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SYSTEMATIC REVIEW

Hylan G-F 20 Versus Low Molecular Weight Hyaluronic Acids for Knee Osteoarthritis: A Meta-Analysis

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Abstract

Background Hyaluronic acid injection has been reported to decrease pain compared with baseline levels in knee joint osteoarthritis. Hylan G-F 20 is distinguished from the other products by its chemical structure and relatively higher molecular weight. Many trials have compared hylan G-F 20 and low molecular weight hyaluronic acids (LMWHAs); however, their relative efficacy and safety are still debated.

Objective The aim was to compare the effectiveness and safety of intra-articular injection of hylan G-F 20 and LMWHA in the treatment of knee joint osteoarthritis.

Methods A comprehensive search of the literature up to February 2016 was performed; multiple databases were searched with 'Synvisc' or 'hylan' or 'hyaluronan' as free word terms. The pain-related outcomes and treatment-related adverse events from intent-to-treat analyzed studies were pooled for meta-analysis; other functional outcomes were included in the qualitative analysis.

Results Twenty trials with a total of 3034 patients and 3153 knees were included, with a pooled dropout rate of 7.2 %. The pooled pain-related outcomes at 2 to 3 months reached a statistically significant difference in favor of hylan G-F 20 ($I^2 = 88$ %; random effects; $P = 0.02$), and the significance still existed with exclusion (in order to eliminate heterogeneity) of the three studies that most favored hylan G-F 20 ($I^2 = 51$ %; fixed effect; $P = 0.03$). No significant difference was reached for other group and subgroup analyses. No significant difference was reached in comparing the patients with treatment-related adverse events (seven trials; 2025 patients; $P = 0.13$) or the treatment-related adverse events (six trials; 1633 patients; $P = 0.14$).

Conclusion According to the current results, limited evidence showed a superior effect favoring hylan G-F 20 over LMWHA in the period from 2 to 3 months post-injection for pain-related outcomes. There was no evidence of increased risk of treatment-related adverse events for hylan G-F 20 injections.

Key Points

Current evidence shows similar pain-relieving effects for knee osteoarthritis between hylan G-F 20 and low molecular weight hyaluronic acids.

The subgroup analysis with limited evidence showed the pain relieving effect favored hylan G-F 20 for the period from 2 to 3 months post-injection in both random and fixed effects models.

No difference was found in comparing the treatment-related adverse events between patients receiving hylan G-F 20 and low molecular weight hyaluronic acid injections.

1 Introduction

Osteoarthritis (OA) is a chronic, degenerative disease caused by deteriorating cartilage, and leads to joint damage, pain, and stiffness. Knee OA is the most common type

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of OA, with an incidence of 6 % in people over 30 years, which increases to 40 % in people aged 70 years or older [1]. Hyaluronic acid (HA) injection was first used as pharmacological therapy for knee OA in the 1970s [2]. A meta-analysis reported that HA injection improves pain by approximately 40–50 % compared with baseline levels, and a weighted mean difference (WMD) of −10.20 compared with saline placebo [3].

Hylan G-F 20 (Synvisc) is derived from hyaluronan, a large, linear glycosaminoglycan that is a natural part of the synovial fluid found in joint cavities. A national primary-care database analysis in Canada showed sustained benefits in terms of pain and physical function from repeat cycles of injections of hylan G-F 20 [4]. A randomized controlled trial (RCT) showed better clinical improvements in knee OA patients treated with hylan G-F 20 than in those with conventional treatment [5]. Hylan G-F 20 is distinguished from the other products by its chemical structure and relatively higher molecular weight [6], which might bestow greater viscoelastic properties than low molecular weight hyaluronic acids (LMWHAs). Many RCTs were designed to compare the high molecular weight hylan G-F 20 and LMWHAs; however, their relative efficacy is still debated. A previous meta-analysis published in 2007 concluded the lack of superior effectiveness of hylan G-F 20 over LMWHAs and an increased risk of local adverse events [7]; however, that meta-analysis combined the pain-related outcomes at different follow-up times, and did not perform subgroup analysis at different time points. Also, the meta-analysis only used random effects for the pain-related outcomes, which may result in lower evidence results. After that meta-analysis, many well designed RCTs were published [8–14]. The objective of the current meta-analysis is to further clarify the outcomes and safety differences between hylan G-F 20 and LMWHAs.

2 Methods

This systematic review and meta-analysis was conducted according to the methodological guidelines outlined by the Cochrane Collaboration. Initially, a prospective protocol was written to describe the objectives, search criteria, study selection criteria, data elements of interest, and plans for analysis. According to the protocol, a broad search of the literature without language limitation was conducted. Protocol-defined data elements from each eligible study were extracted and analyzed.

