Severe Acute Localized Reaction/Pseudosepsis in Patients With Knee Osteoarthritis Receiving Injections of Hyaluronic Acid: A Targeted Literature Review

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abstract

Background: Hyaluronic acid injections for knee osteoarthritis patients can result in pseudosepsis. A targeted literature review was conducted to determine the rate of pseudosepsis in patients receiving intra-articular hyaluronic acid, particularly hylan G-F 20 (SYNVISC®). **Materials and Methods:** Articles were identified through Embase using predefined search strategies. Pseudosepsis event rate was calculated by dividing the number of reported events by the total number of intra-articular injections. **Results:** The pseudosepsis event rate ranged from 0% to 5.6% per injection; most treatment groups had an event rate of ≤2% per injection. **Conclusion:** Pseudosepsis event rates were low across studies for patients treated with hyaluronic acid, including hylan G-F 20.

Osteoarthritis (OA) is the most common disabling joint disease that affected approximately 7.6% of the global population in 2024.[1] Global prevalence of knee OA (KOA) ranges from 1% to 10% among adults and leads to symptoms of stiffness and dull aching with movement, which may progress to pain and decreased range of motion.[2] KOA is a leading cause of disability in the United States (US), resulting in hospitalizations and important economic burden.[3-5] Management of KOA focuses on alleviating symptoms like pain and stiffness, primarily through the use of oral antalgic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and lifestyle modifications. Due to the inflammatory nature of KOA, physicians frequently administer intra-articular injections of corticosteroids and NSAIDs, with NSAIDs being a fundamental component of OA treatment. However, the use of NSAIDs carries potential risks, which may restrict their use in patients with cardiovascular, renal, or gastrointestinal comorbidities. In addition, some NSAIDs have been implicated as being potentially harmful to cartilage matrix. More recent treatment options, such as injection of hyaluronic acid (HA) or platelet-rich plasma (PRP) have shown some efficacy with possible better risk-advantage ratio.[6,7]

HA is an important component of the synovial fluid.[8] HA injections in the knee joint have shown a statistically significant reduction in knee pain and increased function with fewer adverse effects compared with oral NSAIDs.[9] Reported benefits of HA injections include reduced pain and stiffness, leading to improved functionality of the knee joint.[10] However, there have been some concerns suggesting that intra-articular HA injections could lead to severe acute localized reaction (SALR) or pseudosepsis.[10] Patients experiencing this rare complication typically display the following characteristics[11]:

- Severe inflammation of the joint with significant cellular effusion and pain with impaired function, normally occurring within 24 and 72 hours after injection;
- The complication typically occurring after exposure to more than one injection (ie, second or third injection in the first course of treatment or after a repeat course);
- Absence of infectious agents and calcium crystals in the synovial fluid;
- High numbers of mononuclear cells (eg, macrophages, neutrophils, eosinophils) infiltrating the synovial fluid; and
- Condition is not self-limiting and requires clinical intervention (eg, arthrocentesis, intra-articular steroid injection, NSAIDs).

The primary aim of this exploratory study was to determine the rate of SALR/pseudosepsis in KOA patients receiving intra-articular HA in the published literature, with a specific focus on hylan G-F 20 (SYNVISC®). Secondary exploratory objectives included the description and comparisons of hylan G-F 20 versus non-hylan G-F 20 products, single- versus multi-injection regimens, first versus repeat course, and avian versus bacterial fermentation product origin. Finally, one specific objective was to report the definitions of SALR/pseudosepsis used in the different studies and the way the events were described.

Materials and Methods

A targeted literature review was conducted to identify the risk of SALR/pseudosepsis in randomized controlled trials (RCTs) and observational studies on patients with KOA treated with HA injections. The standard methods for conducting and reporting systematic reviews of prevalence and incidence, as recommended by the Joanna Briggs Institute *Reviewer's Manual* for evidence synthesis,[12] was adapted for conducting this review. Results for the review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Relevant articles were identified by searching Embase from database inception to November 21, 2023, using a predefined search strategy (**Table A**, available in the online version of this article). Articles of studies known by the study authors from a previously published systematic literature review, which summarized the safety and efficacy of intra-articular HA preparations for the treatment of KOA, were also reviewed for inclusion.[14]

Eligibility Criteria

Study eligibility criteria defined using the PICO framework (Population, Intervention, Comparator, Outcome) are outlined in **Table 1**.

Observational studies are subject to inherent limitations related to database quality and the rigor of study design. The lost-to-follow-up rate is a crucial consideration, and the persistence of selection and information biases can compromise study results, as can residual confounding factors. Consequently, when reviewing the literature and considering observational evidence, it is essential to focus on selecting studies of the highest quality and those that provide informative insights. To address this concern, a list of criteria was developed to include the most informative observational studies of high-quality to determine the SALR/pseudosepsis event rate (**Table 2**).

Study Selection and Data Analysis

A single reviewer was responsible for reviewing abstracts according to the predefined selection criteria (**Table 1**). All eligible studies identified during title/abstract screening proceeded to the full-text screening phase, where they were assessed for eligibility by the same reviewer. Studies that matched the inclusion criteria following the full-text screening were included for data extraction. A single reviewer extracted all relevant study, patient, and intervention characteristics, as well as relevant outcomes data from the final list of in-

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Table 1

Eligibility Criteria

PICO item	Inclusion criteria	Exclusion criteria
Population	KOA patients treated with HA injection	N/A
	KOA patients with SALR	
	KOA patients with pseudosepsis	
Intervention	HA injections (including number of injections received)	N/A
Comparator	N/A	N/A
Outcomes	Rate of SALR/pseudosepsis following HA intra-articular injections	N/A
	Number of HA injections received	
	Possible causal mechanism of SALR/pseudosepsis (eg, type 4 allergic reaction)	
	Time to SALR/pseudosepsis	
	Relationship between repeated injection and risk of SALR/pseudosepsis	
	Relationship between nature of the HA injected and risk of SALR/pseudosepsis	
	Diagnosis and prevention/prophylaxis of SALR/pseudosepsis	
	Management of SALR/pseudosepsis in KOA patients following HA intra-articular injections	
	Technique of injection (eg, alcohol preparation prior to injection or no preparation, angle of injection)	
	Comorbidities or other predispositions (eg, dermatological disorders, cardiometabolic diseases such as diabetes)	
Study design		
Type	Randomized controlled trial, observational study	Letter, editorial, comment, case study/report
Additional criteria (limits)		
Language	English language	Non-English language

Abbreviations: HA, hyaluronic acid; KOA, knee osteoarthritis; N/A, not applicable; PICO, population, intervention, comparator, outcomes; SALR, severe acute localized reactions.

cluded studies. Accuracy and completeness of data extraction was reviewed by a senior reviewer.

The event rate of SALR/pseudosepsis for each HA treatment group in each included study was calculated by dividing the number of reported events by the total number of intra-articular injections. Comparisons between hylan G-F 20 versus non-hylan G-F 20 HA products, single- versus multi-injection HA regimens, and first versus repeat course of HA treatment were performed. We also compared the rates of events among patients treated by products from avian origin and bacterial fermentation, respectively.

Results

A total of 1,653 records were identified from Embase and an additional 36 records were provided by the study authors through hand-searching. The PRISMA diagram is shown in **Figure 1**. Following full-text screening, 33 unique studies (26 RCTs and 7 observational studies) were included. Of these, 26 studies (23 RCTs and 3 observational studies) were included in the SALR/pseudosepsis event rate analysis based on the following definition: SALR is a non-infectious, non-self-limiting inflammatory reaction that typically arises 24 to 72 hours after a second or subsequent intra-articular injection, characterized by severe joint pain, cellular effusion with predominately mononuclear cells (eg, macrophages, neutrophils, eosinophils), absence of pathogens or calcium crystals in the synovial fluid, and requiring clinical intervention (eg, arthrocentesis, intra-articular steroids, NSAIDs).

