An Oral Preparation Containing Hylauronic acid (Oralvisc®) Can Reduce Osteoarthritis Knee Pain and Serum and Synovial Fluid Bradykinin

Nelson F R, Zvirbulis R, Zonca B: Henry Ford Hospital, Detroit, MI
Pasierb M, Wu W: Bone and Joint Laboratory, Henry Ford Hospital, Detroit, MI
Wilton P: Wayne State University, Detroit, MI
Martínez-Puig, D: Bioiberica SA, Barcelona, Spain

Abstract

Introduction: We set out to test the effectiveness of an oral hyaluronic acid (HA) preparation (Oralvisc®) based on clinical improvement and changes in bradykinin.
Methods: 40 patients were randomized into oral HA and placebo groups. Pain and function were recorded monthly 3 times. Serum and synovial bradykinin levels were measured at the start and end of the study.
Results: In the treatment group pain and function significantly improved gradually over the three months. There was a significant decrease in both serum and synovial bradykinin levels in the treatment group.
Conclusions: An oral HA product has a positive effect on pain, function, and bradykinin levels in knee OA. Further study will be required to determine the mechanism by which this occurs.

Background

- Osteoarthritis (OA) results in a net loss of extracellular matrix and ranks with heart disease in disability and loss of independence. A leading cause of knee osteoarthritis disability is pain. Non steroidals, acetaminophen, and narcotics relieve pain but may have side effects. Injectable hyanluronic acid (HA) may down regulate inflammatory and biochemical pain pathways. Bradykinin is a known neurotransmitter for pain. An effective oral agent would reduce medical and disability costs.
- The purpose of this study was to compare placebo to an oral preparation containing HA and other glycosaminoglycans (GAGs) patented for its use in treating OA (Oralvisc®). The three hypotheses were: (1.) supplementation with oral HA would significantly improve knee pain and function over a 3 months period, (2.) clinical response to oral HA would be related to metabolic syndrome, and (3.) clinical response to oral HA would be related changes in serum and synovial fluid levels of bradykinin.

Methods

- This was a prospective randomized double-blind placebo-controlled study comparing a patented oral HA (Oralvisc®) to placebo for the treatment of knee OA. At completion two placebo patients could not have arthrocentesis due to difficult aspiration. All remaining data was available for 21 drug and 19 placebo patients. Subjects were between 50-75 years old, had OA based on imaging, a visual analog score (VAS) >50 mm, and an effusion where a joint aspiration or intra-articular injection would be clinically indicated. Exclusion included recent trauma, any inflammatory joint disorder, recent surgery, severe comorbidities, recent intra-articular steroids or HA, and oral or topical corticosteroids.

Correspondence: fnelson1@hfhs.org

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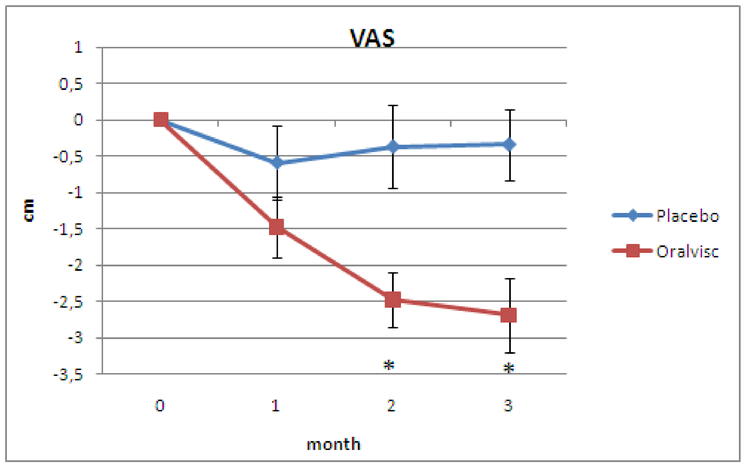
Methods (continued)