2.1 Search Strategy

A comprehensive database search was conducted, including MEDLINE, EMBASE, EBSCO, LILACS, Sinomed, OVID, SCI, Elsevier, MDConsult, Springer, CINAHL Plus, Wiley, HighWire, Cochrane, and Cochrane Centre, to identify relevant papers, abstracts, and protocols. The research was from inception to February 2016 using the term 'Synvisc' [All Fields] OR 'hylan' [All Fields] OR 'hyaluronan' [All Fields]. The search was independently performed by two reviewers (ZHM and LXJ). We firstly combined the entire search results from all databases to exclude duplicates. All of the potential articles were checked by title and abstract according to inclusion and exclusion criteria to select the relevant articles. Then a full-text review and manual reference check of all accepted papers and recent reviews was performed to supplement the electronic searches and to identify any additional potentially relevant studies. All studies meeting the selection criteria were included without language limitation.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) prospective RCTs comparing hylan G-F 20 with LMWHAs in the treatment of symptomatic medial and/or lateral femoro-tibial OA of the knee; (2) studies reporting outcomes and/or treatment-related adverse events (TRAEs); (3) the baseline characteristics, including age, sex, OA stage (Kellgren-Lawrence classification or others), body mass index, and level of symptoms, were comparable between treatment groups.

Exclusion criteria were (1) study focus on the patella-femoral OA; (2) no LMWHA as control or hylan G-F 20 as treatment; (3) multiple publications on the same patient population (overlap)—only included the higher protocol relevant study.

2.3 Evaluation of Methodology

The Jadad scale 1996 and RevMan risk of bias scale were used to evaluate methodological quality of trials [15]. In the Jadad scale 1996, randomization, blinding, and withdrawal were scored. The scores range from 0 (poorest) to a maximum of 5 (best). Randomized allocation concealment has three degrees: adequate, unclear, and inadequate. This judgment was performed by two independent reviewers (LXL and LY).

2.4 Data Sampling

Two reviewers (ZHM and LXJ) screened the titles and abstracts of potentially relevant articles. The full texts of highly relevant articles were read by the same two reviewers to identify inclusion or not. Protocol-defined data elements from each eligible study were extracted and confirmed by two authors (LHL and LY). Differences were resolved prior to data entry. In the case of disagreement, a

third reviewer (ZHM) was consulted and a decision made through discussion.

2.5 Statistical Analysis

Statistical software Review Manager (version 5.2 for Windows, Cochrane Collaboration) was used for the meta-analysis. For continuous variables, pain-related outcomes were analyzed with the use of WMD; for dichotomous variables, TRAEs were analyzed with the use of risk difference (RD); and 95 % confidence intervals (CIs) were shown.

Heterogeneity was tested with the use of the Cochrane Q test ($\alpha = 0.05$). If the heterogeneity was significant, a random effects model resulting in wider CI was used. For the included trials without heterogeneity or if the heterogeneity was eliminated after sensitivity analysis, a fixed-effect model was used. Z test was used to test overall effects. The significant difference (SD) for all statistical tests was set a priori to $\alpha = 0.05$. Data that could not be incorporated into the meta-analysis adopted descriptive study.

3 Results

3.1 Study Characteristics of Included Trials

The primary search generated a total of 4104 potentially relevant articles: 397 from MEDLINE, 546 from EMBASE, 509 from EBSCO, six from LILACS, nine from Sinomed, 485 from OVID, 351 from SCI, 586 from Elsevier, 496 from MDConsult, 346 from Springer, 87 from CINAHL Plus, 213 from Wiley, 69 from HighWire, four from Cochrane, and 0 from Cochrane Centre. The flowchart of literature screening is presented in Fig. 1.

A total of 20 trials with a total of 3034 patients and 3153 knees were included in the meta-analysis [8–14, 16–28]. 218 patients (7.2 %) with 248 knees (7.9 %) were drop-outs; the difference in dropout rate between the two treatment groups was not significant ($P = 0.96$). Finally, a total of 2816 patients and 2905 knees were included for per protocol analysis: 1290 patients with 1332 knees in the hylan group and 1526 patients with 1573 knees in the LMWHA group.

Demographic data and methodological quality scores of the included studies are listed in Table 1. The mean Jadad score was 3.40 (95 % CI 2.68–4.12). The risk of bias summary according to the RevMan scale is shown in Fig. 2. All of the included studies reported no difference in characteristics between the two treatment groups. A total of seven studies with 1829 patients (60.3 %) were financially supported, and 13 studies with 1205 patients (39.7 %) were not.

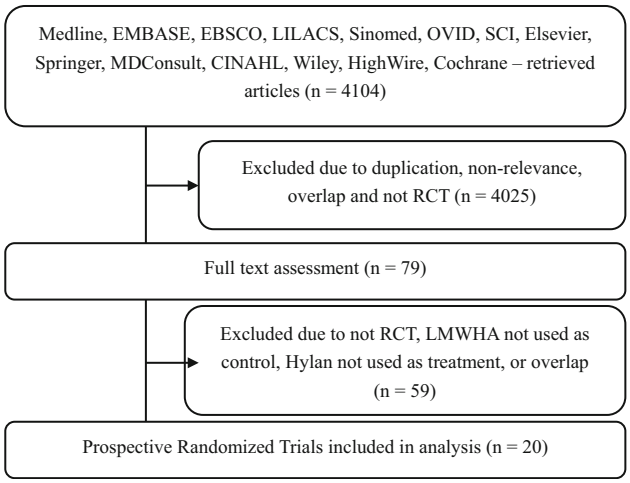

Fig. 1 Flowchart of literature screening. *LMWHA* low molecular weight hyaluronic acid, *RCT* randomized controlled trial

