3)

In the assessment of pain at rest using the VAS score (Figure 3), comparing IA-HA (n=186) and IA-SS (n=140), two studies were included[5,6]. In the analysis, no difference in pain was identified between the -0.27 [-6.34, +5.79] comparisons. The quality of evidence is very low (Table 4).

Lequesne's functional assessment (Figure 4), comparing IA-AH (n=671) and IA-SS (n=601), five studies were included[5-9]. In the analysis, no difference in function was identified between comparisons -0.24 [95%CI -1.24, +0.76]. The quality of evidence is very low (Table 4).

WOMAC – functional subscale (baseline up to 26 weeks) – IA-HA versus IA-SS (Figure 5)

In the functional assessment (WOMAC), comparing IA-HA (n=785) and IA-SS (n=761), four studies were included[2,10-12]. In the analysis, no difference in function (WOMAC) was identified between comparisons -0.18 [95%CI -1.61, +1.26][2,10-12]. The quality of evidence is very low (Table 4).

WOMAC – pain subscale (baseline up to 26 weeks) – IA-HA versus IA-SS (Figure 6)

In the pain assessment (WOMAC), comparing IA-HA (n=830) and IA-SS (n=748), five studies were

Table 3A. Description of results by outcomes (IA-HA versus IA-SS).

Author/ Year	WOMAC function (Baseline REDUCTION) 26 weeks (Median±SD) (N)		WOMAC pain (BASELINEREDUCTION) 26 weeks (Median±SD) (N)		VAS (0-100) PAIN (WALKING) 26-52 weeks (Median±SD) (N)		Lequesne's functional index 26-52 weeks (Median±SD) (N)		Adverse events n/N		VAS (0-100) PAIN REDUCTION (REST) 52 weeks (Median±SD) (N)		WOMAC GLOBAL PAIN 18-26 weeks (Median±SD) (N)	
	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution
Baltzer AWA 2008	3.74 (2.44) (135)	3.94 (2.48) (107)			49.3 (25.9) (135)	48.2 (25.59) (107)			51/135	30/107			3.75 (2.42) (135)	3.93 (2.38) (107)
Chevalier X 2010									70/124	79/129			1.43 (0.06) (124)	1.59 (0.058) (129)
Day R 2004													3.84 (3.27) (116)	4.61 (3.14) (124)
Dougados M 1993					38.9 (30.9) (55)	32.71 (28.8) (55)	4.4(5.1) (55)	2.7 (4.1) (55)	18/55	18/55	17.9 (30.0) (55)	16.9 (23.4) (55)		
Pham T 2004							20.0 (16.5) (131)	18.9 (16.9) (85)			33.5 (28.5) (131)	34.5 (27.4) (85)		
Huskisson EC 1999					39.4 (27.8) (50)	53.7 (29.9) (50)	11.2 (4.4) (50)	12.6 (4.8) (50)	17/50	14/50				
Karlsson J 2002							4.4 (4.1) (88)	4.7 (4.4) (66)	51/88	50/66				
Migliore A 2021					29 (24) (347)	33 (24) (345)	7.4 (4.1) (347)	8.2 (4.3) (345)	187/347	180/345				
Altman RD 2004	5.82 (12.16) (173)	7.42 (13.52) (174)	2.50 (4.00) (173)	2.89 (4.17) (174)					112/173	114/174				
Altman RD 2009	19.6 (31.27) (293)	15.4 (29.33) (295)	19.2 (26.8) (293)	16.3 (26.8) (295)	30.0 (26.1) (293)	36.1 (28.6) (295)			158/293	168/295				
Petterson SC 2019	32.5 (24.8) (184)	33.1 (25.2) (185)			31.9 (22.0) (184)	30.9 (22.9) (185)			121/184	123/185				
Brandt KD 2001			2.1 (0.7) (114)	2.0 (0.7) (112)					76/114	74/112				
Hangody L 2018			39.5 (22.8) (150)	32.9 (23.6) (69)										
Huang TL 2011			29.28 (1.92) (100)	21.52 (1.94) (98)	17.00 (14.32) (100)	21.53 (15.69) (100)			39/100	48/100				
Arden NK 2014									68/108	69/110				
Henderson EB 1994									21/45	10 de 46				
Strand V 2012									172/251	81/128				

Table 3B. Description of results by outcomes (IA-HA versus IA-SS).

