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RESEARCH ARTICLE

Reduced Analgesics Consumption and Pain Intensity after Injections with a New Hyaluronic Acid in Patients with Knee Osteoarthritis

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Objective: To determine the influence of a new intraarticular hyaluronic acid based hydrogel (Hymovis®) injections on the amount of analgesics consumption in patients diagnosed with primary knee OA. **Methods**: A prospective, single-center study that included 35 patients, aged 45-80 years was conducted in our orthopaedics department. Patients received two intraarticular injections of hyaluronic acid (24 mg/3 ml; 500–730 kDa; Hymovis®) at one week apart. Follow-up was scheduled at 2 and 6 months after the injections. Assessment tools included Visual Analogue Scale (VAS) and an in-house designed questionnaire regarding analgesic consumption (quantity, period and product) during the follow-up. **Results**: Compared to baseline, a significant amelioration in visual analogue scale was observed at six months' follow-up (74.2mm ± 11.7 vs. 57.3mm ± 12.1; $p < .0001$). 28% (n=10) of the patients reduced their total analgesic consumption at two months after the injections. At final follow-up, the analgesic intake was reduced by more than 50% in almost every case. **Conclusions**: Intraarticular administered injections with a novel hyaluronan-based hydrogel (Hymovis®) may reduce the amount of analgesic consumption and self-reported pain intensity in patients with knee OA.

Keywords: novel hyaluronan, knee osteoarthritis, analgesics consumption, intraarticular injections

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Introduction

Primary knee osteoarthritis (OA) is commonly occurring after transformations in biomechanical and biochemical properties of the articular cartilage. It is considered the most common chronic joint disorder that leads to functional deficit in the affected joint and impairment in daily quality of life. There are different conservative treatment methods in early and mild osteoarthritis, but many of them have proven to be ineffective or with small beneficial influence in relation to the normal evolution of the disease [1]. However, intraarticular injections with hyaluronic acid (HA) are considered effective in early stages of the disease, exerting positive and beneficial changes within the affected joint not only by its lubrication effect but acting as a cell, cytokine and anti-inflammatory mediator in the synovial fluid [2-6]. Numerous studies sought to asses and compare the clinical effectiveness of different injected HA products in the osteoarthritic knee, many of them providing positive results. Variables such as molecular weight, number of administrations, amount of hyaluronic acid per ml of product may influence the expected clinical results [7-11]. Several authors demonstrated that intraarticular injected low-molecular weight HA products pass easier through the synovial membrane, exerting a stimulating effect on the endogenous synthesis of high-molecular HA [9, 10, 12]. Compared to other intraarticular injected substances (e.g. corticosteroids) HA products have their analgesic effects persisting for extended duration but installed with a longer on-set [13, 14, 15]. According to guidelines from 2014 Osteoarthritis Research Society International (OARSI) all patients diagnosed with OA should be prescribed analgesics as a first line treatment [16]. Given the side-effects of common analgesics used in knee osteoarthritis (paracetamol, ibuprofen, naproxen, codein, tramadol etc.) their consumption is of great interest for clinicians [17]. Our objective sought to determine if intraarticular HA injections (Hymovis®) reduce the amount of analgesics consumption in patients diagnosed with primary knee OA.

Methods

A prospective, single-centre, clinical trial was conducted in our Department of Orthopaedics and Traumatology from Tirgu-Mures County Hospital, Romania. Local ethical committee approval was obtained. After signing the informed consent, patients diagnosed with primary knee OA received intraarticular injections of 24 mg/3 ml of HA (500–730 kDa; Hymovis®, Fidia Farmaceutici S.p.A, Italy). All patients received two injections at one-week apart. Follow-up visits were scheduled at 2 and 6 months after the injections.

Inclusion criteria were predefined as follows: (a) men and women aged 45-80 years, suffering from (b) primary idiopathic knee OA for at least 6 months, (c) radiological knee OA Kellgren-Lawrence grade II or III, (d) minimum 35 mm on the VAS, (e) daily consumption for more than 3 months of one of the following: paracetamol (up to 2g/day), ibuprofen (up to 1200mg/day) and weak opioids (tramadol, codein). Patients that met our inclusion criteria were informed about our study design and objective at the same time they signed the informed consent. Recommendations from Osteoarthritis Research Society International

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(OARSI) from 2014 suggest that knee-only osteoarthritis without comorbidities should be managed with acetaminophen (Paracetamol) or non-selective NSAIDs (i.e Ibuprofen) orally [16]. As the OARSI recommendation for weak opioids (oral) is still marked as "uncertain", they are still prescribed for the majority of patients as a second or third-step conservative treatment option when treating mild to severe knee osteoarthritis due to positive results in current systematic reviews [18]. According to the literature, these three analgesics are also among the most prescribed medications when treating knee osteoarthritis, and that is the reason for making it a major inclusion criterion [16, 19].