3.2 Heterogeneity Analysis

Although patients had similar characteristics, there were clinical heterogeneities between trials. The form of control differed: four trials used Artzal as the control [16, 18–20]; seven trials used Orthovisc as the control [21–24, 26–28]; three trials used Hyalgan as the control [8, 9, 13]; and seven other LMWHAs were used as controls in seven separate trials [10–12, 14, 25, 27, 28]; and one trial did not report which LMWHA was used [17]. The form of intervention also differed: one trial used two injections [10], two trials used one injection (6 ml) [13, 14], and the other 17 trials all used three injections. Two trials compared the functional outcomes of hylan and LMWHA injection after arthroscopic debridement [8, 27], and the other 18 trials were without any adjunctive therapy.

3.3 Pain-Related Outcomes

A total of 18 trials with 2559 knees contributed to the meta-analysis of pain-related outcomes, and the WMD of the overall outcome was −2.67 with a 95 % CI overlapping the null (−5.62 to 0.29). After we excluded the two trials with single-dose (6-ml) treatment, still no SD was reached (WMD −3.02; 95 % CI −6.15 to 0.11; $Z = 1.89$; $P = 0.06$). Also, no SD was reached between single-dose (6 ml) hylan and LMWHAs (WMD 1.62; 95 % CI −1.72 to 4.97; $Z = 0.95$; $P = 0.34$) for overall outcome. In the subgroup analysis, the pooled pain-related outcomes between hylan and LMWHAs reached no SD for studies with or without funding (Table 2). The

Table 1 Characteristics of included randomized controlled trials

Author/year	Center	LMWHA	AMW (kd)	FU (w)	Wash out	Funding	Patients/knees		Dropout (patients/knees)		ITT analysis	Jadad score	Concealed allocation
							Hylan	LMWHA	Hylan	LMWHA			
Wobig 1999 [16]	Single	Artzal	750	12	Yes	Yes	38/38	32/35	4/4	4/4	Yes	4	Unclear
Zhou 2000 [17]	Single	Unclear	1000	26	No	No	18/20	18/20	0/0	0/0	No	1	Unclear
Lin 2002 [18]	Single	Artzal	750	8	No	Yes	20/20	20/20	1/1	2/2	No	2	Inadequate
Karlsson 2002 [19]	Multi	Artzal	750	26	Yes	Yes	86/86	90/90	9/9	14/14	Yes	5	Adequate
Bayramoglu 2003 [21]	Single	Orthovisc	1550	12	No	No	15/23	16/28	3/3	0/0	No	2	Inadequate
Karatay 2004 [22]	Single	Orthovisc	1550	3	No	No	20/20	20/20	0/0	0/0	No	1	Unclear
Rolf 2005 [20]	Multi	Artzal	750	52	Yes	Yes	90/90	91/91	5/5	7/7	Yes	4	Unclear
Karatosun 2005 [23]	Single	Orthovisc	1550	54	Yes	No	46/92	46/92	14/28	16/32	Yes	5	Adequate
Kotevoglu 2006 [24]	Single	Orthovisc	1550	26	No	No	26/26	26/26	5/5	6/6	No	3	Unclear
Kirchner 2006 [25]	Multi	Bio-HA	2400–3600	12	No	Yes	161/161	160/160	3/3	4/4	Yes	5	Adequate
Atamaz 2006 [26]	Single	Orthovisc	1550	54	Yes	No	20/20	20/20	0/0	0/0	No	2	Unclear
Uluçay 2007 [27]	Single	Orthovisc/Adant	1550/900	54	No	No	18/18	59/59	0/0	0/0	No	1	Inadequate
Jüni 2007 [28]	Multi	Orthovisc/Ostenil	1550/700	12	No	Yes	222/222	438/438	11/11	26/26	Yes	5	Adequate
Atay 2008 [8]	Single	Hyalgan	500–730	54	No	No	16/16	14/14	0/0	0/0	No	2	Unclear
Raman 2008 [9]	Single	Hyalgan	500–730	24	No	No	199/199	193/193	5/5	7/7	Yes	4	Adequate
Maheu 2011 [10]	Multi	F60027	2200–2700	26	No	No	140/140	139/139	23/23	20/20	Yes	5	Adequate
Pavelka 2011 [11]	Multi	Sinovial	800–1200	26	Yes	Yes	189/189	192/192	18/18	9/9	Yes	5	Adequate
Iannitti 2012 [12]	Single	Variofil	0.106	26	No	No	20/20	20/20	0/0	0/0	No	3	Inadequate
Khanasuk 2012 [13]	Single	Hyalgan	500–730	26	Yes	No	16/16	16/16	1/1	1/1	No	4	Adequate
Petrella 2015 [14]	Single	Hydros	1900	26	Yes	No	32/32	32/32	5/5	0/0	Yes	5	Adequate