Author/ Year	WOMAC PAIN 12 weeks (Median±SD) (N)		WOMAC PAIN 26 weeks (Median±SD) (N)		VAS (0-100) PAIN 12 weeks (Median±SD) (N)		VAS (0-100) PAIN 26 weeks (Median±SD) (N)		WOMAC GLOBAL 26 weeks (Median±SD) (N)		WOMAC GLOBAL 52 weeks (Median±SD) (N)		Adverse events n/N	
	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution	Hyaluronic acid	Saline solution
Askari A 2016	13.22 (4.24) (71)	12.60 (3.69) (69)			6.7 (2.01) (71)	6.56 (2.15) (69)								
Maia PAV 2019	14.3 (3.6) (16)	7.1 (3.9) (12)												
Caborn D 2004			0.7 (0.1) (113)	0.4 (0.1) (102)			28.0 (2.5) (113)	12.4 (2.6) (102)	18.4 (1.7) (113)	10.4 (1.8) (102)			87/113	71/102
Tammachote N 2016			21 (15) (55)	21 (19) (55)			24 (22) (55)	21 (22) (55)						
Skwara A 2009					44.0 (22.3) (30)	45.8 (27.8) (30)								
Bisicchia S 2016							4.0 (2.0) (75)	5.0 (1.0) (75)	27.3 (10.8) (75)	36.0 (7.1) (75)	39.6 (17.9) (75)	42.3 (7.5) (75)		
Shimizu M 2010							21.5 (19.3) (32)	22.6 (18.3) (29)						
Tasciotaoglu F 2003							23.56 (10.11) (30)	26.46 (14.30) (30)					16/30	13/30
Housman L 2014													91/130	81/132
Leighton R 2014													50/221	9/221

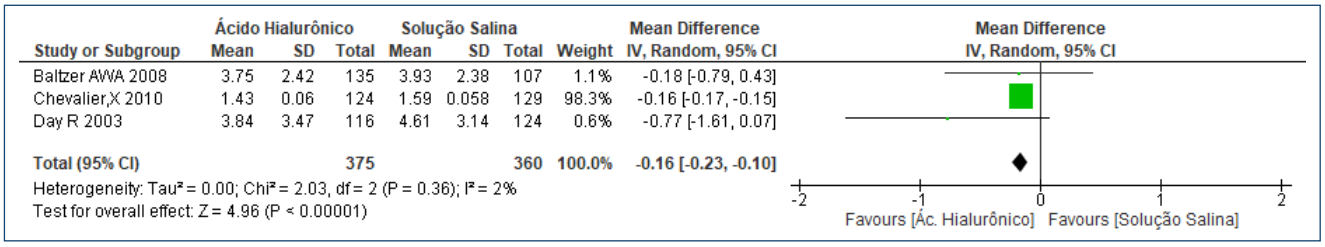

Figure 2. Western Ontario McMaster University Osteoarthritis (WOMAC global) – IA-HA versus IA-SS.

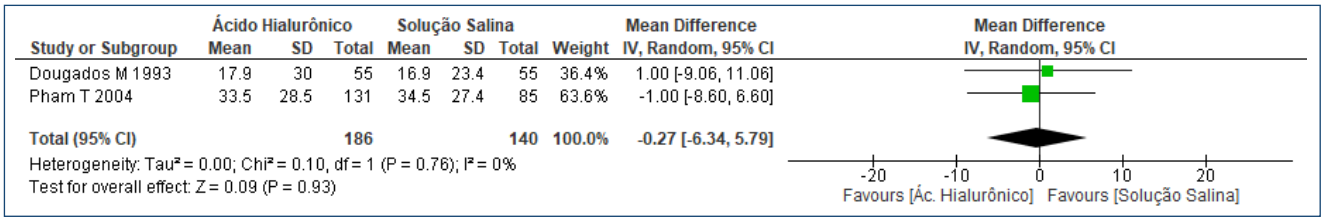

Figure 3. Decreased pain at rest (VAS) – IA-AH versus IA-SS.

