

Intraarticular hyaluronate injection for knee osteoarthritis—reconsider the rationale

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Intraarticular hyaluronate injection, also referred as viscosupplementation, stands as a popular nonsurgical therapy commodity for patients suffering osteoarthritis (OA) of knee. Despite the currently wide use of hyaluronate injection for knee OA treatment, there are still controversies and uncertainties on this supplementation therapy.

The idea of hyaluronate injections comes from the direct understanding that OA derives from excessive mechanical stress applying to osteochondral surfaces (1). Hyaluronan is a naturally occurring polysaccharide of high viscosity in the extracellular matrix of most kinds of tissues, particularly in soft connective tissues. It acts as a major component of the synovial fluid and of cartilage. Exogenous intraarticular hyaluronate injection stands as a nonsurgical treatment of knee OA (2). In the traditional view, therapeutic goals of intraarticular hyaluronate can be divided into short term and long term effects. Instant hyaluronate injection provides an intraarticular lubrication, which improves the viscoelastic properties of synovial fluid (3). It is also claimed that hyaluronate may exert anti-inflammatory, analgesic and chondroprotective influences on cartilages in a longer run (4). The clinical benefits of treatment with intraarticular hyaluronate, which may persist well beyond the intraarticular residence time of the product, have been suggested to be caused by an increase in the endogenous production of hyaluronate that persists long after the exogenous injected material has left the joint (5). Some experimental studies indicate that hyaluronate may exert its action through mechanisms of enhancing prostaglandin synthesis and suppressing proinflammatory mediators. Histological evidence shows that hyaluronic acid (HA) prevents the degradation of cartilage and may promote its

regeneration although its mechanism is largely unknown (5). Still more, the lower incidence of adverse effect of hyaluronate injection makes doctors more apt in using this therapy. Concerning the local and general tolerance of hyaluronate, it shows a relatively satisfactory result as a disease modifying treatment when compared with other drugs with cardiovascular and gastrointestinal complications like NSAIDs or opioids (6,7). Several institutions also did comparative studies to evaluate cost effectiveness between hyaluronate and NSAIDs or other nonsurgical therapies. The results indicated that hyaluronate may be more favorable in economic concerns generally (8) and even save the cost from cancellation or delayed surgical procedures in some knee OA patients (9).

Despite numerous trials and meta-analyses, the efficacy of hyaluronate-related agents in patients with knee OA remains debated and uncertain. As in many of the other trials of hyaluronates, there was a large placebo effect in this trial. A range of systematic reviews and meta-analyses showed discrepant results in term of the efficacy of hyaluronate injection, possibly caused by different search strategies and selection criteria to identify trials for inclusion in these analyses (2). Clinical effects of hyaluronate injections, however, may still be uncertain in several concerns. Although several clinical studies reveal a significant outcome in patients' pain relief, other trials and meta-analyses show a pessimistic result in reduction of knee joint space and uncertainties in its long term chondroprotective effects (10,11). Still, considerable therapeutic heterogeneity exists from study to study. Some of the minor side effects include pain and skin reaction at injection area. More serious side effects like pseudo-septic

reactions and joint infections have both been detected, but with a relatively lower incidence (12,13). Some researches raised concerns about risk of hyaluronates in adverse events gastrointestinal and cardiovascular adverse events, but still with lower incidence than that of NSAIDs (13). Discordances even exist among different brand of product concerning the molecular mass of hyaluronate. Some researches highlighted high molecular mass hyaluronate and some indicated intermediate molecular mass performed better (14), but the overall effectiveness were modest to non-distinguishable from the placebo (2).

Since a range of pooled analyses and trials raised uncertainties in the therapeutic effects of hyaluronate injection, international guidelines for OA started to put it in a secondary priority. The latest version of the evidence from the Osteoarthritis Research Society International (OARSI) in 2014 does not recommend for the treatment of either knee or multiple joint OA (15). Similarly, the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline and 2012 American College of Rheumatology recommendations do not act for or against hyaluronate injections. It is conditionally recommended only when patient do not have a significant to medical therapies, especially in patients over 75 years old (16). The British National Institute for Health and Care Excellence (NICE) do not recommend HA in knee OA either (6). Consensus of these guidelines for OA patients in early or moderate conditions is to lose weight and undertake suitable exercises.

In brief summary, although some clinical doctors observe that intraarticular hyaluronate may have some instant effects, current evidence based facts are non-sufficient to distinguish that effect from placebo. So that the majority of most updated international guidelines do not recommend hyaluronate as a regular nonsurgical treatment for early to moderate knee OA. Experimental investigations on chondroprotective mechanisms and larger sample RCTs with longer following durations of intraarticular hyaluronate injections are needed to further clarify its therapeutic indication and effect.

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