AMW average molecular weight, *FU* follow-up time, *ITT* intent-to-treat, *LMWHA* low molecular weight hyaluronic acid, *w* weeks

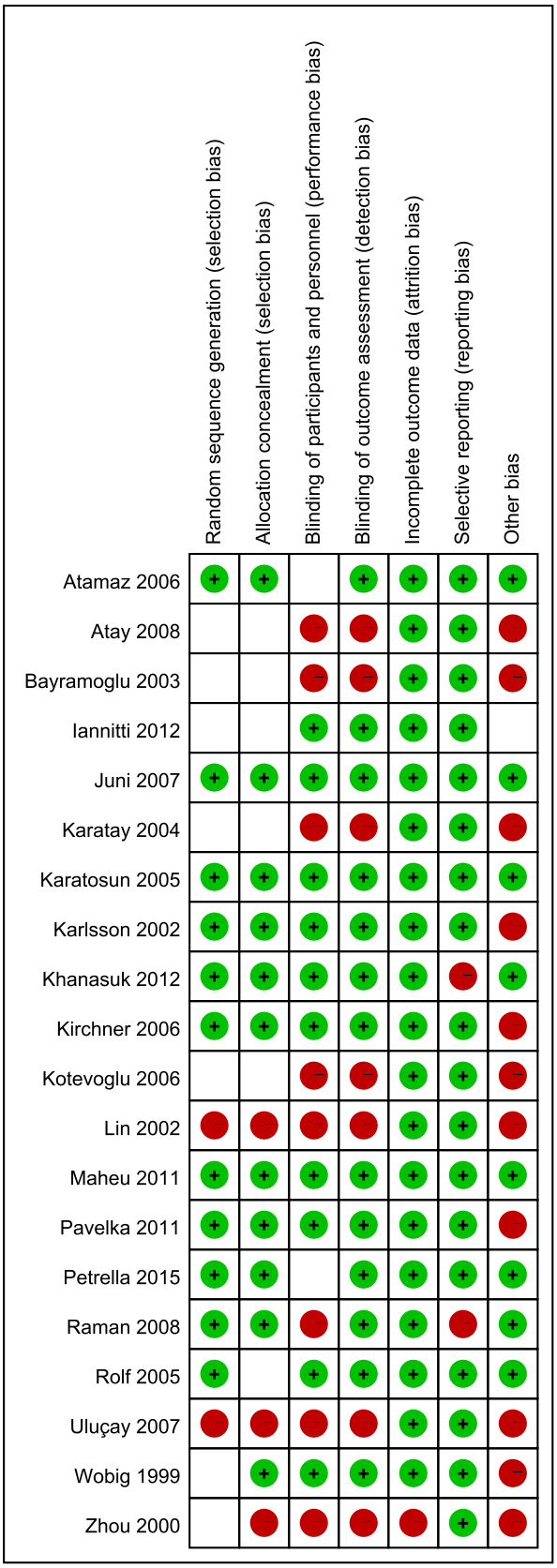

Fig. 2 The risk of bias summary. *Red* '–' means high risk, *green* with '+' means low risk, and *blank* means unclear

pooled pain-related outcomes of the well designed studies (Jadad score of ≥4) also reached no SD. The pooled pain-related outcomes between hylan and any LMWHA (Artzal, Orthovisc, and Hyalgan) reported in more than one trial reached no SD. Six studies reported the pain-related outcomes within 1 month, and the pooled result reached no SD. Also, no SD was reached for the 4–12 months pooled outcomes. However, the pooled outcomes at 2–3 months reached an SD in favor of hylan ($I^2 = 88$ %; random effects; $Z = 2.29$; $P = 0.02$; Fig. 3). The significance still existed when the three studies that most favored hylan (Wobig [16], Atamaz [26], Raman [9]) were excluded to eliminate the heterogeneity ($I^2 = 51$ %, $P = 0.06$; fixed effect; WMD −0.73; 95 % CI −1.38 to −0.08; $Z = 2.19$; $P = 0.03$).

3.4 Treatment-Related Adverse Events

Only the trials that used intent-to-treat (ITT) analysis were included in the safety evaluation. A total of ten trials with 2616 patients (86.2 %) and 2711 knees were included (Table 3). Eight trials reported patients with TRAEs [9–11, 14, 16, 19, 23, 28], and one trial reported that no TRAE was found [23]; the other seven trials were used for the meta-analysis. No heterogeneity was found ($I^2 = 0$ %; $P = 0.74$), and no SD was found between the two treatment groups ($Z = 1.53$; $P = 0.13$; Fig. 4). Six trials that reported TRAE numbers were pooled for meta-analysis [10, 11, 14, 16, 19, 28]; a significant heterogeneity was found between trials ($I^2 = 63$ %; $P = 0.02$), so random effects was used, and no SD was reached ($Z = 1.48$; $P = 0.14$; Fig. 5). The trial by Maheu et al. [10] was found to be significantly heterogeneous from the others after a sensitivity analysis; after exclusion of the trial by Maheu et al., no heterogeneity existed ($I^2 = 0$ %; $P = 0.43$), and still no SD was found between the treatment groups (fixed effect; $Z = 1.64$; $P = 0.10$).