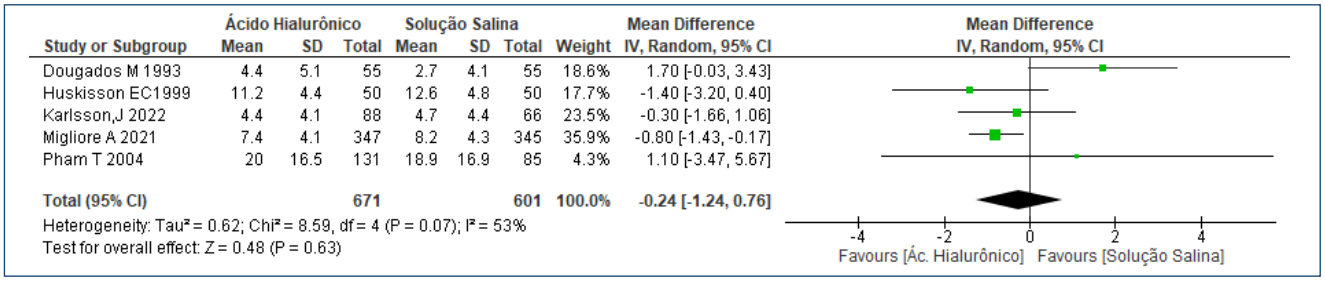

Figure 4. Lequesne's functional index from 26 to 52 weeks – IA-HA versus IA-SS.

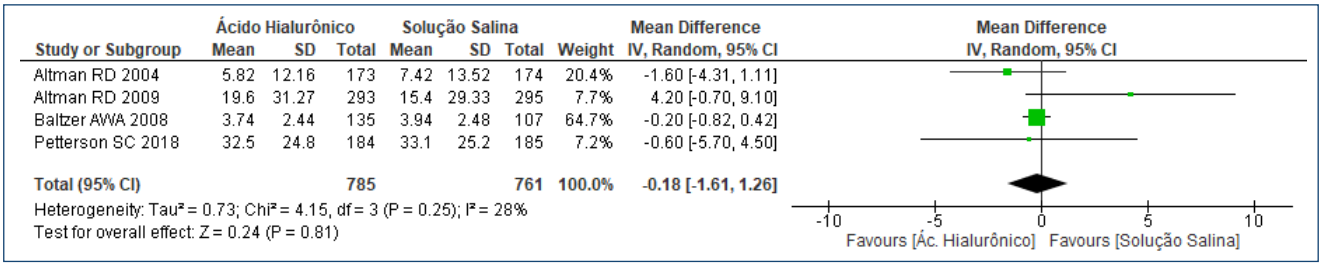

Figure 5. WOMAC (functional subscale) – score decrease – IA-HA versus IA-SS.

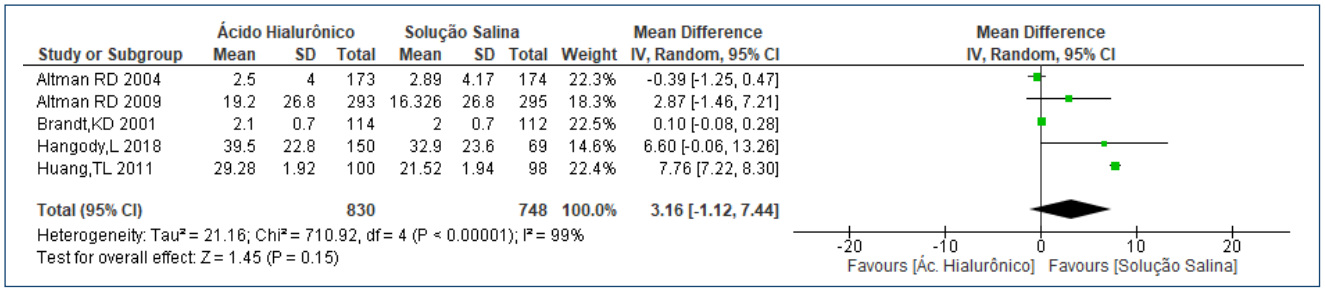

Figure 6. WOMAC (pain subscale) – score decrease – IA-HA versus IA-SS.

