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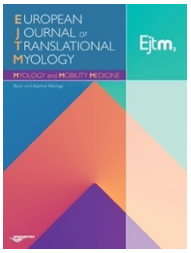

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Intra-articular injections with Carboxymethyl-Chitosan in patients affected by knee osteoarthritis non-responders to hyaluronic acid: a pilot study

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Abstract

Osteoarthritis (OA) is a disabling disease that causes pain and functional limitation. OA symptoms can be treated with intra-articular injections of anti-inflammatory, viscosupplementary, or viscoinductive products. Non-responders to these approaches have limited options, often surgical (e.g. knee replacement). This retrospective study aims to evaluate the efficacy of a single injection of Carboxymethyl-Chitosan for advanced (Kellgren-Lawrence ≥3) and symptomatic knee OA in non-responders to hyaluronic acid. We enrolled 10 patients (5 female, 5 male). Treatment efficacy was assessed through the Visual Analogue Scale (VAS, pain) and the Knee Injury and Osteoarthritis Outcome Score (KOOS, knee function). Data are acquired from rating scales administered at the time of injection (T0), one month (T1), three months (T2), and six months (T3) after treatment as for clinical practice. Results showed a significant improvement in pain and function at T1, with a subsequent gradual resumption of symptoms. In conclusion, the treatment showed a better outcome in the short term (i.e. up to 1 month after treatment); however, raw values of VAS and KOOS did not return to baseline levels showing a maintenance of improvement albeit not statistically significant.

Key words: knee osteoarthritis, intra-articular injections, Carboxymethyl-Chitosan, hyaluronic acid, quality of life.

Introduction

Osteoarthritis

Osteoarthritis (OA) is a debilitating chronic degenerative disease that affects over 300 million patients worldwide. OA is characterized by joint pain and dysfunction, progressive loss of autonomy in Activities of Daily Living (ADL), and worsening of Quality of Life (QoL).[1,2] In particular, knee osteoarthritis has a prevalence of 10% and 13% respectively in men and women aged above 60 years.[3] Joints affected by OA show a progressive degradation of articular cartilage, a thickening and sclerosis of subchondral bone, formation of pseudocysts and osteophytes, inflammation of synovium or bursa, the hypertrophy of joint capsule, and possible associated degeneration of ligaments and menisci.[4] Articular cartilage consists of 95% of water and extracellular matrix and only 5% of chondrocytes, the cellular elements responsible for proteoglycans and glycosaminoglycans synthesis.[5] OA starts with the alteration of the normal process of remodeling of articular cartilage, with a consequent increase in the content of proteoglycans and subsequent increase of catabolic cytokines, including interleukin-1β, which promotes the increase of synthesis of metalloproteases.[6] Synovial damage is often secondary to cartilage and bone damage and consists of a reactive inflammatory thickening resulting from increased activity of synoviocytes; this process leads to an increase in the synthesis of low molecular weight hyaluronic acid, with subsequent alteration of the synovial fluid.[4] The clinical manifestations of osteoarthritis are represented by pain and functional limitation with variable characteristics depending on the joint involved. Arthritic pain often begins insidiously; it is usually localized and accentuated with joint load, while it tends to recede during the night hours to reappear during the day. Morning stiffness may coexist, but it is usually resolved with joint mobilization. Pain is associated with functional limitation of various entities depending on the stage of the disease.[7-9] OA diagnosis is based on clinical detection of pain, functional limitation, bone swelling and radiographic detection of osteophytes, reduction of joint interline and subchondral sclerosis.[10]

Nowadays there is no definitive treatment for OA but only a series of strategies for pain control, and improvement of joint function and mobility, to lead the patient to the recovery of autonomy in ADL and the improvement of QoL. The

pharmacological approach mainly makes use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, additional analgesics (paracetamol, opioids), and vis coinductive/viscosupplementary drugs, administered orally or inside the affected joints.[11-13]