Study and Intervention Characteristics

A summary of the characteristics of each RCT is provided in **Table B** (available in the online version of this article), and the characteristics of the observational studies are summarized in **Table C** (available in the online version of this article). The most prevalent HA brand across trials was hylan G-F 20[15-34]; the three-injection

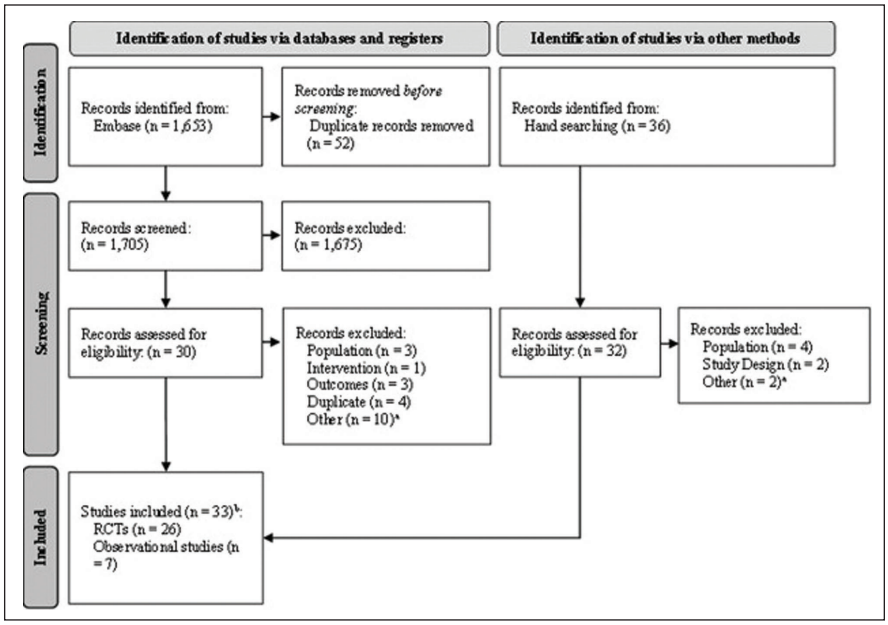

Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.
[a] Conference abstract/poster or full-text article unavailable; [b] 23 randomized controlled trials (RCTs) and 3 observational studies were included in the severe acute localized reaction (SALR)/pseudosepsis event rate analysis.

Table 2

Selection of Observational Studies for Analysis on SALR/Pseudosepsis Event Rate

Criteria[a]
Sample size ≥100
Follow-up period ≥6 months
Population with KOA well identified
Lost to follow-up <10%
Definition or description of SALR/ pseudosepsis events reported

Abbreviations: KOA, knee osteoarthritis; SALR, severe acute localized reactions.
[a] An observational study was included when all criteria were met.

regimen was the most commonly used product (n=13).[15,16,20-24,27-31,34] Most trials (n=22) included just one course of HA treatment,[15-17,19,20,23-30,32-40] but four trials examined multiple (two to three) courses of treatment.[18,21,22,31] Other HA brands investigated across trials included Artz/ Artzal,[24,38] Durolane,[36,38] GO-ON,[35] Hyalgan/Supartz,[26,30,35,37,39,40] Orthovisc,[16,22,23] Ostenil,[22] Sinovial,[29] and Structovial.[28] HA (hylan G-F 20) in combination with a corticosteroid was investigated in two trials,[17,19] and one trial included a study arm that was treated with HA (hylan G-F 20) in combination with an NSAID.[15] All but three RCTs provided sufficient information to calculate the event rate of SALR/pseudosepsis. One trial reported the occurrence of "severe adverse events" but did not further describe these events, and it could not be determined if any of these events were SALR/pseudosepsis.[29] Another trial did not report sufficient information to calculate the number of injections administered or to determine if any of the reported events were SALR/pseudosepsis.[37] The third trial did not report sufficient information to determine if any of the reported events were SALR/ pseudosepsis.[39]

Similar to the RCTs, the most common HA brand across observational studies was hylan G-F 20.[41-45] Other HA brands included Euflexxa,[43] Gel-200,[46] Gel-One,[43] Hyalubrix,[47] Hyalgan/Supartz,[43] Orthovisc,[43] and Monovisc.[43] For the analysis on SALR/pseudosepsis event rates, three of the seven observational studies were included based on the criteria outlined in **Table 2**.[43,45,46] Of the four observational studies excluded from this analysis, two had inadequate sample size,[41,47] and the other two did not report sufficient information to calculate the event rate.[42,44]

Population Characteristics

Population characteristics of the HA treatment arms of the included studies are summarized in **Table D** (available in the online version of this article). Across RCTs, participants' mean age ranged from 57 years to 72 years.[24] The proportion of male participants ranged from 10%[16] to 48%.[27] Mean duration of KOA ranged from 3.9 years[38] to 9.3 years,[31] although there was limited reporting on this characteristic. Kellgren-Lawrence (KL) grading was the most common measure of KOA severity across trials; the majority of patients had KL grade II or III KOA. Mean body mass index ranged from 24.9 kg/m^2 to 32.8 kg/m^2.[31,36] There was also limited reporting on prior therapies and patient comorbidities.

Across observational studies, participants' mean age was similar to those in RCTs, ranging from 61 years[47] to 64.4 years.[41] The proportion of male participants ranged from 30%[44] to 50%.[41] Similar to the RCTs, KL grading was the most commonly reported measure of KOA severity, and the majority of patients had KL grade II or III KOA. Mean body mass index ranged from 22.1 kg/m^2 to 30.9 kg/ m^2.[41,47] There was limited reporting on mean duration of KOA, prior therapies, and patient comorbidities.

SALR/Pseudosepsis Event Rate

Regarding the occurrence of SALR/ pseudosepsis across RCTs, there were a total of 38 different HA treatment groups,

Table 3

SALR/Pseudosepsis Event Rate (as a % of Injections) Across RCT and Observational Study Treatment Arms

Author, year	HA treatment arm	Single or Multi regimen	Course number	No. of injections[a]	No. of events	Event rate (% of injections)
RCTs						
Adams, 1995	Hylan G-F 20	Multi	First	238	2	0.8
Atamaz, 2006	Orthovisc	Multi	First	80	0	0
	Hylan G-F 20	Multi	First	80	0	0
Berenbaum, 2012	GO-ON	Multi	First	669	0	0
	Hyalgan	Multi	First	639	0	0
Buendía-López, 2018	Durolane	Single	First	36	2	5.6
Campos, 2017	Hylan G-F 20	Single	First	36	0	0
	Hylan G-F 20 plus triamcinolone hexacetonide	Single	First	46	0	0
Chevalier, 2010	Hylan G-F 20 (First)	Single	First	123	0	0
	Hylan G-F 20 (repeat course)	Single	Second	77	0	0
	Hylan G-F 20 (First after placebo)	Single	First	83	0	0
de Campos, 2013	Hylan G-F 20	Single	First	52	1	1.9
	Hylan G-F 20 plus triamcinolone hexacetonide	Single	First	52	0	0
Dickson, 2001	Hylan G-F 20	Multi	First	150	2	1.3
Henderson, 1994	Hyalgan	Multi	First	225	2	0.9
Huang, 2023	Hylan G-F 20	Multi	First and second combined	391	6	1.5
Jüni, 2007	Orthovisc and Ostenil combined	Multi	First	1,920	5	0.3
	Hylan G-F 20	Multi	First	984	5	0.5
	Orthovisc and Ostenil combined	Multi	Second	NR	0	NR
	Hylan G-F 20	Multi	Second	NR	4	NR
Karatosun, 2005	Orthovisc	Multi	First	180	0	0
	Hylan G-F 20	Multi	First	192	0	0
Karlsson, 2002	Artzal	Multi	First	270	0	0
	Hylan G-F 20	Multi	First	258	0	0
Ke, 2021	Hylan G-F 20	Single	First	218	0	0
Khanasuk, 2012	Hyalgan	Single	First	15	0	0
	Hylan G-F 20	Single	First	15	0	0
Leopold, 2003	Hylan G-F 20	Multi	First	150	1	0.7

and the event rate, as a percentage of injections across treatment groups, ranged from 0%[16-19,23-26,28,30-32,34,35] to 5.6%[36] (**Table 3**) with a mean rate of 0.48% and median of 0%. Notably, the highest event rates were reported for treatment groups with a relatively smaller sample size (ie, the hylan G-F 20-only group with an event rate of 1.9% in the study by de Campos et al had one event over 52 total injections; the Durolane group with an event rate of 5.6% in the study by Buendía-López et al had two events over 36 total injections)[19,36] or for groups receiving a repeat course of treatment (2.0% in Raynauld et al and 1.5% in Huang et al).[21,31]

