THERAPEUTIC EFFECTS OF HYALURONIC ACID INTRA-ARTICULAR INJECTION IN OSTEOARTHRITIS

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Abstract. This study investigates the safety and efficacy of intra-articular (IA) sodium hyaluronate (HA) in the treatment of synovial joint osteoarthritis. This is a prospective, observational study. The patients were given five IA of HA at interval of one week. Efficacy included self-reported pain Visual Analog Scale (VAS) and the NSAID intake. The patients did not report any adverse reaction during the study. The study shows that IA HA injection decreases the pain (VAS) and reduces the NSAID intake in OA.

Introduction. Osteoarthritis (fig 1,2) is a slow degenerative musculoskeletal disease characterized by damage not only to the articular cartilage but also to the subchondral bone, changes to the osteophyte formation and joint space loss. Osteoarthritis is the most common joint disorder with a calculated prevalence of 10 to 18% in the United States (Lawrence, 1998). Estimates of the prevalence of symptomatic knee OA range from 6% in all adults older than 30 years of age to 9.5% to 12.1% in adults older than 60 years of age. One study has estimated that by age 85 years, nearly half of all adults will have developed symptomatic knee OA. Knee OA is a key cause of disability among noninstitutionalized adults and may lead to substantial productivity losses (Hayes, 2013).

The slow progress of the disease can affect a series of aspects of the patient life including his wellbeing and socio-economical status. Patients usually present with pain, inflammation and reduction in range of motion. The pathologic changes of synovial fluid hyaluronic acid, with its decreased molecular weight and concentration, led to the concept of viscosupplementation. Viscosupplementation came into clinical use in Japan and Italy in 1987, in Canada in 1992, in Europe in 1995 and in the United States in 1997 (Marshall, 1998). Contemporary management of hip OA is directed at pain control, improvement function and improved health-related quality of life. Management of hip OA includes nonpharmacological modalities (patient education, exercise, assistive devices, and weight management) and pharmacological treatments ranging from oral to intra-articular (IA) therapy. NSAIDs drugs are very effective analgesics, but along with the benefits they can cause some harm as well, including gastrointestinal (GI) bleeding (Straube 2009), renal failure (Griffin 2000) and congestive heart failure (Page 2000). The incidence of serious vascular events was 1% per annum in patients treated with COX-2 selective agents compared with 0.9% in those on traditional NSAIDs. A recent Cochrane systematic review of short-term randomized controlled trials (RCT) (Towheed 2000) shows that the risk of NSAIDs caused serious GI complications, such as peptic ulcers, perforations and bleeds increasing with age, concurrent use of other medications, and with the duration of therapy (Moore 1999). These adverse effects can be severe and may result in death (Fries 1991). Recently OARSI recommendations (Zhang 2008) in patients with symptomatic hip or knee OA stated that non-steroidal
anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with coprescription of a proton pump inhibitor (PPI) or misoprostol for gastroprotection may be considered. However, NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with cardiovascular (CV) risk factors. OARSI guidelines for the treatment of the HIP OA include the use of viscosupplementation (VS), which aims to restore physiological and rheological features of the synovial fluid. Viscosupplementation is provided by the intra-articular injection of hyaluronic acid (HA) products, a naturally occurring polymer present in the synovial fluid, or its derivatives.

Hyaluronic acid is an integral component of synovial fluid that acts as a joint lubricant during shear stress and a shock absorber during compressive stress. In the setting of knee osteoarthritis, a marked reduction in concentration and molecular weight of endogenous hyaluronic acid ultimately leads to reduced viscoelastic properties of synovial fluid and induction of proinflammatory pathways (Dahl, 1985).

MATERIALS AND METHODS
Study design:
This was a prospective, observational, open study.
Study population:
Patients with symptomatic knee OA grade I,II,III according to the Kellgren-Lawrence evaluated on an X-ray taken no more than 2 months before enrolment.
Inclusion criteria: primary gonarthrosis stages I-III Kellgren-Lawrence. Exclusion criteria: concomitant use of oral anticoagulant therapy, stage IV Kellgren-Lawrence, secondary gonarthrosis, impossibility to adhere to treatment conditions.
Dosing:
Patients were given five intra-articular injections of a 2 ml solution of HA antero-medial/antero-lateral approach. We have chosen 17 patients ages between 42-81 with clinical and paraclinical diagnostic of OA and we asked...
them to point out on a Visual Analogic Scale (VAS) the intensity of the pain.

![Visual Analogic Scale](image)

**Fig. 3 Visual Analogic Scale**

![Prefilled HA syringe](image)

**Fig 4. Prefilled HA syringe,**

![Knee injection antero-lateral approach](image)

**Fig 5. Knee injection antero-lateral approach**

### RESULT AND DISCUSSION

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Table 1. Patients in the study and relevant data.

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This study was designed to evaluate the therapeutic approach and management, efficacy and safety of IA sodium hyaluronate. IA sodium hyaluronate was found to be generally safe and well tolerated in this study, as no patient developed a adverse reaction which is consistent with the favourable safety profile that has been established for this product (Schieb, 2003).

Fig 6 Evaluation by participants (patients) of the effectiveness of the intra-articular HA syringe device used in this study by Kelgren stage.
Patients characteristics are presented in Table 1. There were no differences between groups; in the global population, the age varied between 42 and 81 years. Patients were affected by primary OA. The most frequent
Kellgren radiological grade was II 64%. Most of the patients were women 89%. Adverse events were not present. The rate of adverse events in other studies using injectable HA was also low (Lussier et al, 1996) recorded a rate of 2.7% (around 40 events in 1500 participants).

The pain due to OA was measured by VAS, a visual analogue scale ranging from 0 to 10 cm self-reported by the patient. VAS value decreased at all patients proving the effectiveness and the safety of the IA injection with HA. It is unlikely that the sustained beneficial effects of HA therapy can be accounted for only by a temporary restoration of synovial fluid lubrication and viscoelasticity. There are at least four potential mechanisms of action for HA, as described in the literature, that could account for the beneficial effects seen. The first mechanism is restoration of elastic and viscous properties of the synovial fluid, the second is the biosynthetic-chondroprotective effect (Frizziero et al 1998), anti-inflammatory effects have been observed with HA (Yasui et al 1992) and an analgesic effect of HA (DeVane, 2001) (Foti et al, 2011) Pain intensity decreased in patients with Kelgren stage II more than patients with Kelgren stage III (fig. 7). Also we see a reduction in the NSAID intake in patients included in the study and we can also see a decrease of pain measured by VAS bigger in the patients which did not take NSAID after the HA treatment (Fig 9). The reduction in NSAID intake not only decrease the treatment cost but can also decrease the consumption of other drugs such as proton pump inhibitors and other medications needed to counteract side effects of NSAIDs. The study can’t make a specific distinction between the patients with or without physiotherapy (Fig.8). We must announce that this is just a small part of a study that is in development.

CONCLUSION
In real practice the IA injection of HA seems to cause a reduction in pain (VAS) in patients with knee OA both in 6 weeks and 6 month. It also decreases the NSAID intake by patients and it can also decrease the intake of other drugs to counteract the side effects of the NSAID.

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