

ONLINE EXCLUSIVE

Do hyaluronic acid injections relieve OA knee pain?

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Evidence-based answer

Yes, hyaluronic acid (HA) injections relieve pain more than placebo. The effect is small but similar to results from oral nonsteroidal anti-inflammatory drugs (NSAIDs) or steroid injection (strength of recommendation ([SOR]: **B**, conflicting

meta-analyses). The various HA products all appear to be equally effective in reducing pain (SOR: **B**, randomized clinical trials [RCTs]). Data concerning the effect of HA on functional ability are conflicting.

Evidence summary

A 2005 meta-analysis evaluated the effectiveness of HA injections for osteoarthritis of the knee compared with saline placebo. Researchers identified 22 studies of 8 HA products that used the common end point of pain with movement.¹ (TABLE 1 lists FDA-approved HA products available in the United States.²) A decrease in pain of 15% was deemed clinically meaningful.

Compared with placebo, the mean difference in pain scores with HA products was -4% (95% confidence interval [CI], -9% to 1%) after 2 to 6 weeks; -4% (95% CI, -8% to -1%) after 10 to 14 weeks; and -7% (95% CI, -12% to -2%) after 22 to 30 weeks. The authors note that the small measured effect of HA was magnified by trials that didn't report intention-to-treat results. The effect of HA was also larger in studies that didn't conceal allocation. A weakness of the analysis was its inability to assess potential differences between HA products.

In this 2005 meta-analysis, HA injection didn't improve knee function in any time interval. But in a Cochrane meta-

analysis conducted the following year, HA was found to have positive results.³

HA relieves pain about as much as NSAIDs

The comprehensive 2006 Cochrane meta-analysis reviewed single- and double-blinded RCTs that evaluated the effect of 12 HA products on osteoarthritis of the knee.³ Studies compared HA products with placebo (40), intra-articular steroids (10), NSAIDs (6), physical therapy (3), exercise (2), and each other (15). Efficacy data for different products couldn't be combined because the studies measured different sets of outcomes at different time points.

Overall, the authors concluded that HA injections effectively reduced pain scores, with the largest benefit occurring within 5 to 13 weeks (TABLE 2). The authors also noted that the reductions in pain with HA injections, although generally small, were comparable to oral NSAID therapy and intra-articular corticosteroids. The trials reported few adverse events.

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Hyaluronic acid injections relieve pain as much as oral NSAIDs or steroid injection.

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TABLE 1

FDA-approved hyaluronic acid products

| TRADE NAME | COMPOSITION | MOLECULAR WEIGHT ($\times 10^6$ DALTONS) | COST PER INJECTION* (3-5 DOSES) | SOURCE |
|------------|--------------------|--|------------------------------------|-----------|
| Hyalgan | Sodium hyaluronate | 0.5-0.7 | \$138 | Avian |
| Supartz | Sodium hyaluronate | 0.6-1.2 | \$136 | Avian |
| Euflexxa | Sodium hyaluronate | 2.4-3.6 | \$133 | Bacterial |
| Orthovisc | Hyaluronin | 1.0-2.9 | \$238 | Avian |
| Synvisc | Hylan G-F 20 | 6.0 | \$230 | Avian |

*Prices from www.drugstore.com (accessed June 18, 2008); all other data from Waddell DD.²

Two RCTs show no difference in efficacy among HA products

The Cochrane review determined that not enough evidence existed to evaluate HA products against each other. Two subsequent RCTs compared HA products and found no differences in efficacy. One study compared Synvisc, Orthovisc, and Ostenil therapy in 660 patients over 6 months.⁴ The other compared Synvisc with Euflexxa in 321 patients over 3 months.⁵ Notably, 8% of patients in this study who used Synvisc developed an effusion, compared with 0.6% of patients who used Euflexxa ($P=.0015$).

Recommendations

A 2007 report from the Agency for Healthcare Research and Quality (AHRQ) states that “viscosupplementation trials generally report positive effects on pain and function scores compared with placebo, but the evidence on clinical benefit is uncertain.”⁶

The 2007 guidelines of the Institute for Clinical Systems Improvement note that synthetic hyaluronates “may be effective” in selected patients with mild to moderate degenerative joint disease (based on evidence of middle quality on a 3-tier grading system).⁷

The American Academy of Orthopaedic Surgeons 2008 guideline on osteoarthritis of the knee indicates that, based on the AHRQ report,⁶ it cannot recommend for or against the use of intra-

articular hyaluronic acid for mild to moderate symptomatic OA of the knee.⁸ ■

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Data concerning the effect of HA on joint function are conflicting.

TABLE 2

How HA products affect pain measures

| PRODUCT | COMPARATOR | OUTCOME | AT 1-4 WEEKS | | AT 5-13 WEEKS | |
|-----------|--------------------|-------------------------|--------------|--|---------------|--|
| | | | N | PERCENT CHANGE VS COMPARATOR* (95% CI) | N | PERCENT CHANGE VS COMPARATOR* (95% CI) |
| HA/hyalin | Placebo | Pain on weight bearing | 2542 | -8 (-11 to -4) | 2090 | -13 (-18 to -8) |
| Hyalgan | Placebo | Pain on weight bearing | 1398 | -6 (-11 to -1) | 1095 | -9 (-14 to -4) |
| Synvisc | Placebo | Pain on weight bearing | 481 | -13 (-20 to -5) | 155 | -10 (-14 to -5) |
| Suplasyn | Placebo | WOMAC pain | 53 | NS | | (Data not available) |
| Durolane | Placebo | WOMAC pain | 346 | 4 (0 to 7) | 436 | NS |
| Orthovisc | Placebo | WOMAC pain | 110 | -12 (-13 to -10) | 69 | -5 (-7 to -4) |
| HA/hyalin | NSAID | Pain after walking | 333 | NS | | (Data not available) |
| Hyalgan | NSAID | Pain after 50-foot walk | 279 | NS | 140 | NS |
| Synvisc | NSAID | Pain at rest | | (Data not available) | 57 | NS |
| Suplasyn | NSAID | Pain after walking | 54 | NS | | (Data not available) |
| Hyalgan | Methylprednisolone | Spontaneous pain | 170 | NS | 170 | -8 (-13 to -3) |
| Synvisc | Triamcinolone | WOMAC pain, walking | | (Data not available) | 215 | -10 (-17 to -3) |
| Orthovisc | Methylprednisolone | Pain, walking | 55 | NS | 55 | -18 (-29 to -8) |

US medications Supartz and Euflexxa were not included in the Cochrane review.

CI, confidence interval; HA, hyaluronic acid; NS, not statistically significant; NSAID, nonsteroidal anti-inflammatory drug; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*Negative values favor HA products.

Source: Bellamy N, et al. *Cochrane Database Syst. Rev.* 2006.³

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HA products apparently do not differ in efficacy, based on 2 RCTs.