Of the three observational studies included in this analysis, two of them,[45,46] representing three HA treatment groups (totaling 309 injections), had zero SALR/pseudosepsis events. The claims analysis

Table 3 (continued)

SALR/Pseudosepsis Event Rate (as a % of Injections) Across RCT and Observational Study Treatment Arms

Author, year	HA treatment arm	Single or Multi regimen	Course number	No. of injections[a]	No. of events	Event rate (% of injections)
Maheu, 2011	Structovial	Multi	First	417	0	0
	Hylan G-F 20	Multi	First	420	0	0
Raman, 2008	Hyalgan	Multi	First	930	0	0
	Hylan G-F 20	Multi	First	582	1	0.2
Raynauld, 2005	Hylan G-F 20 (single course)	Multi	First	306	0	0
	Hylan G-F 20 (repeat course)	Multi	First	231	1	0.4
	Hylan G-F 20 (repeat course)	Multi	Second	201	4	2.0
Tammachote, 2016	Hylan G-F 20	Single	First	50	0	0
Vaishya, 2017	Hylan G-F 20	Single	First	72	1	1.4
Wobig, 1998	Hylan G-F 20	Multi	First	171	0	0
Zhang, 2015	Artz	Multi	First	870	3	0.3
	Durolane	Single	First	175	1	0.6
Observational studies						
Ong, Farr, 2021	Euflexxa	Multi	NR	167,045	NR	1.1
	Gel-One	Single	NR	3,670	NR	3.1
	Hyalgan/Supartz	Multi	NR	248,558	NR	2.8
	Monovisc	Single	NR	1,661	NR	4.5
	Orthovisc	Multi	NR	117,702	NR	2.3
	Hylan G-F 20 (Multi)	Multi	NR	108,628	NR	1.3
	Hylan G-F 20 (Single)	Single	NR	47,140	NR	2.3
Strand, 2012	Gel-200 (retreatment group)	Single	Second	125	0	0
	Gel-200 (First after placebo)	Single	First	74	0	0
Yan, 2015	Hylan G-F 20	Single	First	110	0	0

Abbreviations: HA, hyaluronic acid; NR, not reported; RCT, randomized controlled trial; SALR, severe acute localized reaction.
[a] Total number of injections across all patients in treatment arm.

by Ong et al reported on seven different HA treatment groups, and the event rates across these groups ranged from 1.1% (167,045 injections) to 4.5% (1,661 injections) based on the study's SALR/pseudosepsis definition of a steroid injection or arthrocentesis within 3 days post-HA injection. In the study by Ong et al, the mean percentage across all observational studies was 1.74% and the median 1.8%.[43]

Hylan G-F 20 vs Non-Hylan G-F 20 HA

The comparison of SALR/pseudosepsis occurrence between hylan G-F 20- and non-hylan G-F 20-treated groups showed a large overlap. **Table 4** displays the main comparisons. Among RCTs, the event rate of SALR/pseudosepsis across hylan G-F 20-treated groups (n=25) ranged from 0%[16-19,23-26,28,31,32,34] to 2% (mean=0.43%, median=0%).[31] Among non-hylan G-F 20-treated groups (n=13) in the included RCTs, the event rate of SALR/pseudosepsis ranged from 0%[16-19,23-26,28,31,32,34] to 5.6% (mean=0.59%, median=0%).[36] However, this mean value in the non-hylan G-F 20-treated groups is strongly influenced by the outlier value of 5.6% from Buendía-López[36]; if this value is removed, the new mean for the non-hylan G-F 20 treated group becomes 0.18%.

Among the observational studies (**Table 3**), Yan et al reported zero SALR/pseudosepsis events in a group of hylan G-F 20-treated patients.[45] Ong et al reported event rates of 1.3% and 2.3% for multi-injection hylan G-F 20 and single-injection hylan G-F 20, respectively.[43] Regarding non-hylan G-F 20-treated groups, Strand et al reported zero SALR/pseudosepsis events in two separate Gel-200 groups.[46] In the claims analysis by Ong et al, event rates across non-hylan G-F 20-treated groups ranged from 1.1%

to 4.5% (mean=1.97%, median=2.3%).[43]

Single- vs Multi-injection Regimen

In the included RCTs, among patients who received a single-injection, the event rate of SALR/pseudosepsis varied from 0%[16-19,23-26,28,31,32,34] to 5.6%.[36] Among the multi-injection HA regimen groups in the included RCTs, the event rate of SALR/pseudosepsis ranged from 0%[16-19,23-26,28,31,32,34] to 2%.[31] Among the observational studies, zero SALR/pseudosepsis events occurred across the three single-injection HA groups in the studies by Strand et al and Yan et al.[45,46] Ong et al reported event rates between 2.3% and 4.5% across single-injection HA regimens, and between 1.1% and 2.8% across multi-injection HA regimens.[43] Receiving a single injection or multiple injections did not affect the event rate of SALR/pseudosepsis in a definite direction (**Table 4**).

Table 4

Summary of the Main Comparisons Conducted in This Study

	Event rate of SALR/pseudosepsis per injection (%)		
Patient population (no. of study arms)	**Mean**	**Median**	**Range**
RCTs			
Overall	0.48	0	0-5.6
Hylan G-F 20 group (n=25)	0.43	0	0-2.0
Non-hylan G-F 20 group (n=13)	0.59 (0.18 after removing outlier)	0	0-5.6
Single injection (n=14)	0.68 (0.30 after removing outlier)	0	0-5.6
Multi-injection (n=24)	0.37	0	0-1.5
First course (n=35)	0.42	0	0-5.6
Repeat course (n=2)	1.00	0	0-2.0
Observational studies			
Overall	1.74	1.80	0-4.5
Hylan G-F 20 group (n=3)	1.20	1.30	0-2.3
Non-hylan G-F 20 group (n=7)	1.90	2.30	0-4.5
Single injection (n=6)	1.65	1.15	0-4.5
Multi-injection (n=4)	1.90	1.18	0-2.8
First course (n=1)	0	0	-
Repeat course (n=1)	0	0	-

Abbreviations: HA, hyaluronic acid; KOA, knee osteoarthritis; N/A, not applicable; RCT, randomized controlled trial; SALR, severe acute localized reactions.