Exclusion criteria were as follows: (a) conditions other than primary idiopathic knee OA, (b) any type of intra-articular injections in the previous 6 months, (c) heparin or platelet anti-coagulation treatment in the last month, (d) non-steroidal anti-inflammatory drugs (NSAIDs) usage 7 days prior to injection, (e) allergy to HA injections, (f) systemic diseases that may influence the results, (g) presence of any infection or pregnancy and lactation. Primary idiopathic gonarthrosis has the highest prevalence in the etiology of this particular disease, therefore, patients that presented other etiologies that add up biases that interfere with our results were excluded from the trial ((i) post-traumatic osteoarthritis, (ii) birth defects in joint geometry that may lead to osteoarthritis, (iii) chronic corticosteroid infiltrations that lead to cartilage erosions and finally to osteoarthritis) [20].

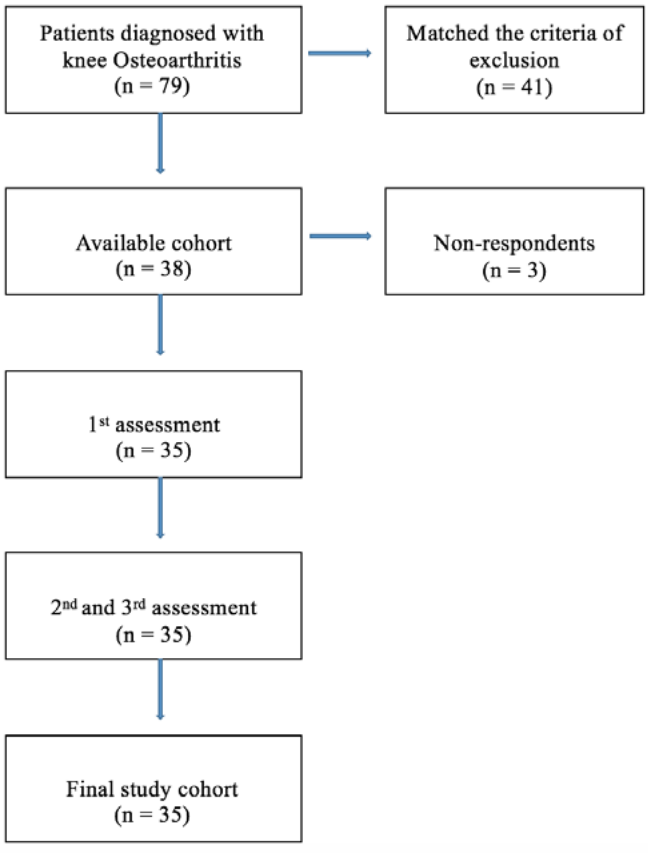

Fig. 1. Flow diagram of study cohort selection

After completing the required registration forms, thirty-five subjects were enrolled and received two injections of HA. Excluded patients and final cohort is presented in Figure 1.

An in-house made questionnaire regarding previous analgesic consumption (quantity, period and product) was completed by each patient before the first injection and at two and six months after. The changes were assessed by comparing any change in analgesic consumption since the previous visit. Visual Analogue Scale (VAS) was completed along with our in-house made questionnaire at each scheduled follow-up meeting. Every patient rated his pain by drawing a mark on a horizontal line of 100mm; afterwards the distance was measured by our study nurse. The score ranges from 0 to 100 on a 100mm scale. The scale is most commonly described by "no pain" (score 0) and "pain as worse as it could be" or "worst imaginable pain" (score 100). VAS is a consistent and validated instrument in measuring chronic pain intensity [21, 22, 23]. As 38% of Mures population consists of Hungarians [24], the questionnaires used in the study were translated into two languages: Romanian and Hungarian.

GraphPad (InStat) and EpiInfo v 7.1.4.0 (Centers for Disease Control and Prevention, Atlanta, USA) softwares were used to analyze data (chi-square test and student t-test). The level of statistical significance was set at $p<0.05$.

