Evidence-based Rheumatology

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Intra-articular sodium hyaluronate reduces pain and improves function in osteoarthritis of knee

Authors: R.D. Altman *et al.*
Title: Intra-articular sodium hyaluronate (Hyalgan®) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial
Source: *J Rheumatol* 1998; 25: 2203-12.

Aim: Osteoarthritis (OA) of the knee is a common condition, often producing disability. In synovial fluid of patients (pts) with OA the depolymerization of hyaluronic acid (HA) favours the susceptibility of cartilage to injury. Previous studies have shown that intra-articular (IA) injections of HA improved function and reduced pain in knee OA. A 26-week, randomized, multicenter, double blind study was conducted to compare IA HA to placebo IA and to oral naproxen, and to assess the safety and long term efficacy of HA.
Methods: Consecutive pts with OA of the knee, diagnosed according to ACR criteria (1), from 15 centers were screened for the study. The pts were included if they had not received IA HA within one year prior to the study and no other IA injections including corticosteroids for the previous 3 months. In bilateral OA the more severely affected knee was selected for treatment.
The multicenter study was double blind, placebo and naproxen controlled, using stratified, randomized, parallel groups subjected to three treatments: HA, placebo and naproxen. After screening the pts were evaluated for abstinence from non-steroidal anti-inflammatory drugs (NSAIDS) or analgesics other than acetaminophen and stratified within each center by "moderate" or "marked" pain.
Patients assigned to the HA group received subcutaneous anesthesia with lidocain followed by the aspiration of synovial fluid (if present) and by the IA injection of 2 ml (20 ml) HA in a saline vehicle at baseline and then once a week for a total of 5 injections. They also received an oral placebo (identical to naproxen) twice daily for 26 weeks.
Patients in the naproxen group received subcutaneous anesthesia with lidocain without joint penetration by the needle. Aspiration of synovial fluid was performed only if effusion was evident. The subcutaneous injections were performed in the knee at baseline and then once weekly for a total of 5 injections. Patients in this group received oral naproxen 500 mg twice a day for 26 weeks.
Patients in the placebo group received anesthesia with subcutaneous lidocain, then aspiration of synovial fluid (if present) and injection of a saline vehicle (with no HA) in the knee at baseline and then once weekly for a total of 5 injections. They also received an oral placebo (identical to naproxen) twice daily for 26 weeks.
All pts were supplied with 500 mg acetaminophen and were permitted up to 4000 mg/day for escape analgesia as needed for knee pain. Efficacy was assessed at each visit. Measurements were obtained at the time of the screening, at baseline (week 0), and weekly to week 5. Additional assessments were obtained at weeks 9, 12, 16, 21 and 26. The primary efficacy measure was pain experienced on a 50-foot walk test for pts who completed the study (completers) as measured on a 10 cm visual analog scale (VAS). The secondary efficacy measures included the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (pain, stiffness, function) and categorical assessment of pain.
Adverse events were recorded at each visit and when needed. Routine clinical laboratory and hematologic assessments were performed at baseline and at weeks 9 and 26. Synovial fluid, when aspirated, was also analyzed.
Results: A total of 607 pts were screened for the study; 495 (332 with moderate OA and 163 with severe OA) entered and 333 completed the study. Pts receiving HA improved more with respect to pain on the 50-ft walk test compared to placebo at week 26 (in HA vs placebo the difference was 8.8 mm; $p < 0.005$ by ANCOVA analysis of covariance); 56% of HA treated pts compared to 41% of the placebo group had > 20 mm reduction in the VAS continuously from week 5 to week 26 ($p = 0.031$). At week 26 more HA treated pts (47.6%) had slight or no pain with respect to the placebo (33.1%; $p = 0.039$) or naproxen groups (38.9%; $p = 0.022$). Improvement in secondary outcome variables was generally superior in the HA group compared to pts taking placebo, and at week 26 was significantly better with respect to pain and physical function as evaluated by WOMAC ($p = 0.041$ and 0.047). The HA group also tended to have better results than the naproxen group in the primary and secondary assessments, although the difference did not reach significance. For all randomized patients there was a ≥ 20 mm improvement in pain on the 50-foot walk test in 36% of placebo group vs 28% HA pts.
Injection site pain was the cause of withdrawal in 6 pts (4%), being more significant in the HA group (38/164 pts) with respect to the placebo group. Adverse gastrointestinal effects were significantly more frequently reported in the naproxen group than in the HA and the placebo groups, resulting in the withdrawal of 14 pts (8.3%).
Conclusions: OA of the knee is a common condition leading to disability and pain. Its treatment is transient and often unsuccessful. This trial shows that 5 weekly IA injections of HA are generally safe, result in pain reduction, improve patient function and have a long-term efficacy, being at least as efficacious as continuous treatment with naproxen for 26 weeks.

Comment

Among the increasing number of studies performed to investigate the usefulness of intra-articular (IA) sodium hyaluronate (HA) in the treatment of osteoarthritis (OA) of the knee, that reported by Altman et al. (1) may be considered

one of the most convincing. The study was designed as a double blind, double dummy, stratified, randomized, parallel group, multicenter (15 centers) trial with 3 treatment groups: HA, placebo, and naproxen. Of interest was the choice of NSAIDs, the most common drugs used for OA, as one of the treatment groups against which IA HA was compared.