Chitosan

Chitosan is a linear biocompatible and biodegradable polymer obtained from the N-deacetylation of chitin, with mucoadhesive, antioxidant, and antimicrobial properties, which make it useful in various medical fields. Due to its physical, chemical, and biological characteristics, chitosan and its derivatives have been extensively studied for many medical applications, including wound healing, drug administration, and tissue engineering.[14-19] Various studies conducted in vitro and ex vivo have shown that intra-articular administration of this polymer could prevent the degradation of articular cartilage, inducing chondrogenic differentiation of mesenchymal stem cells, triggering the production of type I and II collagen and reducing the production of inflammatory and catabolic mediators by chondrocytes.[15,20-22] The Carboxylated and Methylated form of Chitosan (Carboxymethyl-chitosan, CM-C) is extracted from the fungus *Agaricus bisporus*. If applied to the biological tissue, the degradation of CM-C occurs through a physiological macrophage reabsorption process, in which granuloma formation has not been observed and no cytotoxic potentials have been demonstrated in vivo. However, macrophage activation may present with a transient and reversible post-injection inflammatory reaction that responds well to treatment with oral NSAIDs.[23] Experimental studies conducted on intra-articular administration of this macromolecule in animal models have shown a low incidence of post-administration side effects, limited to minimal local tissue reactions.[23,24] Further studies recently conducted in vitro and ex-vivo found a higher lubricating capacity by CM-C, with a significant reduction in coefficient of friction, compared to traditional formulations of cross-linked hyaluronic acid (HA), with a more significant recovery of joint mobility.[25,26]

Aim

This study aims to evaluate the efficacy of a single intra-articular knee injection with CM-C in non-responders to HA with advanced OA (KL≥3) on pain and functional outcomes.

Materials and Methods

The study has a retrospective design.

Data were collected from patients attending the Physical Medicine and Rehabilitation outpatient clinic at the Tor Vergata University Hospital, Rome.

The study analyzed data from patients treated with intra-articular CM-C (a compound of CM-C (60 mg/3 ml) consisting of 2% (w/w) CM-C in phosphate buffer supplemented with 3.5% sorbitol) who met the inclusion criteria within the period from September 2022 to October 2023.

Data were acquired from rating scales administered by a physiatrist with several years of experience in knee OA and injection therapy at the time of injection (T0), one month (T1), three months (T2), and six months (T3) after treatment as for clinical practice.

The clinical protocol was conducted, recorded, and reported by Good Clinical Practice guidelines and the Declaration of Helsinki and approved by the the Territorial Ethics Committee "Lazio Area 2" (173.24).

Before collecting the data, an informed consent form was signed by all the participants.[27]

Inclusion and exclusion criteria

Subjects were enrolled according to the following criteria.

Inclusion criteria: i) male and female patients of all ages with advanced and symptomatic gonarthrosis [radiographic Kellgren-Lawrence (KL) grade ≥ 3];[28] ii) patients previously unsuccessfully treated with intra-articular HA injections in the knee and subsequently treated at the same level with CM-C; iii) patients with a minimum 6-month follow-up who underwent scheduled clinical assessments at 1, 3, and 6 months.

Exclusion criteria: i) patients not treated with CM-C; ii) patients for whom KOOS and VAS were not completed.

Rating scales

For this study, two rating scales were considered: the Visual Analogue Scale (VAS) for pain measurement and the Knee Injury and Osteoarthritis Outcome Score (KOOS) as a functional outcome.

VAS is a pain rating scale developed by Scott and Huskisson[29] that consists of a straight line, generally 100mm long, at the extremes of which it is possible to read the indications "absence of pain" and "maximum pain". The patient has to self-report pain intensity by placing a sign according to his or her current pain level. The proximity of the sign to one of the two extremities indicates more or less intense pain.