3.5 Functional Outcomes

The two most frequently used scales for functional outcome evaluation were the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index [8, 9, 11, 13, 14, 19, 20, 22, 24–28] and the visual analog scale (VAS) [9–13, 16, 18, 19, 26, 27] (Table 4). Four studies used the Lequesne Index (LFI) [10, 11, 19, 21]; three studies used the Medical Outcomes Study Short Form Health Survey (SF-36/SF-12) [10, 19, 26]; two studies used the European Quality of Life questionnaire (EuroQol) [9, 28]. For the functional outcomes, four studies reported results favoring hylan [9, 15, 17, 26], two studies reported results favoring LMWHAs [12, 20], and 14 studies

Table 2 Subgroup analysis of pooled pain-related outcomes between hylan G-F 20 and LMWHAs of included studies

Pain outcomes	References	Knees		I^2 (%)	WMD (95 % CI)	*P* value
		Hylan	LMWHA			
Overall	[9–14, 16, 18–28]	1203	1356	98	−2.67 (−5.62 to 0.29)	0.08
Without funds	[9, 10, 12–14, 21–24, 26, 27]	541	579	97	−2.75 (−6.39 to 0.90)	0.14
With funds	[11, 16, 18–20, 25, 28]	662	777	90	−1.44 (−4.97 to 2.08)	0.42
Jadad score of ≥4	[9–11, 13, 14, 16, 19, 20, 23, 25, 28]	1065	1171	96	−4.73 (−11.62 to 2.17)	0.18
Versus Artzal	[16, 18–20]	223	218	98	−4.89 (−14.39 to 4.62)	0.31
Versus Orthovisc	[21–24, 26–28]	273	427	0	0.12 (−0.35 to 0.58)	0.72
Versus Hyalgan	[9, 13]	209	201	93	−16.44 (−44.52 to 11.65)	0.25
≤4 weeks	[14, 18, 19, 22, 26, 27]	186	225	61	0.79 (−4.24 to 5.81)	0.76
5–12 weeks	[9, 12, 14, 16, 18, 19, 23, 25, 26, 28]	732	823	88	−2.63 (−4.88 to −0.38)	0.02
13–26 weeks	[9–14, 16, 19–21, 23, 24, 26, 28]	988	1103	98	−2.72 (−6.26 to 0.82)	0.13
27–52 weeks	[9, 23, 26]	278	266	96	−14.11 (−33.68 to 5.46)	0.16

CI confidence interval, *LMWHA* low molecular weight hyaluronic acid, *WMD* weighted mean difference

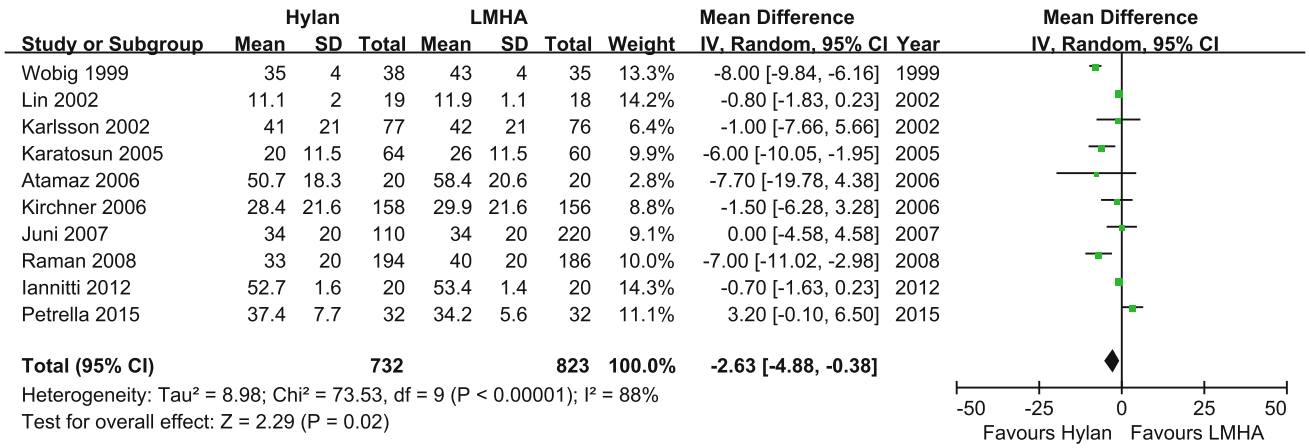

Fig. 3 Forest plot of pain-related outcomes from 2 to 3 months. *CI* confidence interval, *LWHA* low molecular weight hyaluronic acid, *SD* standard deviation