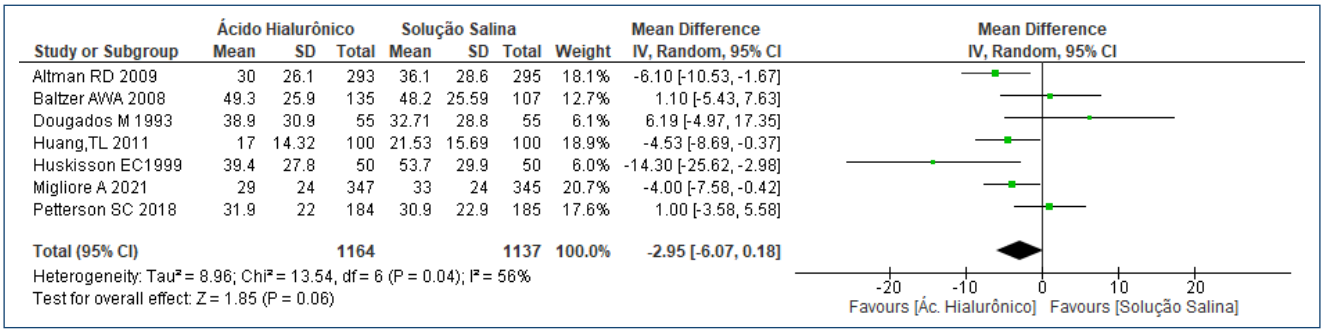

Figure 7. Decreased walking pain (VAS) – IA-HA versus IA-SS.

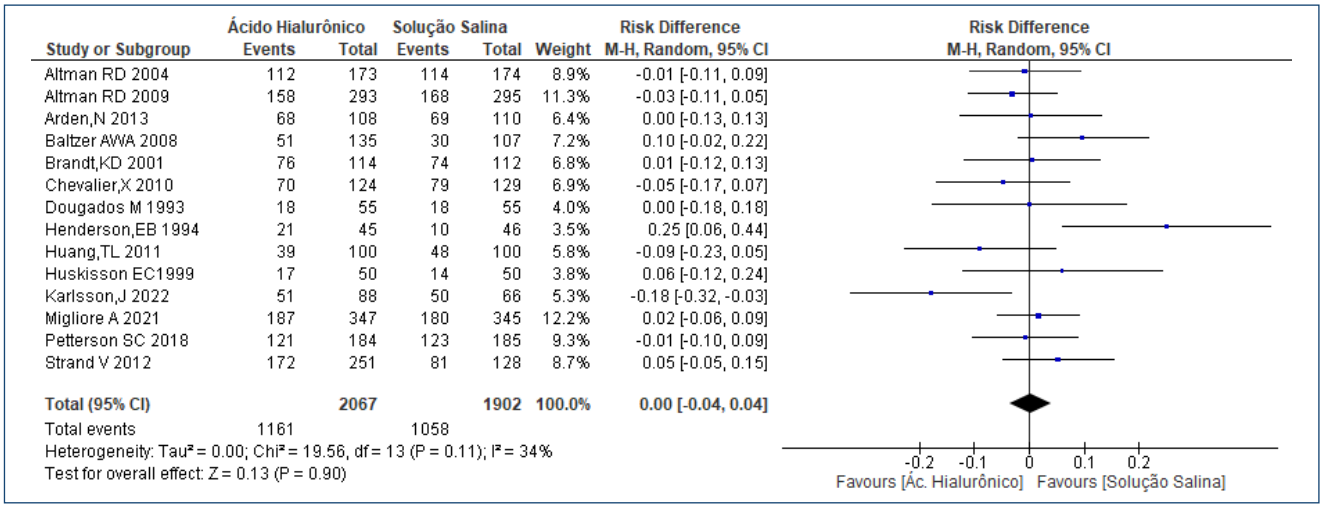

Figure 8. Adverse events – IA-AH versus IA-SS.

