

# Viscossuplementação Intra-Articular na Osteoartrite do Joelho: Um Estudo Retrospectivo de um Departamento de Medicina Física e Reabilitação

## *Intra-Articular Viscosupplementation in Knee Osteoarthritis: A Retrospective Study of a Department of Physical Medicine and Rehabilitation*

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### Resumo

**Introdução:** A osteoartrose do joelho é a patologia articular mais frequente e encontra-se associada a elevada morbidade. A viscossuplementação intra-articular é uma das terapêuticas mais usadas na osteoartrose refractária à terapêutica convencional, usando o nosso serviço esta técnica desde o ano 2000. Os objectivos deste estudo foram os de avaliar os resultados do tratamento da osteoartrose do joelho com viscossuplementação intra-articular e comparar os resultados entre os três tipos de dispositivos mais frequentemente usados no nosso serviço.

**Material e Métodos:** Os critérios de inclusão foram três administrações sequenciais do mesmo dispositivo de hialuronato, afastados no tempo até 30 dias entre si. Os critérios de exclusão foram a realização de tratamento concomitante para a osteoartrose do joelho. O grupo Hyalartâ (A) teve 176 indivíduos, o grupo Structovialâ (B) foi composto por 117 indivíduos e o grupo Orthoviscâ (C) constituído por 44 indivíduos, totalizando 337 indivíduos. As classificações analisadas basearam-se nos registos padronizados das respostas à mesma questão colocada no início de cada consulta: “Como estão as suas queixas de dor desde a última consulta?”, existindo cinco respostas possíveis dadas pelo doente numa escala tipo Likert: 1- pioria, 2- sem melhoria, 3- melhoria ligeira, 4- melhoria moderada, 5- melhoria acentuada.

**Resultados:** No final dos três tratamentos, existiu uma proporção semelhante de doentes a referir uma “melhoria acentuada”: 19% no Hyalart® (A) e Structovial® (B) e 12%

no Orthovisc® (C). O primeiro tratamento não foi eficaz (pioria ou inexistência de melhoria) em 39% dos doentes com “A” (9% pioraram), 17% dos doentes com “B” (7% pioraram) e 75% dos doentes com “C” (28% pioraram).

**Conclusão:** A viscossuplementação intra-articular é um tratamento eficiente das queixas de dor causadas pela gonartrose. O dispositivo derivado de biofermentação teve um resultado mais favorável ao longo dos tratamentos.

**Palavras-chave:** Ácido Hialurónico; Dor; Osteoartrite do Joelho/tratamento; Viscosuplementação; Viscosuplementos.

### Abstract

**Introduction:** Knee osteoarthritis is the most frequent articular pathology and is associated with high morbidity. The intra-articular viscosupplementation is one of the most used therapeutics in osteoarthritis refractory to conventional therapy and is used at our department since the year 2000. The goals of this study are to evaluate the results of osteoarthritis treatment with intra-articular viscosupplementation and compare the results between the three most frequently used devices in our department.

**Material and Methods:** The inclusion criteria were patients with knee osteoarthritis with three sequential administrations of the same hyaluronic device, separated in time no more than 30 days among them. The exclusion criteria were any other concomitant treatment to knee osteoarthritis. The studied Hyalart® (A) group had 176 patients, the Structovial®

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Data de submissão: junho de 2016

Data de aceitação: junho de 2018

(B) group had 117 patients and the Orthovisc® (C) group had 44 patients, with a total number of 337 studied patients. The analyzed classifications were based in the padronized answer to the same question made in the beginning of each medical appointment: “How is your pain since the beginning of the treatment?”, with five possible answers in a Likert-like scale: 1-worse; 2-no improvement; 3- slight improvement; 4- moderate improvement; 5- high improvement.

**Results:** In the end of the three injections, there was a similar proportion of patients referring an “high improvement”: 19% with “A” and “B” and 12% with “C”. The first treatment was not efficient (worse or no improvement) in 39% of the patients with “A” (9% were worse), 17% of the patients with “B” (7% were worse) and 75% of the patients with “C” (28% were worse).

**Conclusion:** The intra-articular viscosupplementation is an efficient treatment of the pain caused by knee osteoarthritis. The device derived from biofermentation had a more favourable outcome along the treatments.