First vs Repeat Course

The comparison of SALR/pseudosepsis occurrence between first and repeat courses showed the similar low rate in each group. Among first-course HA groups in the included RCTs, the event rate of SALR/pseudosepsis ranged from 0%[15,17-19,23-26,28,30-32,34,35] to 5.6%.[36] Among the repeat-course HA groups in the included RCTs, the event rate of SALR/pseudosepsis ranged from 0%[18] to 2%.[31] Among the observational studies, zero SALR/pseudosepsis events occurred among patients who received first course only or repeated courses of HA in the studies by Yan et al[45] and Strand et al,[46] respectively, which included one group who received their first course of treatment and another group who received a repeat course of HA, while Yan et al included only a single group who received one course of treatment.[45] It was unclear how many courses of treatment the groups in the study by Ong et al received.[43] This review did not find any important differences between first injection and subsequent injections of HA or multiple course of treatment; it did not corroborate previous results reporting that SALR/pseudosepsis events were more likely to occur after exposure to more than one injection or more than one course of treatment.[11,44]

Avian Origin vs Bacterial Fermentation

The comparison between products from avian origin and from bacterial fermentation did not show important differences. Most RCTs (n=33) included drugs from avian origin in contrast to only 4 studies that included drugs from bacterial fermentation (among which, the study by Buendía-López[36] generated the outlier value of 5.6% in SALR). If we remove this extreme value, the mean percentage of SALR/pseudosepsis is 0.36% in the avian product group compared to 0.2% in the bacterial fermentation group.

Definition and Description of SALR/Pseudosepsis

The definitions and descriptions of SALR/pseudosepsis events, when reported, are presented in **Table E** (available in the online version of this article). SALR/pseudosepsis events were predominantly defined or described as resulting in pain; swelling or effusion, with warmth; erythema; and pruritis.[11,15,19-22,30,32,36,38,40-42,44,48] SALR/pseudosepsis events were most often reported to occur within 24 to 72 hours after an injection,[11,15,21,22,27,31,41-44,48] although some studies reported such events occurring at 5 days,[31] 1 week,[19] or 2 weeks[36] post-injection. The most reported methods of treating SALR/pseudosepsis events were corticosteroid injections, arthrocentesis, and NSAIDs.[15,17-19,23-26,28,30-32,34-36] The recovery

duration of SALR/pseudosepsis events varied across studies, ranging from 24 hours[44] to 4 weeks.[30]

Discussion

This targeted review of the literature of SALR/pseudosepsis occurrence after HA injections showed an overall low rate among the included studies, with a mean rate per injection of 0.48% (median=0%). There was no important difference between hylan G-F 20 and non-hylan G-F 20 products, single- and multi-injection regimens, or first and repeat courses of treatment. The definition/description of SALR/pseudosepsis events, despite some variability, showed overall agreement considering the acute occurrence of painful symptoms within a short time span after the injection and requiring urgent intervention after verifying the absence of infection. The definitions and descriptions of SALR/pseudosepsis events were generally consistent between the included studies and previously published literature addressing this topic.[11,44,48,49] Regarding the impact of SALR/pseudosepsis, a previous systematic literature review on the management of SALR/pseudosepsis reported that 57.1% of patients (n=28) showed significant improvement within 3 weeks and only 2 patients (7%) had persistent symptoms by 6 months.[49]

It has previously been proposed that the risk of SALR/pseudosepsis is significantly higher with hylan G-F 20 or avian-derived HA injections[10,43,48-51]; however, these events have also been reported in patients who received non-hylan G-F 20 or non-avian-derived HA injections.[10,43,49,52-55] The current review demonstrated low absolute event rates (per injection) in most hylan G-F 20-treated and non-hylan G-F 20-treated groups in RCTs. Observational studies provided further evidence that these complications can occur following any HA injection. A large claims data analysis by Ong et al that directly compared SALR rates between hylan G-F 20 and non-hylan G-F 20 HA injections found an overall low event rate and that the risk of a SALR was similar between groups.[10]

Increased exposure to HA injections has previously been described as a risk factor for SALR/pseudosepsis[11,41,49]; however, overall, the evidence included in the current review indicated no distinguishable difference between single- and multi-injection regimens or between single and repeated courses of HA injections. Additionally, the specific cause of these reactions requires further investigation.[10] Given the conflicting evidence presented above and other potential confounding factors on SALR/pseudosepsis risk, uncertainty still exists regarding whether certain HA brands are associated with an increased risk of this complication. Finally, the technique of injection was not described with enough precision in the included studies, which prevented assessing the possible impact of this factor. The results from this review identify the need for consistent clinical definitions and descriptions to categorize and report adverse events across all future injectable therapies (eg, PRP, bone marrow aspirate concentrate, novel investigational agents).

At present, this is the largest literature review that includes both RCTs and observational studies to determine the rate of SALR/pseudosepsis in KOA patients receiving intra-articular HA. This review has several additional strengths to note. It was conducted according to standard recommendations for performing literature reviews. Publications were not restricted to specific countries to obtain a more global understanding of SALR/pseudosepsis, helping ensure the generalizability of the results. Characteristics of the various HA products were extracted to allow for additional comparisons based on these factors. It is the first analysis to evaluate SALR/pseudosepsis event rates across RCTs. The number of injections received was used to standardize event rates across treatment groups to help ensure better comparability between studies, as opposed to using the number of patients, which can skew results if the number of injections is inconsistent.

This review has also some limitations. The selection was restricted to studies published in English, potentially missing insights from non-English language publications. Of note, this review did not exclude studies based on funding characteristics (ie, industry-, health institute-, and academic-funded studies were included). Of the 26 studies included in this review, 11 were industry-sponsored studies. Overall, the funding source was not observed to have any bearing on the results. As this was a review with a more targeted search strategy (eg, only one electronic database was searched), it is possible that the search was not comprehensive enough to capture other relevant studies. Another limitation was the limited representation of non-hylan G-F 20 HA products across the included studies, and among this limited evidence, there was inconsistency in the event rates for these products between the RCT and observational evidence (ie, event rates were generally lower in the RCTs than in the observational studies for non-hylan G-F 20 HA products), resulting in more uncertainty around these estimates. Notably, event rates for hylan G-F 20 products were similar between the RCT and observational evidence. Finally, there was a limited description of patient comorbidities and injection technique details, which prevented assessing whether these factors may affect the risk of SALR/pseudosepsis.

Conclusion

This review found generally low event rates for SALR/pseudosepsis across the included studies of patients with KOA treated with HA. Furthermore, no higher rates were found for hylan G-F 20 compared to other HA products. Additionally, when SALR/pseudosepsis events do occur, they are generally manageable with treatments. This must be considered given the therapeutic value of HA injections in this patient population. Additional research is required to determine the specific cause of SALR/

pseudosepsis and if patient characteristics (eg, comorbidities) or treatment characteristics (eg, injection technique) affect the risk of this rare complication.

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Table A: Search strategy for Embase via OvidSP

Database: Embase 1974 to November 17, 2023 **Search executed: November 21, 2023**		
#	**String**	**Hits**
1	exp hyaluronic acid/ or exp viscosupplementation/ or exp hyaluronic acid derivative/	54815
2	(viscosupplementation or hyaluronic acid or hyaluronan or hyaluronate or Hyalgan or Synvisc or Orthovisc or Artzal or Supartz or Suplasyn or BioHy or Euflexxa or Nuflexxa or Hylan GF-20 or Hylan*GF*20 or hyaluron*).ti,ab.	53660
3	or/1-2	68838
4	exp intraarticular drug administration/	7249
5	(intra-articular or intra*articular or intraarticular).ti,ab.	32078
6	or/4-5	34805
7	or/3,6	99875
8	Severe Acute Inflammatory Reaction.mp.	21
9	(acute local reaction* or inflamm* reaction* or systemic reaction*).ti,ab.	43790
10	(acute pseudoseptic arthriti* or acute aseptic arthriti* or arthriti* reactive* or pseudogout).ti,ab.	1162
11	pseudoseptic.mp.	70
12	septic.ti,ab.	95567
13	(flare-up or flare up or flare*up or flare*).ti,ab.	37717
14	exp sepsis/	339543
15	(Pseudo*sepsis or pseudo*septic or pseudo-septic or pseudo-sepsis or SALR).ti,ab.	198
16	or/8-15	451692
17	and/7,16	2386
18	(exp animal/ or nonhuman/) not exp human/	7191336
19	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment).pt.	3780409
20	Case Study/	97839
21	case report.tw.	548983
22	or/18-21	11399773
23	17 not 22	1653