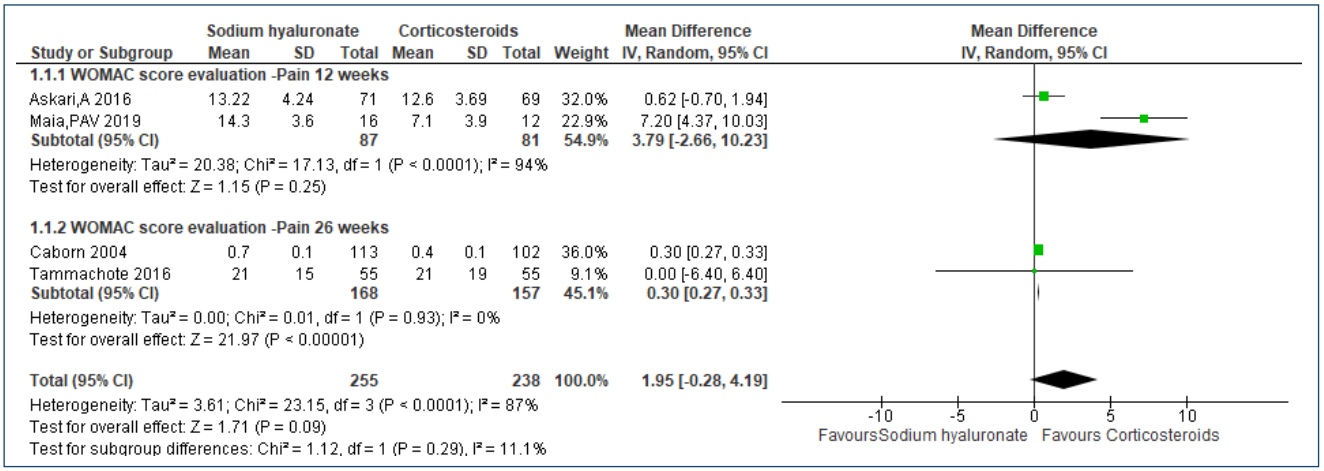

Figure 9. WOMAC pain score (12 and 26 weeks) – IA-HA versus IA-SS.

included[10-11,13-15]. In the analysis, no difference in function (WOMAC) was identified between comparisons +3.16 [95%CI -1.12, +7.44][10-11,13-15]. Very low quality of evidence (Table 4).

Walking pain at 26–52 weeks (VAS) – IA-HA versus IA-SS (Figure 7)

In the assessment of pain on walking using the VAS score (Figure 7), comparing IA-HA (n=1,164) and IA-SS (n=1,137), seven