Results

Gender distribution and demographic data are presented in Table I. There were no correlations between smoking status and analgesics consumption reduction or VAS decline.

28% (n=10) of patients reduced their analgesic consumption compared to baseline at two months follow-up. At the final follow-up the reduction was over 50% in most cases. In six cases (17%) patients completely stopped analgesics intake. Rescue analgesic intake was reported by twelve patients.

The baseline VAS score was 74.2 ± 11.7 before the treatment. At the second follow-up the pain score decreased to 69.6 ± 9.8 with no statistically significant difference from baseline (Table II).

VAS improved significantly from 69.6 ± 9.8 at two months to 57.3 ± 12.1 at the end of the study ($p< 0.0001$). No major complications were reported during the follow-up. Minor adverse effects included arthralgia and pain at the injection site.

Table I. Demographic Data

Age (years), mean ± SD	63.2 ± 8.1
Height (cm), mean ± SD	168 ± 8.2
Weight (kg), mean ± SD	82.2 ± 16.2
Sex, male/female	10/25
Smokers	14

Table II. Analgesic consumption and VAS results

	Baseline	First follow-up (2 months)	Second follow-up (6 months)	P value*
Analgesic consumption reduction, mean %	n.s	35%	58%	-
Visual Analogue Scale, mean ± SD	74 ± 11	69 ± 9	57 ± 12	<.0001

n.s – not significant; * P value – comparison between the first and second follow-up

Discussions

Our study demonstrates that two injections of low-molecular weight HA may reduce the daily analgesic consumption in patients diagnosed with knee OA by more than 50% in a six-month period. Additionally, Hymovis® injections proved to be a safe, successful and well-tolerated treatment in mild to moderate knee OA. VAS score reduction was correlated with the reduced consumption of analgesics at the end of the study, showing that the intensity of pain is in relationship with the amount of self-administered analgesics.

The product used in our study has proven to inhibit the expression of degrading enzymes (MMP1, MMP13, ADAMTS5) and inflammatory mediators (IL6, PTGS2) [25]. In 2011, Finelli et al. published an experimental comparative study in which they compared the rheological properties of different HA products; from the variety of gel-like HA products presented in their research, Hymovis® was the only product with the capability to completely recover its viscoelastic properties after several cycles of mechanical stress [26]. Benazzo et al. studied the efficacy of Hymovis® on 49 patients with clinical and radiological confirmed knee OA. At one-year follow-up, stiffness, physical function and pain were significantly improved [27]. They concluded that patients who received two cycles of Hymovis® had reduced pain for up to twelve months post-injection. Additionally, only 26% of patients had radiological progressed OA compared to baseline after two cycles of HA injections. Conrozier et al. also questioned the amount of analgesics consumption after injecting HA of different molecular weight in knees affected by OA [28]. Their results were similar to ours; they reported a reduction in analgesics intake by more than 50% for every patient. Pain reduction was an interesting point to study in our trial. Even though pain intensity was only assessed using a validated subjective method (VAS), outcomes at six months follow-up were promising. According to VAS results, HA treatment was able to ameliorate the existing pain in knee OA. Intraarticular injected HA therapy shown to have prolonged effects in relieving pain compared to other similar treatments. This is consistent with other published studies to date [14, 29, 30].

Compared to other treatments for alleviating pain, Hymovis® proved its safety in patients with knee OA, having no adverse effects related to the product. Pain and swelling at the injection site were not considered to be product-based adverse or secondary effects.

Our study also had limitations that should be mentioned. The small sample of patients and absence of a control group may be considered limitations for the study design. Moreover, the tools used to assess reported pain might be exposed to biases in orthopaedics due to their subjectivity. Pain intensity and analgesics consumption were the only variables studied due to that fact that United States Food and Drug Administration Draft Guidance for Clinical development of Drugs, Devices and Biologic products, recommends that this should be a variable to be assessed when testing a new product in this particular type of disease [31]. Studies based on larger cohorts are required to strengthen the evidence regarding pain management in this type of treatment.

Conclusions

Two intraarticular injection cycles of the novel hyaluronan (Hymovis®) could reduce the amount of analgesics consumption and this type of treatment may be considered viable in patients with mild to moderate knee OA. Future studies should aim to assess the functional and biomechanical benefits induced by this new HA-based hydrogel.

Conflict of interest

None declared.

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