**Keywords:** Hyaluronic Acid; Osteoarthritis, Knee/drug therapy; Pain; Viscosupplementation; Viscosupplements.

## Introduction

Knee osteoarthritis is the most frequent joint pathology affecting 10% of the men and 13% of the women above 60 years old. It is also associated with a high morbidity.<sup>1</sup>

The hialuronic acid (HA) is a high-volume viscoelastic molecule of glicosaminoglicans and may be found in normal synovial fluid and cartilage. Its properties allow shock absorption, energy dissipation, cartilage protection and lubrication.<sup>2</sup>

The intra-articular viscosupplementation is a medical procedure applied to knee osteoarthritis that is refractory to conventional treatment and consists in the injection of hyaluronic acid inside the affected joint. Its use in knee osteoarthritis has been widely studied, with a recent meta-analysis of 54 randomized controlled trials comparing hyaluronic acid injection versus placebo injection reporting a significant peak effect 8 weeks after the injection.<sup>3</sup> Despite the pain relief effects of viscosupplementation being consensual, its regenerative capacities are still controversial. Guidolin *et al* studied cartilage histology 6 months after a hyaluronic acid injection and found a significant reconstitution of the superficial layer together with an improvement in chondrocyte density and territorial matrix.<sup>4</sup> On the other hand, Jubb *et al* found no difference in the evolution of radiological joint space narrowing nor Prasad *et al* found an improvement in cartilage morphology measured by a magnetic resonance imaging (MRI) protocol.<sup>5,6</sup>

The kind of hyaluronic acid that is injected may influence the

final outcomes. In fact, there is some evidence of exuberant inflammatory reactions (pseudoseptic arthritis) consequent to the administration of hyaluronic devices obtained from rooster coomb.<sup>7</sup> There are also reports of the presence of antibodies against rooster’s proteins after the injection of devices obtained from rooster coomb, suggesting an immune mechanism to this inflammatory reactions.<sup>8</sup> The physiopathologic mechanism of this reactions is not well defined, being described pro-inflammatory cytokines increases and activation of CD44 receptors, involved in the migration and leukocyte recruitment during inflammation.<sup>9,10</sup> According to recent studies, molecular weight or hyaluronic acid concentration are the main studied device characteristics. However, the origin of the molecule may have an important role in the treatment’s outcomes, because of the immunomediated reactions associated with rooster coomb devices.

The mesotherapy unit from our Physical Medicine and Rehabilitation (PMR) department began using knee hyaluronic acid injections in the year 2000, having a patient file of 15 years of procedures. Hyalart® (A), Structovial® (B) and Orthovisc® (C), are the most frequently used devices.

“A” is obtained from roost coomb, with sodium chloride, sodium monophosphate and sodium diphosphate as excipients and has a molecular weight of 0.5-0.73 million of Dalton. It has a concentration of 10 mg/mL with a total of 20 mg of hyaluronic acid per dose.

“B” is obtained from biofermentation, with sodium chloride, sodium monophosphate and citric acid as excipients and has a molecular weight of 2.2-2.7 million Dalton. It has a concentration of 10 mg/mL and a total of 20 mg of hyaluronic acid per device.

“C”, used in our department until 2005, was obtained from rooster comb until 2006, being nowadays obtained from biofermentation. “C” had sodium chloride as excipient, a molecular weight of 1.5 million Dalton, a concentration of 15 mg/mL and 30 mg of hyaluronic acid per dose.

The goals of our study were to:

1. Evaluate how intra-articular knee viscosupplementation influences patient’s knee pain.
2. Compare the results of the three most commonly used intra-articular viscosupplementation formulations in our unit

## Material and Methods

We analysed retrospectively the clinical files of all patients referred for a knee intra-articular viscosupplementation with the diagnosis of knee osteoarthritis, from 07/01/2000 to

01/09/2013. The collected data included age, injection device and knee pain compared to the beginning of the treatment in a Likert-like scale. The scale was applied by the doctor who administered the intra-articular injection.