Table 3 Treatment-related adverse events of included studies with use of intent-to-treat analysis

Author/year	Injected patients/knees		TRAE patients		TRAEs	
	Hylan	LMWHA	Hylan	LMWHA	Hylan	LMWHA
Wobig 1999 [16]	38/38	32/35	2	2	2	1
Karlsson 2002 [19]	86/86	90/90	1	2	1	2
Rolf 2005 [20]	90/90	91/91	NR	NR	NR	NR
Karatosun 2005 [23]	46/92	46/92	0	0	0	0
Kirchner 2006 [25]	161/161	160/160	NR	NR	NR	NR
Jüni 2007 [28]	222/222	438/438	22	33	27	38
Raman 2008 [9]	199/199	193/193	39	30	NR	NR
Maheu 2011 [10]	140/140	139/139	60	56	120	102
Pavelka 2011 [11]	189/189	192/192	4	1	5	1
Petrella 2015 [14]	32/32	32/32	6	6	9	7

LMWHA low molecular weight hyaluronic acid, *NR* not reported, *TRAE* treatment-related adverse event

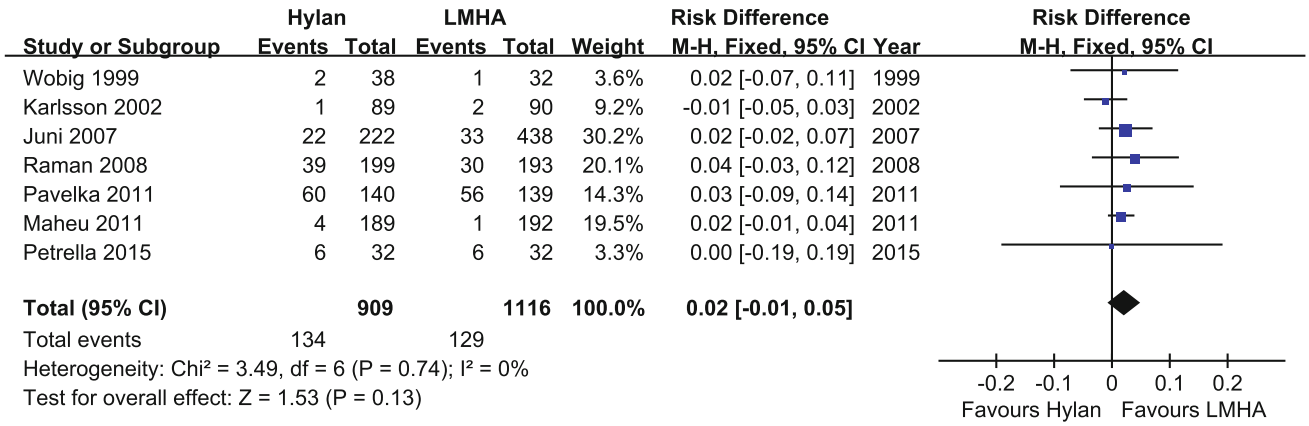

Fig. 4 Forest plot of patients with treatment-related adverse events. *CI* confidence interval, *LWHA* low molecular weight hyaluronic acid

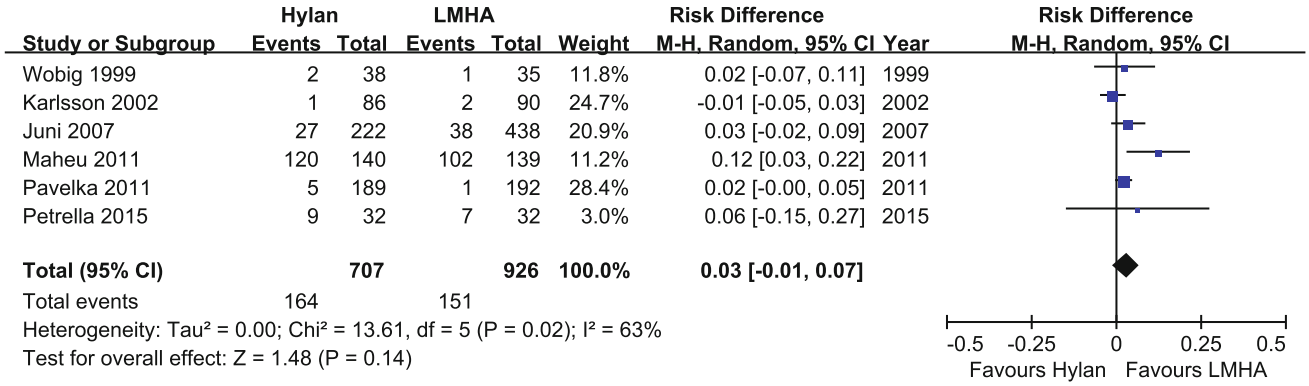

Fig. 5 Forest plot of treatment-related adverse events. *CI* confidence interval, *LWHA* low molecular weight hyaluronic acid

reported no SD between hylan and LMWHA groups [8, 10, 11, 13, 14, 18, 19, 21–25, 27, 28].