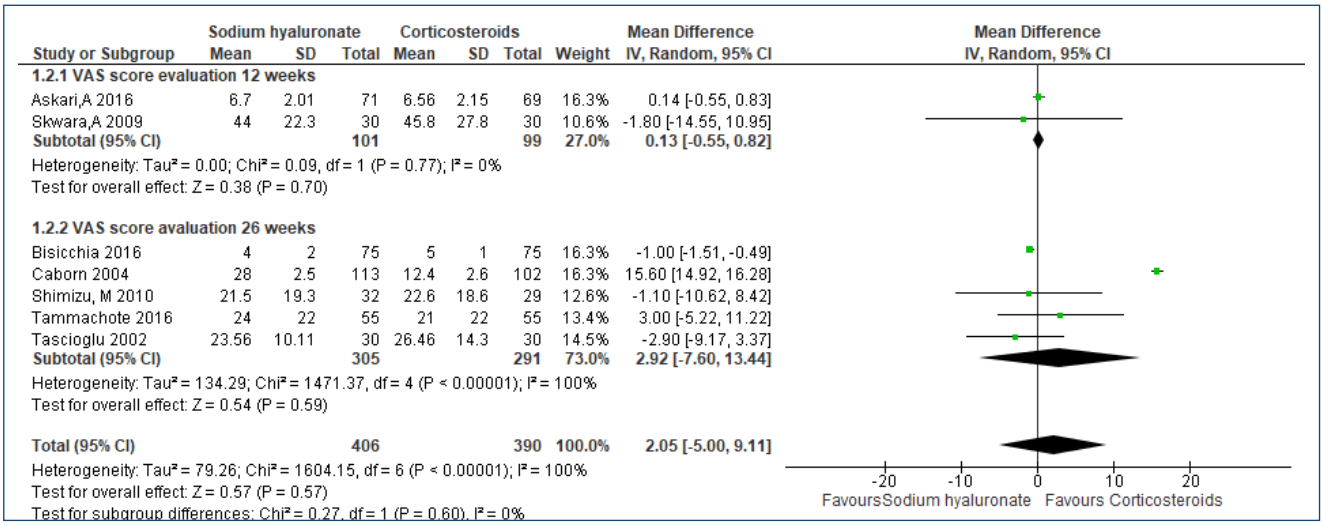

Figure 10. Pain assessment – VAS (12 and 26 weeks) – IA-HA versus IA-SS.

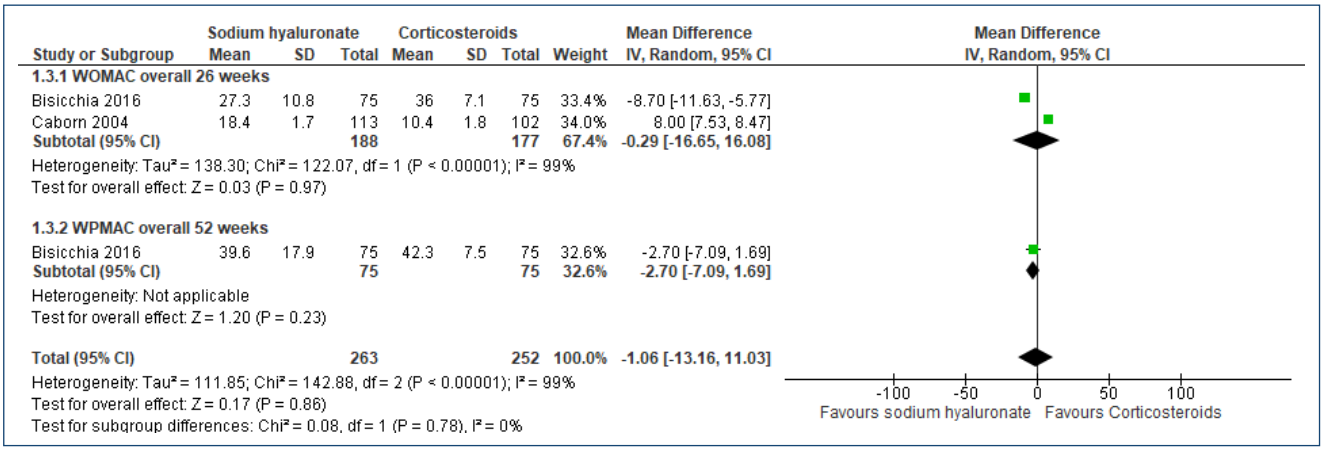

Figure 11. Pain assessment – overall WOMAC (26 and 52 weeks) – IA-HA versus IA-SS.

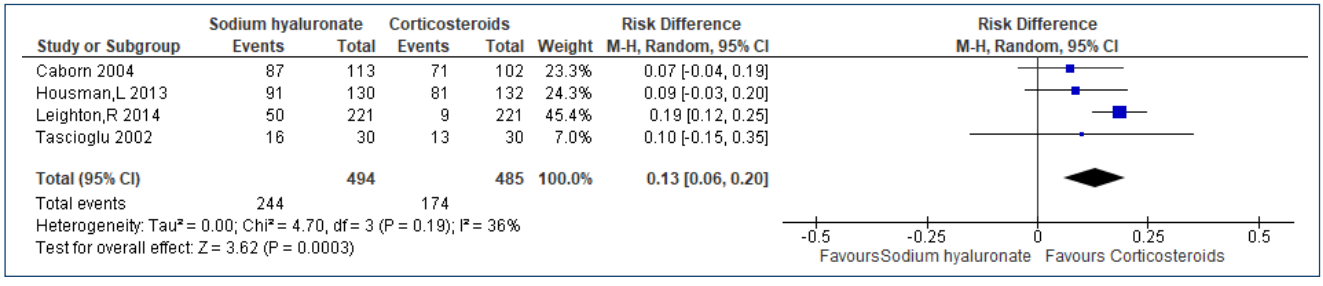

Figure 12. Adverse events – IA-HA versus IA-SS.

studies were included[2,5,7,9,11,12,15]. In the analysis, no difference in pain was identified between the -2.95 [-6.07, +0.18] comparisons. The quality of evidence is very low (Table 4).