The knee osteoarthritis diagnostic criteria used at our department are the ones from the American College of Rheumatology, in which the diagnosis is made by the presence of knee pain and 3 other factors among: age >50 years old, morning stiffness inferior to 30 minutes, crepitations during the knee movement, bony tenderness, bony enlargement and no palpable warmth of the synovium.<sup>11</sup>

The knee pain classification was based in the padronized answers to the same question that was made in the beginning of each appointment: "How is your knee pain, related to the beginning of the treatment?", existing 5 possible answers that could be given by the patient in a Likert-like scale: 1- worse; 2- no improvement; 3- slight improvement; 4- moderate improvement; 5- high improvement. The evaluation of the last treatment was made in the beginning of the next medical appointment.

The inclusion criteria were patients with 3 hyaluronic acid injections of the same device, administered with no more than 30 days between them, performed by the two doctors of the Mesotherapy Unit by anatomic references. Exclusion criteria were conducting concurrent treatment for osteoarthritis of the knee.

Due to the reduced number of injections with some of the brands, we only considered the 3 most commonly used formulations. "A" and "B" (both hyaluronic acid with a concentration of 20 mg/2 mL) and "C" (hyaluronic acid with 30 mg/2mL)

## Results

We obtained a total of 1189 patients that, after being submitted to the inclusion criteria, resulted in 337 patients, presented in Table 1.

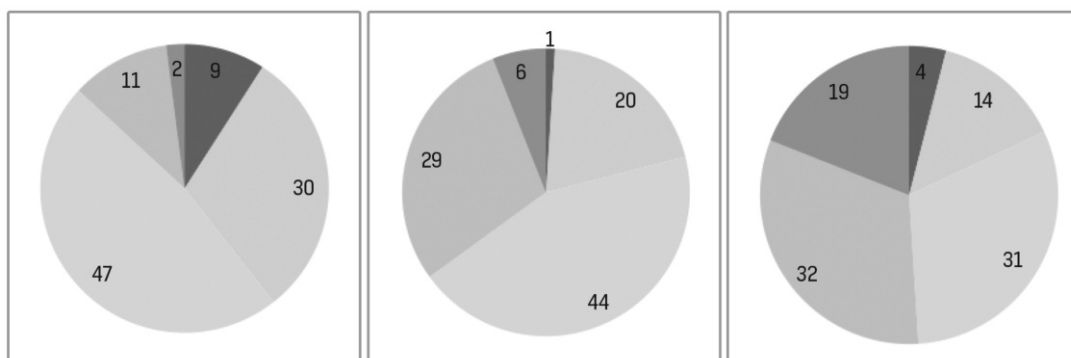
**Table 1** - Number of patients in each group

	Number of patients	Age (average)
<b>Hyalart®</b>	176	75,7
<b>Structovial®</b>	117	73,1
<b>Orthovisc®</b>	44	70,8

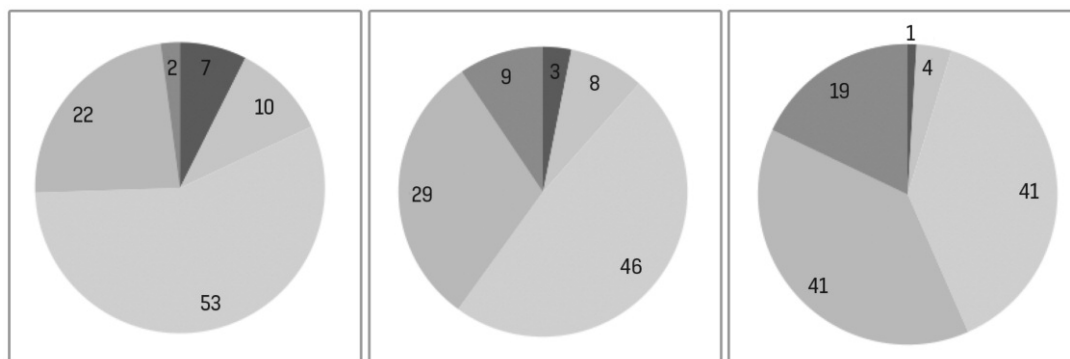
According to the Figs. 1, 2 and 3 the first treatment had a "non responders" (worse or not better) percentage of 39% with "A" (9% were worse), 17% with "B" (7% were worse) and 75% with "C" (28% were worse).

In the end of the 3 sequential treatments, there were a similar proportion of patients referring that were "much better": 19% in "A" and structovial and 12% in "C". However, in the end of the treatment there was a "non responder" percentage of 18% in "A", 5% in "B" and 26 in "C".