4 Discussion

Intra-articular HA injections have been used to relieve symptoms of knee OA and have the potential to delay the need for total knee arthroplasty [23, 29]. A recent study evaluated the cost effectiveness of different forms (Euflexxa, Synvisc, Supartz, Durolane, and Hyalgan) of intra-articular injections for the treatment of knee OA, and reported all five treatments to be cost effective compared with no treatment and also with conventional care. All HA products also had incremental cost-effectiveness ratios below the willingness-to-pay threshold when compared with conventional care [30]. However, the differences between products, especially between high and low molecular weight HAs, are still in debate. Some clinical trials reported an increased efficacy of high molecular weight HA products over the LMWHAs [9, 15, 17, 26, 31]. Sato et al. [32] reported the high molecular weight HAs, especially hylan G-F 20, significantly induced aggrecan and proteoglycan accumulation, nodule formation, and messenger RNA expression of chondrogenic differentiation markers in a time- and dose-dependent manner, and prevented tumor necrosis factor-α-induced inhibition of chondrogenic differentiation, with no effect on cell proliferation or viability. But some clinical trials have reported negative results [12, 20].

According to the current meta-analysis, the overall pain-related outcomes were similar between the hylan G-F 20 and LMWHA groups. This was in accordance with the previous studies [3, 7]. Although a previous study suggested the one 6-ml injection performed at least as well as three 2-ml injections for pain-related outcomes at 6 months post-injection [33], we excluded the two trials with one 6-ml injection to decrease the potential heterogeneity of intervention difference. And still no SD between groups was reached. The placebo-controlled study demonstrated that, in patients with knee OA, a single 6-ml intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks [34]. Decreasing the number of intra-articular

Table 4 The functional outcomes and conclusions of included studies

Author/year	Methods	Outcomes
Wobig 1999 [16]	VAS	Change in VAS scores at 12 weeks were all better than LMWHA ($P < 0.05$)
Zhou 2000 [17]	Knee score	Hylan group reached better outcome at 3 and 6 months ($P < 0.05$)
Lin 2002 [18]	VAS; knee score	No SD of VAS and knee score at any time point between hylan and LMWHA
Karlsson 2002 [19]	VAS; WOMAC; LFI; SF-36	No SD in outcomes between groups during 26 weeks
Bayramoglu 2003 [21]	LFI; muscular strength	No SD regarding LFI scores at 3 weeks and 3 months; as well as concentric quadriceps and hamstring muscle strengths measured at 60°/s and 90°/s
Karatay 2004 [22]	WOMAC; synovial fluid level of ICAM-1 and VCAM-1	No SD was noted between the 2 groups in respect to ICAM-1 levels, VCAM-1 levels, WOMAC pain score, stiffness score, or physical function score at any time
Rolf 2005 [20]	WOMAC	No SD between groups in patient overall assessment of response to treatment at 26 weeks; however, a greater mean decrease of WOMAC stiffness score in Artzal group
Karatosun 2005 [23]	HSS score	No SD between the 2 groups and both had improved in all parameters at the latest follow-up (52 weeks)
Kotevoglu 2006 [24]	WOMAC	No SD between the 2 groups at 3 and 6 months
Kirchner 2006 [25]	WOMAC	The effectiveness of Bio-HA was not inferior to hylan
Atamaz 2006 [26]	VAS; WOMAC; SF-36	Reduction of night pain, pain at rest, pain on touch and WOMAC-function, SF-36 pain and social functioning were greater in hylan group than that of LMWHA
Uluçay 2007 [27]	VAS; WOMAC; satisfaction questionnaire	Comparison of the 3 groups did not yield any SD with respect to patient satisfaction, WOMAC, and VAS scores
Jüni 2007 [28]	WOMAC; EuroQol;	Pain relief was similar in all 3 groups; as well as other WOMAC scores and EuroQol score
Atay 2008 [8]	WOMAC	No SD between groups at 6 and 12 months
Raman 2008 [9]	VAS; WOMAC; Oxford knee score; EuroQol	Improvement in VAS score was superior in hylan group at 6, 26, and 52 weeks ($P < 0.05$); as well as WOMAC pain and activity scores, and Oxford score at 26 and 52 weeks
Maheu 2011 [10]	VAS; LFI; SF-12	No SD between groups at 24 weeks
Pavelka 2011 [11]	VAS; WOMAC; LFI	No SD between groups at 26 weeks
Iannitti 2012 [12]	VAS; WOMAC	Treatment with Variofill resulted a high percentage of improvement in VAS and WOMAC pain and physical activity scores at 6 months
Khanasuk 2012 [13]	VAS; WOMAC; SF-36	No SD between groups at any time-point during 26 weeks
Petrella 2015 [14]	WOMAC	No SD between groups at any time-point during 26 weeks

EuroQol European Quality of Life questionnaire, *HSS* Hospital for Special Surgery Knee Score, *ICAM* intercellular adhesion molecule, *LFI* Lequesne Index, *LMWHA* low molecular weight hyaluronic acid, *SD* significant difference, *SF* Medical Outcomes Study Short Form Health Survey, *VAS* visual analog scale, *VCAM* vascular cell adhesion molecule, *WOMAC* Western Ontario and McMaster University Osteoarthritis Index

injections can reduce the potential related side effects and cost, and thereby offer potential comfort and safety benefits to patients, and may be an acceptable alternative in the future. The subgroup analysis in our study showed that funding support and the quality of study design did not influence current pooled outcomes. The subgroup comparisons of hylan G-F 20 versus LMWHAs that were used in more than two trials also reached no SD. These results have not been reported in the literature previously.