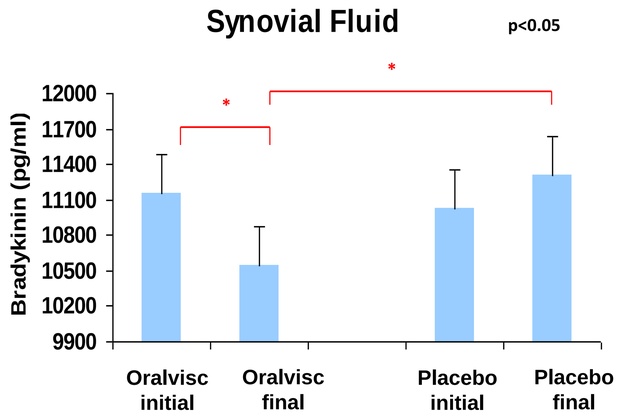
- 576 patients were screened. 51 were recruited and randomized. 3 drug patients did not return and 1 had surgery. 3 placebo patients did not return and 3 had enrollment errors. All patients took their preparation daily for 3 months. 21 patients took Oralvisc® and 19 took identical appearing placebo
- They were evaluated monthly for VAS and WOMAC pain and joint function. Serum and synovial fluid was collected at the beginning and at 12 weeks. Bradykinin was measured by an ELISA. Patients were assessed each month for any unused capsules receiving capsules for the next four weeks
- Initial body mass index (BMI), metabolic score (MS) 0 – 4, MRI changes, Kellgren-Lawrence (KL) scores, age, race, and sex were reviewed for the two groups. Repeated measures analyses were used for all clinical comparisons including pain and function scores as well as BMI. There were no restrictions on the use of non steroidal anti-inflammatories, other pain medications, or other therapies such as ice, wraps, and external aids. Of those 40 subjects who remained in the study capsule usage was high.

Results

- Demographics, BMI, and KL scores were even for both groups. The initial high VAS for placebo was 6.18±0.24cm and for drug was 6.75±0.28cm. After 3 months, the values fell to 5.84±0.76cm and 4.06±0.85cm respectively (p=0.0035). The initial high WOMAC pain score for placebo was 8.05±1.17 and for drug was 8.81±0.81. After 3 months the score rose to 8.16±1.13 for placebo and fell to 5.79±1.34 for the drug group (p=0.0259). The initial WOMAC function score was 40.53±5.18 for placebo and 40.29±3.07 for drug. After 3 months of treatment, the score was reduced by 31% (27.62±7.44) for the drug group but maintained for placebo (39.58±6.17), resulting in statistical differences between treatment groups (p=0.0132). The reduction in VAS score (p=0.0098) WOMAC pain (p=0.0121) and WOMAC function (p=0.0169) was significant for those taking HA but not for those taking placebo ($p < 0.05$), showing significant differences on the time evolution of the studied parameters.



Results (continued)



- The final serum bradykinin levels were significantly lower for oral HA, 144 pg versus placebo 151 pg ($p < 0.05$) with synovial fluid decrease significantly more for oral HA, 61 pg, versus placebo -29 pg ($p < 0.05$). Change in bradykinin was inversely related to MS.

Discussion

- Intra-articular HA may improve the symptoms of OA by mitigating the activities of proinflammatory mediators and pain producing neuropeptides released by activated synovial cells[1]. Chondrocyte receptors increase interleukin on stimulation[2]. Bradykinins participate in innate immunity, inflammation, and pain[3]. The relationship of reduction of bradykinin and decreased pain in the oral HA group is consistent with the role of bradykinin in joint pain. Further research will be required to determine how this very promising agent leads to changes in bradykinin levels.

Significance

- **A patented hyaluronic acid formulation for oral use, Oralvisc®, lowers joint pain and improves function over three months of daily use. The relationship of reduction of bradykinin and decreased pain in the Oralvisc® group is consistent with the role of bradykinin in joint pain.**

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