Adverse events – IA-HA versus IA-SS (Figure 8)

In the evaluation of adverse events between IA-HA and IA-SS, 14 studies were included with 2,067 patients in the

Table 4. Question: knee infiltration with hyaluronic acid versus saline solution – GRADE.

Certainty assessment							Patients number		Effect		Certainty	Importance
Studies number	Study design	Bias risk	Inconsistency	Indirect evidence	Imprecision	Other considerations	Hyaluronic acid	Saline solution	Relative (95%CI)	Absolute (95%CI)		
WOMAC global – pain – 18–26 weeks												
3	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	375	360	–	MD **0.16 lower** (0.23 lower to 0.1 lower)	⊕◯◯◯ Very low	
VAS – pain reduction (rest) – 52 weeks												
2	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	186	140	–	MD **0.27 lower** (6.34 lower to 5.79 higher)	⊕◯◯◯ Very low	
Lequesne's Functional Index – 26 and 52 weeks												
5	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	671	601	–	MD **0.24 lower** (1.24 lower to 0.76 higher)	⊕◯◯◯ Very low	
WOMAC - Functional – Reduction from Base Line – 26 weeks												
4	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	785	761	–	MD **0.18 lower** (1.61 lower to 1.26 higher)	⊕◯◯◯ Very low	
WOMAC - Pain – Reduction from Base Line – 26 weeks												
5	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	830	748	–	MD **3.16 higher** (1.12 lower to 7.44 higher)	⊕◯◯◯ Very low	
VAS 0-100 Pain (walking) – 26–52 weeks												
7	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	1,164	1,137	–	MD **2.95 lower** (6.07 lower to 0.18 higher)	⊕◯◯◯ Very low	
Adverse events												
14	Randomized clinical trials	Serious[a,b]	Serious[c]	Not serious	Serious[d]	None	1,161/2,067 (56.2%)	1,058/1,902 (55.6%)	L	**0 less by 1,000** (40 less to 40 more)	⊕◯◯◯ Very low	

CI: confidence interval; MD: mean difference. [a]Without intention to treat analysis. [b]Unblided. [c]High heterogeneity. [d]Large confidence interval.

HA group (intervention) and 1,902 in the SS group (control). There was no difference in the risk of adverse events 0.00 [95%CI -0.04, +0.04][2,3,5-7,9-13,15-18]. The quality of evidence is very low (Table 4).

Comparison between HA IA (IA-HA) and Steroid IA (IA-SS) (Figures 9–12)

In this comparison and analysis, it was possible to aggregate the results of 10 studies, in relation to four outcomes:

Table 5. Question: knee infiltration with hyaluronic acid versus steroids – GRADE.

Certainty assessment							Patients number		Effect			
Studies number	Study design	Bias risk	Inconsistency	Indirect evidence	Imprecision	Other considerations	Hyaluronic acid	Steroids	Relative (95%CI)	Absolute (95%CI)	Certainty	Importance
WOMAC score evaluation – Pain												
4	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	None	255	238	–	MD **1.95 higher** (0.28 lower to 4.19 higher)	⊕⊕⊕⊕ High	
VAS score evaluation – Pain												
7	Randomized clinical trials	Not serious	Serious[a]	Not serious	Serious[b]	None	406	390	–	MD **2.05 higher** (5 lower to 9.11 higher)	⊕⊕◯◯ Low	
WOMAC overall												
2	Randomized clinical trials	Not serious	Serious [a]	Not serious	Not serious	None	150	150	–	MD 1.06 **lower** (13.16 lower to 11.03 higher)	⊕⊕⊕◯ Moderate	
Adverse events												
4	Randomized clinical trials	Not serious	Serious[a]	Not serious	Not serious	None	244/494 (49.4%)	174/485 (35.9%)		**130 less by 1,000** (200 less to 60 less)	⊕⊕⊕◯ Moderate	

CI: confidence interval; MD: mean difference. [a]High heterogeneity. [b]Large confidence interval.