According to current results, the pain-related outcomes vary over time. In the periods within 1 month, no significant superiority was reached between the comparators. From 2 to 3 months, hylan G-F 20 appeared to be more effective for pain relief; however, the superior effectiveness disappeared from 4 months. The effectiveness for pain-related outcomes during the period from 2 to 3 months was further evaluated with a sensitivity analysis, and the superiority still existed after exclusion of the three studies that most favored hylan G-F 20 and with the use of a fixed-effect model. However, even with sensitivity analysis, there was still some clinical heterogeneity between the seven included trials. Lin et al. [18] reported the 2-month outcomes, while others evaluated at 3 months. Only four trials had a Jadad score of 5 points [12, 14, 19, 25], and the pooled results of these four trials reached no SD between the two groups ($I^2 = 42$ %; fixed effect; WMD −0.46; 95 % CI −1.33 to 0.42; $Z = 1.03$; $P = 0.30$). Thus, there is only limited evidence for us to

infer that the pain relieving effect of hylan G-F 20 injection for knee OA from 2 to 3 months is superior to LMWHAs. Raman et al. [9] have reported the superior outcome favoring hylan G-F 20 long term (12 months, $P = 0.007$); however, no SD was reached by another two trials [23, 26]. And after we combined the three results with a fixed effect, no SD was reached ($P = 0.16$).

Because of the high dropout rate of included trials (7.9 %), only studies with ITT analysis were used for the safety analysis to decrease the influence of outcomes. Also, because the patients included in the trials were older (pooled mean of 62.8 years), some of the adverse events were judged as unrelated to study treatment [10, 19, 28]; thus, only the patients with TRAEs and the TRAEs were compared. The pooled patients with TRAEs rate was 14.7 % (134/909) in the hylan group and 11.6 % (129/1116) in LMWHA group. The pooled TRAE rate was 23.2 % (164/707) in the hylan group and 16.3 % (151/926) in the LMWHA group. The pooled results reached no SD with a fixed-effect model for the TRAE patients and TRAEs. This finding was in conflict with the previous meta-analysis [7], which used a random-effects model, and the adverse events from some studies were double-counted.

Our meta-analysis is based on an extensive literature search without language limitation, and the trial selection, data extraction, and quality assessment were performed by two independent authors to minimize bias and transcription errors. However, the current meta-analysis still has some limitations. Our study is limited by the quality of the included trials, as are most meta-analyses. Nine of the included trials (45 %) had low Jadad scores ($\leq$3 points) [8, 12, 17, 18, 21, 22, 24, 26, 27]; however, the pooled overall pain-related outcome with or without these nine trials reached the same results. Also, some other heterogeneity existed between the included studies, which has been described above. We used sensitivity analyses to decrease the heterogeneities, and only the differences of pooled outcomes with a fixed-effect model were used as evidence for conclusions. Also, only the trials with ITT databases were included in the safety analysis to decrease the influence of dropout patients.

For future studies, as suggested by Colen et al. [3], it is still important to compare different intra-articularly administered HA products with different molecular weights to determine if one product or specific molecular-weight range is superior for the treatment of knee joint OA. Large-sample, well designed, double-blind RCTs with an ITT analysis directly comparing the different products (especially the high molecular weight hylan and LMWHAs) of intra-articularly administered HA are still required to further clarify the efficacy and safety of the different products.

5 Conclusion

According to current results, the high molecular weight hylan G-F 20 has almost the same pain-relieving effect for knee OA as LMWHAs, no matter whether administered with three injections (2 ml) or with single-dose (6-ml) products. However, the limited evidence according to the current study showed a superior effect favoring hylan G-F 20 for a period from 2 to 3 months post-injection. There was no evidence of an increase in TRAEs after hylan G-F 20 injection in comparison with LMWHAs according to pooled ITT results.

Author Contributions The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study. ZHM conceived and designed the study; ZHM and LXJ searched the databases and identify the included articles; LHL, LY, and ZHM extracted and confirmed the protocol defined data elements; ZHM and LC wrote the manuscript; ZHM, LHL, LXJ, and LC contributed to the discussion and reviewed the manuscript. ZHM acts as guarantor for the paper. All authors saw, commented upon, and approved the final version of the paper.

Compliance with Ethical Standards

Conflict of interest ZHM, LHL, LY, LXJ, and LC declare that they have no conflicts of interest.

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