Table B: Study characteristics of the included RCTs (n = 26)

Author & Year (Countries)	Study Setting	Blinding	Follow-up Duration	Study N	HA Injection Technique	Comparison	HA Brand(s) Investigated	Injection Regimen
Adams 1995 (Canada)	Multi-center	Double-blind	26 weeks	102	Any effusion present in the joint was withdrawn prior to treatment.	HA alone vs. HA plus NSAID vs. NSAID alone	Hylan G-F20 (with or without NSAID)	Once weekly for 3 weeks
Atamaz 2006 (Turkey)	Single-center	Single-blind	12 months	82	All the intra-articular injections were given by the same physicians using aseptic procedures. If effusion was present, the joint was aspirated before injecting HA.	HA vs. HA	Orthovisc	Once weekly for 3 weeks plus 1 more at 6 months
							Hylan G-F20	Once weekly for 3 weeks plus 1 more at 6 months
Berenbaum 2012 (France, Germany)	Multi-center	Double-blind	6 months	426	Lateral femoropatellar.	HA vs. HA	GO-ON	Once weekly for 3 weeks
							Hyalgan	Once weekly for 3 weeks
Buendía-López 2018 (Spain)	Multi-center	Single-blind	52 weeks	106	NR	HA vs. PRP vs. NSAID	Durolane	Single injection
Campos 2017 (Brazil)	Single-center	Double-blind	6 months	120	Injections were administered through an anterolateral access with the knee flexed at 90° following appropriate asepsis and antisepsis procedures, in a clean hospital environment, using sterile instruments, after disinfecting the area with a 2% chlorhexidine digluconate solution.	Corticosteroid alone vs. HA alone vs. HA plus corticosteroid	Hylan G-F20	Single injection
							Hylan G-F20 plus triamcinolone hexacetonide	Single injection
Chevalier 2010 (Belgium, Czech Republic, France, Germany, Netherlands, UK)	Multi-center	Double-blind	26 weeks	253	NR	HA vs. placebo	Hylan G-F20	Single injection, with an open-label repeat treatment phase (2nd injection) 26 weeks after the initial injection. Additionally, patients in the comparator (placebo) group could receive a 1st course of hylan G-F20 26 weeks after the initial injection.
De Campos 2013 (Brazil)	Single-center	Double-blind	24 weeks	104	All procedures were performed in an outpatient setting with the patients receiving local anesthesia. The joint punctures were performed by three orthopaedic surgeons who had experience in viscosupplementation. If present, knee effusion was extracted before injection.	HA alone vs. HA plus corticosteroid	Hylan G-F20	Single injection
							Hylan G-F20 plus triamcinolone hexacetonide	Single injection
Dickson 2001 (UK)	Multi-center	Double-blind	12 weeks	165	Arthrocentesis to remove all fluid from the joint was performed in all patient groups.	HA vs. NSAID vs. placebo	Hylan G-F20	Once weekly for 3 weeks
Dixon 1988 (UK)	Multi-center	Double-blind	48 weeks	63	NR	HA vs. placebo	Hyalgan	Patients could receive up to 11 total injections during the trial. The first intra-articular injection was given at baseline. Patients were seen again for further injections at intervals of 1, 2, 3, 5, 7, 9, 11, 15, 19, and 23 weeks after the first injection.

Author & Year (Countries)	Study Setting	Blinding	Follow-up Duration	Study N	HA Injection Technique	Comparison	HA Brand(s) Investigated	Injection Regimen
Henderson 1994 (UK)	Single-center	Double-blind	6 months	91	The patient's most severely affected knee was aspirated through a green (21 G) needle inserted into the patellofemoral space via the medial approach using an aseptic technique. Through the same needle, the patient received an intra-articular injection of either 20 mg Hyalgan in 2 ml of sterile buffered saline or 2 ml of the vehicle alone. Any effusion, if present, was aspirated to dryness before injection. Four subsequent aspirations and injections were administered in an identical fashion at weekly intervals.	HA vs. placebo	Hyalgan	Once weekly for 5 weeks
Huang 2023 (US)	Multi-center	Double-blind	34 weeks	94	Arthrocentesis involved the insertion of a needle attached to an empty sterile 2-mL glass syringe and was performed on all patients (treatment and control group) at each injection visit, before hylan G-F20 administration in the treatment group, to remove any fluid in the joint.	HA vs. arthrocentesis	Hylan G-F20	Once weekly for 3 weeks, with an option to receive a 2nd course of treatment after 10 weeks. Additionally, patients in the comparator (arthrocentesis alone) group could receive a 1st course of hylan G-F20 after 10 weeks.
Huskisson 1999 (UK)	Single-center	Double-blind	6 months	100	Patient received 5 weekly injections of HA or placebo using standard aseptic techniques after aspiration of any effusion present.	HA vs. placebo	Hyalgan	Once weekly for 5 weeks
Jüni 2007 (Switzerland)	Multi-center	Double-blind	12 months	660	Injections were performed according to the guidelines of the Swiss Association of Rheumatologists.	HA vs. HA	Orthovisc	Once weekly for 3 weeks, with a 2nd course offered at 7-12 months.
							Ostenil	Once weekly for 3 weeks, with a 2nd course offered at 7-12 months.
							Hylan G-F20	Once weekly for 3 weeks, with a 2nd course offered at 7-12 months.
Karatosun 2005 (Turkey)	NR	Double-blind	12 months	92	NR	HA vs. HA	Orthovisc	Once weekly for 3 weeks
							Hylan G-F20	Once weekly for 3 weeks
Karlsson 2002 (Sweden)	Multi-center	Double-blind	52 weeks	246	NR	HA vs. HA	Artzal	Once weekly for 3 weeks
							Hylan G-F20	Once weekly for 3 weeks
Ke 2021 (China)	Multi-center	Double-blind	26 weeks	440	The technique for injection followed a standardized method of aseptic no touch technique.	HA vs. placebo	Hylan G-F20	Single injection
Khanasuk 2012 (Thailand)	Single-center	Double-blind	26 weeks	32	The intraarticular injection was blindly performed by a senior surgeon using a supero-lateral approach without any anesthetic agent. Following the injection, no pain medication was prescribed.	HA vs. HA	Hyalgan	Single injection
							Hylan G-F20	Single injection
Leopold 2003 (US)	Single-center	Single-blind	6 months	100	Prior to the administration of hylan G-F20, knee effusions were aspirated into a separate syringe; the same needle was left in place, and the syringe that had been prefilled with hylan G-F20 was used for the injection. All injections were performed in a similar manner by one of the attending knee surgeons involved in the trial. The patient was placed in the supine position, the knee was prepared in a sterile fashion, and a needle was placed superolaterally into the suprapatellar pouch. Ethyl chloride spray was used	HA vs. corticosteroid	Hylan G-F20	Once weekly for 3 weeks