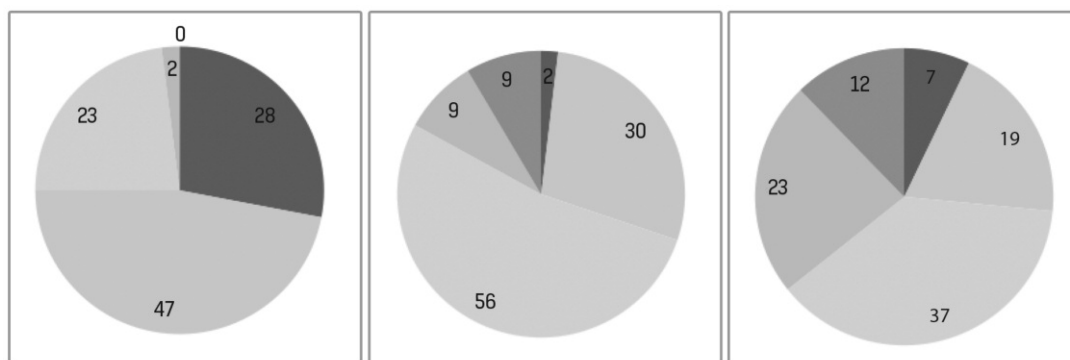
According to the Figs. 1, 2 and 3, the pain improvement was progressive along the 3 treatments. According to the same Figs., in the end of the 3 treatments, most of the patients had a pain score between 2.5 and 4. "B" was the device with the most favorable outcome.



**Figure 1** - Hyalart® device results, sequentially from the first to the third administration. Red-worse; Yellow-no improvement; Light green- slight improvement; Intermediate green- moderate improvement; Dark green- high improvement



**Figure 2** - Structovial® device results, sequentially from the first to the third administration. Red-worse; Yellow-no improvement; Light green- slight improvement; Intermediate green- moderate improvement; Dark green- high improvement



**Figure 3** - Orthovisc® device results, sequentially from the first to the third administration. Red-worse; Yellow-no improvement; Light green- slight improvement; Intermediate green- moderate improvement; Dark green- high improvement

## Discussion

In our study, the most efficient device in reducing knee pain at the end of the 3 injections was the one obtained from biofermentation (“B”). Among the devices obtained from rooster coomb, the one with the highest molecular weight (“C”) was the less efficient one. This device was also the one with the worst results after the first injection (75% of the patients were worse or not better).

There are several other studies comparing different hyaluronate devices, most of them highlighting the different molecular weights between the devices (not even mentioning their origins in some cases).<sup>12</sup> However, a recent meta-analysis encompassing 68 articles took the origin of the device into account, concluding that biofermentation-derived devices had significantly less acute post-injection flare-ups.<sup>13</sup> In fact, there are some studies that report a pro-inflammatory cytokine decrease in the synovial fluid after the injection of an hyaluronic acid formulation.<sup>14,15</sup> However, all of these studies refer to hyaluronic acid with its origin from biofermentation. Since rooster coomb devices are still being developed with increased molecular weights, it’s urgent that the immunomediated mechanisms associated with this reactions are better characterized.

Our study’s strenght is in a sample with a high number of patients, using data that was systematically collected by the Mesotherapy Unit’s doctors. The retrospective character of the study is associated with weaker points, like the evaluation of the treatment with a Likert-like scale, that was simpler to use in a daily basis (instead of other specific scales, that also take more time to apply). The administration of the scale by the same doctor who applied the procedure may also be a bias factor. Our study didn’t also take in consideration other environmental factors such as physical activity or other comorbidities.

## Conclusion

Intra-articular viscosupplementation of hyaluronic acid is an efficient treatment in knee osteoarthritis.

The formulation of the hyaluronic acid may have relevant implications in the final results of the treatment, besides hyaluronic acid concentrations and molecular weight.

We need more studies on this subject, not only to find the safest and most efficient hyaluronic acid formulation (molecular weight, concentration etc.), but also to explain the physiopathologic mechanism of the inflammatory reactions to the intra-articular injection of hyaluronic acid.

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho. **Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo. **Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial. **Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

*Conflicts of Interest: The authors report no conflict of interest. Funding Sources: No subsidies or grants contributed to this work. Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki). Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.*

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