**Table 2.** Summary of included studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study type** | **Comparison** | **Sample size** | **Study population** | **Primary outcome** | **Findings** | **Adverse Events** | **Limitations/Potential source of bias** |
| Al-Omran, 2014 | RCT | Synvisc vs Durolane vs Osteonil | 227 | Grade 1-3 OA with >3 ACR criteria | WOMAC | Significant improvement in WOMAC for all 3 groups: Synvisc most effective and Osteonil superior to Durolane | Local reactions in 11 patients (4.8%) | Lack of details on baseline characteristics aside from WOMAC |
| Atay, 2008 | RCT | Synvisc vs Hyalgan vs controls | 45 | KL grade 2-3 following arthroscopic debridement, symptomatic after 3 months of conservative treatment | WOMAC | 6-month WOMAC improved in all 3 groups. At 12 months, greater improvement in both HA groups compared to controls | Local side effects in 11.1% | Small sample size, lack of blinding |
| Carrabba, 1992 | RCT | Placebo vs Arthrocentesis vs 1/3/5x Hyalgan | 100 | Knee OA by Altman criteria, VAS >40, pain >6 months, presence of effusion | VAS pain and ISOAK scores | Significant reduction in pain and ISOAK scores with 3/5 vs 1 injection or arthrocentesis. Trend toward greater improvement and longer effect with 5 vs 3 injections | None reported | No change in volume or molecular weight with dosing schedule. High drop-out rate in last 2 months of study |
| Chou, 2009 | Prospective cohort study | 5x Artz vs 3x Synvisc | 37 | Mild to moderate bilateral knee OA, >55 years, fulfilled ACR criteria, stage I-III in Ahlback classification | VAS, WOMAC, Lesquesne’s index, HSS Knee score | Synvisc showed significant improvement with VAS, not with WOMAC, Lequesne’s, and HSS Knee scores. Synvisc less expensive than Artz | Only a few local events reported (focal pain and swelling at injection site) | Not randomized, as patients chose the treatment for each knee. No placebo group. Small sample size and short-term 6 month follow-up |
| Conrozier, 2008 | RCT | Varying dosing schedule of Hylan | 100 | KL grade 2-3, >40 years, VAS between 40-80, active lifestyle | VAS score | Largest improvement seen with 3x2ml, followed by 1x6ml and 3x4ml | Most adverse events in 3x4ml group, including mild injection site pain and synovitis | Industry-sponsored study |
| Estades-Rubio, 2017 | RCT | NASHA (single injection) vs 5 HA injections | 54 | KL grade 2-3, WOMAC >7, pain for last 3 months, active lifestyle | WOMAC | Improved WOMAC and lower cost of single-injection NASHA compared to 5x HA | No details reported | Small sample size, 6-month follow-up |
| Gigis, 2016 | RCT | HMW 3x HA vs LMW 5x Hyaluronate Sodium injections | 80 | Ages 65-80 with primary OA | VAS and WOMAC scores | Improvement seen in both groups with no significant difference | None reported | Lack of placebo group |
| Lee, 2006 | RCT | HMW 3x Hyruan Plus vs LMW 5x Hyal | 146 | >40 years, KL grade 1-3, VAS >30, failure to respond to conservative treatment | VAS, WOMAC, physical examination of knee | No significant differences between groups | 31% of HMW and 35% of LMW reported >1 adverse event | Open-label study, not double-blinded |
| Raman, 2008 | RCT | Hylan 3x vs Sodium Hyaluronate 5x | 392 | Primary OA and VAS >6 | VAS score | Greater reduction in VAS for Hylan at 6 and 12 months | 30-40 patients reported minor adverse events | Selection bias, as patients were seeking viscosupplementation. Low number of patients with severe KL grade 4 OA |
| Scale, 1994 | RCT | 2x vs 3x Hylan | 80 | >18 years, OA diagnosis with KL grade 2-4 | VAS, joint mobility, improvement in knee motion | Better outcomes with 3x injections at 8-12 weeks, no significant differences at 6 months | 1 reported pain at site of injection | Industry-sponsored study |
| Stitik, 2007 | Prospective cohort study | 5x vs 3x Hyalgan vs 3x Hyalgan + Home exercise program | 60 | >50 years, ACR criteria and KL grade 2-3 | VAS and WOMAC | 3x Hyalgan + exercise had greatest improvement. No significant differences between 3 and 5 injections at 1 year | No significant difference among groups. No severe events | Non-randomized study, lack of compliance data on exercise program |

ACR: American College of Rheumatology; HMW: high molecular weight; KL: Kellgren-Lawrence; LMW: low molecular weight; OA: osteoarthritis; QALY: quality-adjusted life year; RCT: randomized controlled trial

**APPENDIX A**

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search Strategy:

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1 Hyaluronic Acid/

2 (hyaluronic acid or amo vitrax or amvisc or biolon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3 (etamucine or healon or hyaluronan or hyvisc or luronit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

4 (sodium hyaluronate or adant or arthrease or artz or bionect).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5 (duovisc or durolane or eyecon or "go-on" or halonix).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6 ("healon5" or healonid or hialid or hyalcon or hyalein).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7 (hyalgal or hyalgan or hyalovet or hyalubrix).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8 (hyaluronate or hyaluronic acid component or hyladerm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9 (hylaform or hylan or "hylartin v" or "hylo-comod").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10 (hylumed or hyruan or ialugen or juvederm or lagricel ofteno).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11 (laservis or "me 3710" or monovisc or "na hylan").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12 ("na-hylan" or "nrd 101" or "nrd101" or ophthalin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13 (orthovisc or ostenil or perlane or potassium hyaluronate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14 (provisc or radiaplexrx or restylane or "si 4402").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

15 (sinovial or "sl 1010" or supartz or suplasyn).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16 (synocrom or synvisc or teosyal or unihylon or viscoseal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17 (vismed or vitrax or Euflexxa or "Gel 1" or Hymovis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 Viscosupplements/ (

20 (visco supplement\* or viscosupplement\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21 19 or 20

22 Viscosupplementation/

23 Viscosupplementation\*.mp.

24 22 or 23

25 18 or 21 or 24

26 Injections, Intra-Articular/

27 (intra articular injection\* or intra-articular injection\* or intraarticular injection or intra-articular administration or intra-articular deliver\* or intra-articular drug administration\* or intra-articular drug deliver\* or intra-articular infusion\* or intra-articular medication\* or intra-articular treatment\* or intraarticular administration\* or intraarticular deliver\* or intraarticular infusion\* or intraarticular medication\* or intraarticular treatment\* or intracoxal drug administration\* or joint infusion\* or joint injection\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

28 26 or 27

29 Knee Joint/

30 (knee joint\* or superior tibiofibular joint\* or Knee or articulatic genus or genopathy or knee compartment or knee movement or knee stiffness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31 29 or 30

32 28 and 31

33 Osteoarthritis, Knee/

34 (knee osteoarthritides or knee osteoarthritis or osteoarthritis of knee\* or femorotibial arthrosis or gonarthrosis or knee arthrosis or knee joint arthrosis or knee joint osteoarthritis or knee osteo-arthritis or knee osteo-arthrosis or knee osteoarthrosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

35 33 or 34

36 Osteoarthritis/

37 (degenerative arthritides or degenerative arthritis or osteoarthritides or osteoarthritis or osteoarthrosis or osteoarthrosis or arthrosis or degenerative arthritis or degenerative joint disease or osteo-arthritis or osteo-arthrosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

38 36 or 37

39 31 and 38

40 32 or 35 or 39

41 25 and 40

42 Animals/ not (Animals/ and Humans/)

43 41 not 42