Author & Year (Countries)	Study Setting	Blinding	Follow-up Duration	Study N	HA Injection Technique	Comparison	HA Brand(s) Investigated	Injection Regimen
					immediately prior to the injection for patient comfort, and all injections were performed with a 22-gauge needle, unless an aspiration was performed prior to injection, which was done with an 18-gauge needle that was then left in place for the injection.			
Maheu 2011 (Belgium, Czech Republic, Estonia, France, Poland)	Multi-center	Double-blind	24 weeks	279	NR	HA vs. HA	Structovial	Once weekly for 3 weeks
							Hylan G-F20	Once weekly for 3 weeks
Pavelka 2011 (Czech Republic, France, Italy, Switzerland, the Slovak Republic, Germany)	Multi-center	Double-blind	6 months	381	NR	HA vs. HA	Sinovial	Once weekly for 3 weeks
							Hylan G-F20	Once weekly for 3 weeks
Raman 2008 (UK)	Single-center	Single-blind	12 months	392	All injections were performed using the default blind technique by the same surgeon, who did not participate in the evaluation of the patients. Any synovial fluid that was present in the knee was aspirated before the injection.	HA vs. HA	Hyalgan	Once weekly for 5 weeks
							Hylan G-F20	Once weekly for 3 weeks
Raynauld 2005 (Canada)	Multi-center	Single-blind	1 year	255	NR	HA plus appropriate care vs. appropriate care alone	Hylan G-F20 (single course)	Once weekly for 3 weeks
							Hylan G-F20 (repeat course)	Once weekly for 3 weeks for a total of 2 to 3 courses
Tammachote 2016 (Thailand)	Single-center	Double-blind	6 months	110	All procedures were performed in an outpatient clinic. Injections were performed by the senior author, who has experience of >500 cases per year in knee joint injections or aspirations. Patients were in a supine position with the eyes blinded. The knee was flexed approximately 60 degrees and was prepared in a sterile fashion, and 1 mL of 2% lidocaine hydrochloride with 1:80,000 epinephrine was infiltrated into the skin and subcutaneous tissue at the lateral soft spot of the knee joint just inferior to the lower pole of the patella with a 27-gauge needle for patient comfort. A 21-gauge needle (0.8 · 50 mm) was then inserted through the same area into the joint capsule. The accuracy of the injection was assessed by an unobstructed injection of 1 mL of air into the knee joint. If an effusion was present, it was aspirated into a separate syringe. The same needle was left in place and then the syringe prefilled with the study drug was injected.	HA vs. corticosteroid	Hylan G-F20	Single injection

Author & Year (Countries)	Study Setting	Blinding	Follow-up Duration	Study N	HA Injection Technique	Comparison	HA Brand(s) Investigated	Injection Regimen
Vaishya 2017 (India)	NR	NR	6 months	82	Injections were given after aspiration of synovial fluid, under sterile conditions.	HA vs. corticosteroid	Hylan G-F20	Single injection
Wobig 1998 (Germany)	Multi-center	Double-blind	26 weeks	110	The arthrocentesis and injections were performed under aseptic conditions using 18- to 22-gauge needles, with optional use of local anesthesia. The investigators determined optimal joint positioning and site of needle insertion for each knee according to the anatomic and pathologic conditions present. Arthrocentesis was performed before each injection to verify that effusion was not present.	HA vs. placebo	Hylan G-F20	Once weekly for 3 weeks
Zhang 2015 (China)	Multi-center	Double-blind	26 weeks	349	Disinfectants containing quaternary ammonium salts such as benzalkonium chloride, which can induce HA precipitation, were avoided. Anesthetization of the injection site was permitted using a topical anesthetic. Physicians were allowed to inject HA at the knee portal with which they were most experienced (lateral upper patellar, lateral mid patellar, or medial mid patellar). Needles (sizes 20 G and 22 G) were supplied to each study site and unblinded personnel chose the appropriate needle. Joint fluid was withdrawn using an empty 20 ml syringe and the volume of aspirated fluid was recorded. Leaving the needle in place, the syringe was removed and replaced by a prefilled Durolane or Artz syringe. Care was taken when exchanging syringes to avoid displacement of the needle and to ensure that the syringe with the study product was securely attached prior to injection.	HA vs. HA	Durolane	Single injection
							Artz	Once weekly for 5 weeks

Abbreviations: HA, hyaluronic acid; N, number of patients; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma; RCT, randomized controlled trial; UK, United Kingdom; US, United States.

Table C: Study characteristics of the included observational studies (n = 7)

Author & Year (Countries)	Study Setting	Study Design	Follow-up Duration	Study N	HA Injection Technique	HA Brand(s) Investigated	Injection Regimen
Galluccio 2002 (NR)	Single-center	Prospective registry	60 months	60	All the injections were performed under ultrasound guidance with a 3-12MHz linear probe and with a 21Gx2" (0.8 x 50 mm) needle from the superolateral access, with the knee in slight flexion, with sterile disposable material, and dual skin disinfection with chlorhexidine and iodopovidone (10% alcoholic solution).	Hyalubrix	Once weekly for first 3 weeks, then single booster every 3 months until completing the 5th year
Leopold 2002 (US)	Single-center	Retrospective cohort	≥ 6 months	61	All injections were performed, with strict aseptic technique and a 22-gauge needle (or an 18-gauge needle when knee effusion was present), by one of the two fellowship-trained knee surgeons involved in the trial. All injections were administered through the straight-leg superolateral approach with the patient supine, as this technique has been associated with fewer painful reactions to hylan G-F20. In accordance with the manufacturer's instructions, knee aspiration was performed with use of a separate syringe but the same (18-gauge) needle, when a knee effusion was present.	Hylan G-F20 (single course)	Once weekly for 3 weeks
						Hylan G-F20 (multiple courses)	Once weekly for 3 weeks for a total of 2 to 3 courses
Marino 2006 (US)	Single-center	Case-control	3 to 7 days	39	NR	Hylan G-F20	Variable across patients.
Ong, Farr, 2021 (US)	Multi-center	Claims analysis	≥ 6 months	NR	NR	Euflexxa	NR
						Gel-One	Single injection
						Hyalgan/Supartz	NR
						Orthovisc	NR
						Monovisc	Single injection
						Hylan G-F20	Once weekly for 3 weeks or single injection
Pullman-Mooar 2002 (US)	NR	Case series	6 months	8	Injected by a medial approach after standard aseptic preparation of the skin. No radiographic localization was used for the injection. Before the first injection, none of the 8 patients had been noted to have significant effusions.	Hylan G-F20	Once weekly for 3 weeks for a total of 1 to 2 courses
Strand 2012 (US)	Multi-center	Open-label retreatment phase of RCT	26 weeks	199	NR	Gel-200 (single course following placebo)	Single injection
						Gel-200 (retreatment)	Single injection for a total of 2 courses
Yan 2015 (Hong Kong)	Multi-center	Prospective case series	1 year	95	Single intra-articular preparation of 6 mL of hylan G-F20 was injected into the patients' knees in the out-patient clinic. Strict aseptic technique was adopted with skin disinfection and draping. The injection was administered through a direct lateral parapatellar approach. Knee joint aspiration was performed using a separate syringe before injection of the viscosupplement.	Hylan G-F20	Single injection

Abbreviations: N, number of patients; NR, not reported; RCT, randomized controlled trial; US, United States.