WOMAC (pain) (12 and 26 weeks), pain at rest (VAS) (12 and 26 weeks), WOMAC overall for pain, and adverse events (Table 3B).

WOMAC pain score (12 and 26 weeks) – IA-HA versus IA-SS (Figure 9)

In assessing pain using the WOMAC score and comparing IA-HA and IA-SS, two studies were included in the 12-week evaluation (87 patients in the IA-HA group and 81 in the IA-SS group), and two studies were included in the 26-week evaluation (168 patients in the IA-HA group and 157 in the IA-SS group). The result of the analysis of subgroups by follow-up time does not identify a difference between the comparisons at 12 weeks: 3.79 [95%CI -2.66, +10.23] and results in an increase in the pain score with HA of 0.30 [95%CI +0.27, +0.33] at 26 weeks. In the global analysis (regardless of the follow-up time), no difference was identified between the comparisons: 1.95 [-0.28, +4.19] (Figure 9)[19-22]. High quality of evidence (Table 5).

PAIN assessment (VAS) at 12 and 26 weeks – IA-HA versus IA-SS (Figure 10)

In the assessment of pain using the VAS score comparing IA-HA and IA-SS, two studies were included in the 12-week assessment (101 patients in the IA-HA group and 99 in the IA-SS group), and at 26 weeks, five studies were included (305 patients in the IA-HA group and 291 in the IA-SS group). No differences were identified in the score at the 12-week follow-up [0.13 (95%CI -0.55, +0.82)], the 26-week [2.92 (95%CI -7.60, +13.44)], or in the global analysis regardless of follow-up time [2.05 (95%CI -5.00, +9.11)] (Figure 10)[19-26]. Low quality of evidence (Table 5).

Overall WOMAC for pain at 26 and 52 weeks – IA-HA versus IA-SS (Figure 11)

In pain assessment (global WOMAC score), comparing IA-HA and IA-SS, two studies were included in the 26-week follow-up (188 patients in the IA-HA group and 177 in the IA-SS group), and one study in 52 weeks of follow-up (75 patients in groups IA-HA and IA-SS). There was no difference between the two groups at the follow-up of 26 [-0.29 (95%CI -16.65, +16.08)], or 52 weeks [-2.70 (95%CI -7.09, +1.69)], or at global assessment [- 1.06 (95%CI -13.16, +11.03)] (Figure 11)[21,24]. Moderate quality of evidence (Table 5).

Adverse events – IA-HA versus IA-SS (Figure 12)

In the evaluation of adverse events, in the comparison between IA-HA and IA-SS, four studies were included (494 patients in the IA-HA group and 485 in the IA-SS group). The analysis demonstrates that there is an increase in the risk of adverse events with the 13% HA [95%CI 6–20%][21,26-28]. Moderate quality of evidence (Table 5).

Quality of evidence by comparison and outcome (Tables 4 and 5)

Knee infiltration comparing hyaluronic acid to saline solution (placebo) in osteoarthritis

Outcomes: Overall WOMAC for pain, pain at rest (VAS), functional index (Lequesne), WOMAC (functional), WOMAC (pain), pain (VAS) while walking, and adverse events.

Knee infiltration comparing hyaluronic acid to steroids in osteoarthritis

Outcomes: WOMAC (pain) (12 and 26 weeks), pain at rest (VAS) (12 and 26 weeks), overall WOMAC for pain, and adverse events.

SUMMARY OF EVIDENCE

There were seven analyses (seven outcomes) comparing IA injection with HA and saline solution and four analyses (four outcomes) comparing steroids, with follow-up at different times (8 weeks to 52 weeks). In only two outcomes, there was a difference in effect between the comparisons: (1) In the comparison between HA and saline solution: reduction in the Western Ontario McMaster University Osteoarthritis (global WOMAC) score of 0.16 points favorable to HA on a scale ranging from 0 to 96 points; (2) Increase in adverse events by 13% (NNH: 8) with the use of HA compared to steroids.

RECOMMENDATION

Despite the frequent and disseminate use of IA-HA in the treatment of knee OA, there is no high-quality evidence sustaining this form of treatment.

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