Patients assigned to the HA group received 2 ml/20 mg of Hyalgan (Fidia SpA, Italy, MW 500-730 x 10^5) at baseline and then once weekly for a total of 5 injections. Attention was paid to limit differences due to "additive" therapeutic effects of the injection procedure or oral assumption in the three groups. The results demonstrated that HA was superior to placebo and at least as effective as oral naproxen, with significantly more premature terminations due to gastrointestinal side effects in the naproxen group. It is of relevance that the IA HA benefits were observed by the third injection and persisted for the entire course of observation, fixed at 6 months. This time course is characteristically observed for the drugs classified as symptomatic slow-acting drugs for OA.

This large US multicenter study further substantiates the usefulness of a cycle of IA HA in OA of the knee, confirming its superiority versus placebo as observed in previous and subsequent (2) studies, but also showing a trend to better results and tolerability relative to the naproxen group in various measurements. This is of relevance in particular for the treatment of elderly patients, due to the possible risks associated with NSAIDs.

Finally, it is possible that these results have contributed to convince the authors of the study themselves, in addition to some others, of the potential of IA HA in the treatment of the OA of the knee, as demonstrated by the inclusion of this treatment in the recent Recommendations for the Medical Management of OA suggested by the ACR (3).

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Raynaud's phenomenon is linked to unopposed estrogen replacement therapy in postmenopausal women

Authors: D. Fraenkel *et al.*
Title: The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women
Source: *Ann Intern Med* 1998; 129: 208-211

Aim: The pathophysiology of Raynaud phenomenon (RP) is still unclear, but its predominance in women and the increased severity of symptoms in the childbearing age suggest that female sex hormones may play an important role in the genesis of the phenomenon. The aim of this work was to study the association between hormone replacement therapy and RP in postmenopausal women participating in the Framingham Offspring Study.

Methods: Between 1992 and 1995 a well validated instrument – a color chart designed to help in the diagnosis of RP – was administered to 800 women from the Framingham Offspring Cohort. In addition, in the routine Framingham Offspring Survey they were also asked to report any unusual cold sensitivity or color changes (white, red or blue) of the fingers. Women were classified as having RP if they met the criteria of the validated instrument, or if they described their fingers as being unusually sensitive to cold and turning at least two colors. Women not meeting any of these criteria were considered as controls.

Standardized questionnaires were administered to participants about any current use of estrogens (oral or patch) or progestins. Most of the women used conjugated equine estrogens; only 12 were using an estrogen patch. Factors known to be associated with RP, such as age, body, mass index, smoking status, alcohol consumption and use of -adrenoceptor antagonists were examined as potential confounders.

In this cross-sectional study the women were divided into 3 groups based on their current use of hormones: 1. None, 2. Estrogen alone, 3. Estrogen plus progesterone. Odds ratios were then calculated for any associations between prevalent RP and estrogen alone and estrogen plus progesterone, with non-estrogen users as the reference group. A propensity score was used to adjust for potential confounding effects. First, by regressing unopposed estrogen and estrogen plus progestins on the covariates (age, body, mass index, smoking status, alcohol consumption and use of -adrenoceptor antagonists) exposure values were calculated. Then, values for the fitted exposure were stratified by quartiles and, by Mantel-Haenszel methods, the association between RP and either unopposed estrogen or estrogens plus progesterone was measured.

Results: 497 out of the 800 women evaluated were postmenopausal. Forty-nine women were classified as having RP (9.9%). Thirty-four were identified by the validated instrument, 7 by the routine Framingham Offspring Survey, and 8 by both methods. Only 2 women with RP had evidence of

atherosclerotic disease, and none had evidence of collagen vascular disease.

The prevalence of RP was 8.4% among women not receiving hormone replacement therapy, 19.1% among women receiving estrogen alone and 9.8% among women receiving estrogen plus progesterone. The adjusted odds ratio for RP was 2.5 (95% CI, 1.2 to 5.3) for unopposed estrogen and 0.9 (CI, 0.3 to 2.6) for estrogen plus progesterone, with non-users as the reference group. The crude and adjusted estimates were almost identical, a finding suggesting that the covariates considered had little confounding effect.

Conclusions: The results show that unopposed estrogen therapy was associated with RP in postmenopausal women. This association was not present in women receiving combined estrogen plus progesterone therapy. This suggests that estrogens may play a role in RP, and that physicians should prescribe combined hormone therapy and not estrogen alone in postmenopausal women with RP.

Comment

Fraenkel et al. make the interesting observation that there is a more than two-fold greater prevalence of Raynaud's phenomenon (RP) in postmenopausal women using unopposed estrogen alone compared to women on no hormone therapy or women receiving combination therapy.

This finding seems to be in opposition to the finding that hormone replacement is associated with a reduction in cardiovascular events in postmenopausal women. Studies demonstrate that estrogen can improve endothelium-dependent vasodilatation of postmenopausal women (1) and in individuals with RP. However, RP is more likely caused by increased activity of $_2$-adrenergic receptors on vascular smooth muscle of digital vessels rather than by endothelial disease (2).

Although direct studies of estrogen's effect on vascular smooth muscle $_2$-receptors are not reported, this epidemiological study suggests that unopposed estrogen may increase $_2$-adrenergic activity. This possibility needs further study.

There are several important methodological issues to remember when evaluating this report: the findings only relate to postmenopausal women; there is little data on the classification of patients into primary or secondary RP; the cross-sectional design does not address the temporal relationship between RP and the use of estrogen (causality); and there was a four-fold greater use of -blockers in the unopposed estrogen group, suggesting that they may have some underlying cardiovascular disorder.

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