Table D: Population characteristics of the included studies (RCTs and observational studies)

Author & Year	HA Arm	Mean Age (SD/SE), years	Male (%)	Mean Duration of KOA (SD/SE), years	Prior therapies (%)	Disease Severity (%)	Mean BMI (SD/SE), kg/m^2
RCTs							
Adams 1995	Hylan G-F20	61 (SE: 2)	32	5 (SE:0.8)	NR	NR	NR
	Hylan G-F20 plus NSAID	60 (SE: 2)	41	5 (SE: 0.6)	NR	NR	NR
Atamaz 2006	Orthovisc	62.4 (SD: 9.3)	10	NR	NR	NR	30.1 (SD: 5.2)
	Hylan G-F20	60.4 (SD: 9.0)	25	NR	NR	NR	29.9 (SD: 2.7)
Berenbaum 2012	GO-ON	67.2 (SD: 7.8)	38	NR	NR	KL grade II: 46 KL grade III: 54	28.0 (SD: 3.0)
	Hyalgan	66.1 (SD: 8.1)	36	NR	NR	KL grade II: 54 KL grade III: 46	27.7 (SD: 3.1)
Buendía-López 2018	Durolane	56.6 (SD: 2.9)	46.9	NR	NR	KL grade II: 56.3 KL grade III: 43.8	24.9 (SD: 0.4)
Campos 2017	Hylan G-F20	NR	NR	NR	NR	NR	NR
	Hylan G-F20 plus triamcinolone hexacetonide	NR	NR	NR	NR	NR	NR
Chevalier 2010	Hylan G-F20	63.6 (SD: 9.6)	25.8	6.4 (SD: 6.4)	Corticosteroid injection: 32	KL grade II: 51.2 KL grade III: 48.8	29.1 (SD: 4.8)
De Campos 2013	Hylan G-F20	61 (SD: 12)	25	NR	NR	KL grade I: 13 KL grade II: 27 KL grade III: 35 KL grade IV: 25	30 (SD: 5.2)
	Hylan G-F20 plus triamcinolone hexacetonide	65 (SD: 9)	23	NR	NR	KL grade I: 11 KL grade II: 30 KL grade III: 35 KL grade IV: 23	29 (SD: 4.1)
Dickson 2001	Hylan G-F20	65 (SE: 1)	43	NR	NSAIDs: 43.4	NR	29 (SE: 0.6)
Dixon 1988	Hyalgan	NR	NR	NR	NR	NR	NR
Henderson 1994	Hyalgan	NR	33.3	NR	NR	KL grade II: 44.4 KL grade III: 37.8 KL grade IV: 17.8	NR
Huang 2023	Hylan G-F20	62 (SE: 2)	38	9 (SE: 1)	NR	NR	NR
Huskisson 1999	Hyalgan	65.8 (SD: 8.8)	24	NR	NR	KL grade II: 60 KL grade III: 40	NR
Jüni 2007	Orthovisc	63.5 (SD: 11.1)	31.5	NR	NR	Slight: 20 Moderate: 58 Severe: 22	28.1 (SD:5.0)
	Ostenil	63.3 (SD: 11.5)	34.7	NR	NR	Slight: 22 Moderate: 60 Severe: 18	28.6 (SD: 5.2)
	Hylan G-F20	63.3 (SD: 12.3)	35.1	NR	NR	Slight: 24 Moderate: 57 Severe: 19	28.2 (SD: 4.9)
Karatosun 2005	Orthovisc	60.6 (SD: 9.6)	19.6	NR	NR	KL grade III: 100	29.6 (SD: 4.4)
	Hylan G-F20	60.5 (SD: 9.5)	17.4	NR	NR	KL grade III: 100	30.7 (SD: 4.9)
Karlsson 2002	Artzal	72 (SD: 7)	33	NR	NR	Ahlback grade I: 60 Ahlback grade II: 40	NR

Author & Year	HA Arm	Mean Age (SD/SE), years	Male (%)	Mean Duration of KOA (SD/SE), years	Prior therapies (%)	Disease Severity (%)	Mean BMI (SD/SE), kg/m^2
	Hylan G-F20	70 (SD: 7)	35	NR	NR	Ahlback grade I: 61 Ahlback grade II: 39	NR
Ke 2021	Hylan G-F20	61.5 (SD: 7.9)	22.7	NR	NR	KL grade I: 14.1 KL grade II: 47.7 KL grade III: 38.2	25.6 (SD: 3.1)
Khanasuk 2012	Hyalgan	67 (SD: 9.5)	20	NR	NR	KL grade II: 6.7 KL grade III: 66.7 KL grade IV: 26.7	25.4 (SD: 2.5)
	Hylan G-F20	65.1 (SD: 9.6)	20	NR	NR	KL grade II: 13.3 KL grade III: 66.7 KL grade IV: 20	26.6 (SD: 5.7)
Leopold 2003	Hylan G-F20	66 (NR)	48	NR	NSAIDs: 64	NR	28.8 (NR)
Maheu 2011	Structovial	64.5 (SD: 7.1)	26.9	6.21 (SD: 6.0)	Corticosteroid injection: 28.6 HA injection: 10.9	KL grade II: 57.1 KL grade III: 42.9	Males: 29.4 (SD:4.2) Females: 29.9 (SD: 5.3)
	Hylan G-F20	63 (SD: 6.6)	20.5	5.61 (SD: 4.6)	Corticosteroid injection: 35.9 HA injection: 12	KL grade II: 60.7 KL grade III: 39.3	Males: 29.6 (SD: 3.7) Females: 30.0 (SD: 5.1)
Pavelka 2011	Sinovial	65.1 (SD: 9.1)	27.6	6.3 (SD: 5.8)	NR	KL grade II: 44.3 KL grade III: 55.7	27.1 (SD: 3.1)
	Hylan G-F20	64.9 (SD: 8.7)	26.6	5.6 (SD:5.6)	NR	KL grade II: 45.2 KL grade III: 54.8	27.0 (SD: 3.1)
Raman 2008	Hyalgan	NR	NR	NR	NR	KL grade III: 61	NR
	Hylan G-F20	NR	NR	NR	NR	KL grade III: 59	NR
Raynauld 2005	Hylan G-F20 (single course)	63.8 (SD: 9.5)	33.3	9.3 (SD: 10.6)	NSAIDs: 93.6	KL grade 0: 3.9 KL grade I: 15.4 KL grade II: 28.2 KL grade III: 33.3 KL grade IV: 19.2	31.8 (SD: 7.6)
	Hylan G-F20 (repeat course)	60.8 (SD: 9.2)	29.2	8.7 (SD: 7.6)	NSAIDs: 95.8	KL grade 0: 2.1 KL grade I: 10.4 KL grade II: 18.8 KL grade III: 47.9 KL grade IV: 20.8	32.8 (SD: 8.8)
Tammachote 2016	Hylan G-F20	62.6 (NR)	14	NR	NR	KL grade I: 20 KL grade II: 22 KL grade III: 44 KL grade IV: 14	26.3 (NR)
Vaishya 2017	Hylan G-F20	NR	31	NR	NR	KL grade II: 43 KL grade III: 57	NR
Wobig 1998	Hylan G-F20	60 (SE: 2)	44	6 (NR)	NR	Larsen grade I: 16 Larsen grade II: 56 Larsen grade III: 25 Larsen grade IV: 3	NR

Author & Year	HA Arm	Mean Age (SD/SE), years	Male (%)	Mean Duration of KOA (SD/SE), years	Prior therapies (%)	Disease Severity (%)	Mean BMI (SD/SE), kg/m^2
Zhang 2015	Artz	60.4 (SD: 7.8)	19.6	4.0 (SD: 4.8)	NR	KL grade II: 60.1 KL grade III: 39.9	NR
	Durolane	60.2 (SD: 8.1)	26.1	3.9 (SD: 5.3)	NR	KL grade II: 58.4 KL grade III: 41.6	NR
Observational Studies							
Galluccio 2002	Hyalubrix	61.1 (SD: 9.2)	48.3	NR	NR	KL grade I: 46.7 KL grade II: 26.7 KL grade III: 26.7	22.1 (SD: 2.4)
Leopold 2002	Hylan G-F20 (single course)	64.4 (NR)	50	NR	NR	Severe: 36	30.9 (NR)
	Hylan G-F20 (multiple courses)	61 (NR)	37	NR	NR	Severe: 32	30.9 (NR)
Marino 2006	Hylan G-F20	NR	NR	NR	NR	NR	NR
Ong, Farr, 2021	Euflexxa	NR	35.8	NR	NR	NR	NR
	Gel-One	NR	37.6	NR	NR	NR	NR
	Hyalgan/Supartz	NR	37	NR	NR	NR	NR
	Monovisc	NR	38.1	NR	NR	NR	NR
	Orthovisc	NR	36.7	NR	NR	NR	NR
	Hylan G-F20 (multi-injection)	NR	37.5	NR	NR	NR	NR
	Hylan G-F20 (single injection)	NR	39	NR	NR	NR	NR
Pullman-Mooar 2002	Hylan G-F20	NR	30	NR	NR	KL grade III: 87.5 KL grade IV: 12.5	NR
Strand 2012	Gel-200 (retreatment group)	61.4 (SD: 10.3)	39.3	NR	NR	KL grade I: 8.2 KL grade II: 33.6 KL grade III: 58.2	28.6 (SD: 4.1)
	Gel-200 (initial course following placebo)	61.6 (SD: 10.5)	35.1	NR	NR	KL grade I: 9.5 KL grade II: 31.1 KL grade III: 59.5	29.1 (SD: 4.0)
Yan 2015	Hylan G-F20	62 (SD: 9.8)	32.6	NR	NR	KL grade I: 4.5 KL grade II: 27.3 KL grade III: 34.5 KL grade IV: 33.6	27.7 (SD: 4.6)

Abbreviations: BMI, body mass index; HA, hyaluronic acid; KOA, knee osteoarthritis; KL, Kellgren-Lawrence; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; SD, standard deviation; SE, standard error.

Table E: Definitions and descriptions of SALR/pseudosepsis across studies

Author & Year	Definition or Description
RCTs	
Adams 1995	• Local reactions observed after intra-articular injection of hylan G-F20 that were attributable to the device. • Pain within 24 hours after injection, accompanied by warmth and effusion. • Effusion removed by arthrocentesis and analyzed for cells, crystals and microbiology. One of the synovial fluids was reported to have a high macrophage count, but they were otherwise unremarkable. • Patients recovered within several days without sequelae.
Berenbaum 2012	• Cites the following reference when defining "acute pseudoseptic arthritis": Maheu E, Bonvarlet JP and the Paris Rheumatologists Association. Acute pseudoseptic arthritis post hyaluronane (HA) intra-articular injections. Results of a French survey in rheumatology practice (Abstract). Ann Rheum Dis 2003;62:268.
Buendía-López 2018	• Pain and swelling, related to the HA infiltration, in the period immediately after the infiltration (2 weeks). • Required use of NSAIDs for over a week.
De Campos 2013	• Severe effusion and pain at Week 1 and treated with arthrocentesis and an intraarticular corticosteroid injection.
Dickson 2001	• Local reaction/symptom (pain, swelling, effusion) occurring within 28 days of the first injection graded as severe. • All events resolved without sequelae.
Henderson 1994	• Severe increase in pain or swelling in the treated knee. • Usually lasted less than four days.
Huang 2023	• Local reaction (pain or swelling at injected joint) that required arthrocentesis to remove excess fluid. • Usually occurring within 24 hours of injection. • Slowly disappeared within 1 to 2 weeks.
Jüni 2007	• Local adverse events, defined as the occurrence of an effusion (evidence from clinical examination or arthrocentesis) or a flare (hot, painful, swollen knee occurring within 48 hours of injection of the study preparation). • Treated with corticosteroid injections.
Karlsson 2002	• Cites the following reference: Puttick MPE, Wade JP, Chalmers A, Connell DG, Rango KK. Acute local reactions after intra-articular Hylan for osteoarthritis of the knee. J Rheumatol 1995; 22:1311–4.
Leopold 2003	• Acute local reaction developed within 24 hours after an injection. • The reaction was treated with aspiration of a large effusion of straw-colored synovial fluid and intra-articular administration of the corticosteroid (betamethasone), and the symptoms were relieved.

Maheu 2011	• Cites the following references:
	  ○ Maheu E, Bonvarlet JP and the Paris Rheumatologists Association. Acute pseudoseptic arthritis post hyaluronane (HA) intra-articular injections. Results of a French survey in rheumatology practice (Abstract). Ann Rheum Dis 2003;62:268.
	  ○ Goldberg VM, Coutts RD: Pseudoseptic reactions to hylan viscosupplementation. Clin Orthop 2004; 419: 130-7.
	  ○ Pullman-Mooar S, Mooar P, Sieck M, Clayburne G, Schumacher HR: Are there distinctive inflammatory flares after hylan G-F20 intraarticular injections? J Rheumatol 2002; 29: 2611-4.

Raman 2008	• Severe pain, moderate effusion, erythema, and swelling in the treated knee 5 days following an injection. • Admitted to the hospital and clinical examination revealed a picture akin to 'pseudosepsis' in the knee. • The knee aspirate was sterile and the symptoms settled completely by 4 weeks with oral NSAID.
Raynauld 2005	• Local adverse events (emergent signs or symptoms occurring in the knee) that occurred within 48 hours of an injection. • Intra-articular intervention after local reaction (arthrocentesis with or without steroid).
Tammachote 2016	• Acute local reactions were adverse reactions related to the injected drug. Drug-related side effects consisted of injection-site reaction, erythema, swelling, injection-site pain, and pruritus.
Vaishya 2017	• Acute inflammatory reaction at the site of injection. • Settled down in 5 days with ice therapy, anti-inflammatory drugs, and rest.
Zhang 2015	• Severe injection site pain, arthralgia, or joint swelling.

Author & Year	Definition or Description
Observational Studies	
Leopold 2002	• An acute local reaction was defined as an acute onset of pain and swelling in the knee that occurred within 72 hours after an injection, in the absence of another cause such as acute trauma. • All of the acute local reactions were rather severe and not difficult to distinguish from typical arthritic effusions and baseline arthritic pain levels. • All patients noted severe pain and limitation of activity, and all underwent aspiration and corticosteroid injection with prompt amelioration of symptoms.
Marino 2006	• Increased local pain and swelling starting within 24 hours of injection and requiring medical treatment.
Ong, Farr, 2021	• Intra-articular corticosteroid injection or arthrocentesis. • Within 3 days of HA injection.
Pullman-Mooar 2002	• Acute onset of knee pain and swelling occurred after the second or third injection or during a second course of hylan G-F20 (i.e., injections 4, 5, and 6). • The swelling occurred as soon as 1 hour after the injection, and the longest interval before pain onset was 48 hours after the injection. • No patient reported fever or chills. • The knees were reaspirated under sterile conditions, and the fluids were sent for cultures to exclude septic arthritis. • The majority of patients were treated with intraarticular steroids and/or oral NSAIDs, and the flares subsided after 24–48 hours. • All fluids were carefully searched for birefringent crystals. Only 1 patient had intracellular calcium pyrophosphate dihydrate crystals. This patient had no history of inflammatory arthritis or chondrocalcinosis on radiograph.
Strand 2012	• Cites the following references: ○ Puttick MPE, Wade JP, Chalmers A, Connell DG, Rango KK. Acute local reactions after intra-articular Hylan for osteoarthritis of the knee. J Rheumatol 1995; 22:1311–4. ○ Goldberg VM, Coutts RD: Pseudoseptic reactions to hylan viscosupplementation. Clin Orthop 2004; 419: 130-7. ○ Pullman-Mooar S, Mooar P, Sieck M, Clayburne G, Schumacher HR: Are there distinctive inflammatory flares after hylan G-F20 intraarticular injections? J Rheumatol 2002; 29: 2611-4. ○ Roos J, Epaulard O, Juvin R, Chen C, Pavese P, Brion JP. Acute pseudoseptic arthritis after intra-articular sodium hyaluronan. Joint Bone Spine. 2004;71:352-4. ○ Tahiri L, Benbouazza K, Amine B, Hajjaj-Hassouni N. Acute pseudoseptic arthritis after viscosupplementation of the knee: a case report. Clin Rheumatol. 2007;26:1977-9.
Yan 2015	• Cites the following reference: Goldberg VM, Coutts RD: Pseudoseptic reactions to hylan viscosupplementation. Clin Orthop 2004; 419: 130-7.

Abbreviations: HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; SALR, severe acute localized reaction.