KOOS is a self-administered questionnaire that aims to assess the reported symptoms in the knee joint.[30] The scale consists of 42 items and 5 domains that respectively assess Symptoms, Pain, ADL, Sports and Recreational Activities, and QoL. All items on the scale have the same response mode, using a 5-point Likert scale ranging from 0 (no problems or difficulties) to 4 (problems or high difficulties). The results of each subscale are calculated separately using the formula:

$$100 - (\text{score obtained} \times 100) / (\text{maximum score})$$

The score will then be expressed as a percentage for each subscale, ranging from 0 (condition of severe disability) to 100 (excellent condition).[31]

Statistical analysis

All data were initially entered into an Excel spreadsheet (Microsoft, Redmond, Washington, U.S.A.) and analysis was performed using the statistical package for the social sciences Windows, version 15.0 (SPSS, Chicago, Illinois, U.S.A.). Descriptive statistics shows mean ± standard deviation (SD) since all variables were normally distributed parameters after confirmation by the Kolgomorov-Smirnov test.[32] Range (min; max) is also reported as additional data. Comparisons between variables at

different times were performed with ANOVA for repeated measures and post-hoc Bonferroni test.[33,34]

A value of $p<0.05$ was considered statistically significant.

Results

According to the inclusion and exclusion criteria, 10 patients were enrolled in this study; male (5, 50%) and female (5, 50%) were equally distributed. The anthropometric data of the sample are reported in Table 1.

Table 2 shows the descriptive analysis of the variables over time.

VAS (Figure 1) showed statistically significant changes over time at the ANOVA for repeated measures test ($p<0.01$). At the post-hoc analysis with the Bonferroni test, changes were found between T0 and T1 ($p<0.01$) representing a significant reduction of pain. However, VAS scores had an ascending trend after T1, with a significant worsening when comparing this timepoint to T3 ($p=0.02$) and T6 ($p<0.01$).

All KOOS domains (Figure 2-6) showed statistically significant changes over time at the ANOVA for repeated measures test (Pain $p=0.02$; Symptoms $p<0.01$; ADL $p<0.01$; QoL $p=0.01$). The only exception was the Sport and Recreational Activities related domain ($p=0.07$).

Specifically, at the post-hoc analysis with the Bonferroni test all the domains analyzed showed a significant improvement at T1 compared to T0 (Pain $p<0.01$; Symptoms $p=0.02$; ADL $p<0.01$; QoL $p=0.02$). Similar to VAS, KOOS domain scores showed a deterioration trend after T1, too. However, the worsening wasn't statistically significant, except for the Symptoms domain (Figure 2) at T6 compared to T1 ($p=0.03$).

Discussion

HA is a viable treatment option for advanced knee OA.[35] In case of treatment failure, arthroscopic or surgical approaches (*i.e.* knee replacement) are available. Total knee arthroplasty is a surgical option with a success rate, but with bio-mechanical implications that often cause progression of OA in the contralateral knee; arthroplasty is often required at the contralateral knee as well, with all the consequent surgical risks and additional biomechanical implications.[36] Nowadays, non-surgical

alternatives for non-responders with advanced OA are however very limited.[37] Research is ongoing on this topic but there is still little data available. A recent paper involving 9 patients (4 female, 5 male), KL 2-3, showed a reduction of pain and an increase of functional outcomes after intra-articular injections in the knee with clodronate plus lidocaine.[38] Finding a new treatment option would thus be of paramount importance for two reasons. The first is to give the patient time to think without rushing about the management of their body, having the opportunity to choose the course of care and eventual surgical setting they prefer, considering the possible need for knee replacement surgery. The second, and probably the most important, is to improve patients' QoL even if only for a short period (e.g., up to 4-6 months) by increasing their independence in ADL and empowering them to carry on their personal passions, hobbies, and even work activities. The bio-psycho-social approach of the ICF and the holistic view of the person dictate that these aspects must be kept in mind in the rehabilitation setting.[39]

To the best of our knowledge, at the current time, only two studies have been published regarding the use of CM-C for the treatment of knee OA via injection therapy in human beings, both by Emans *et al.* One of them[40] is the post-hoc analysis of the other.[26] The important difference between our study and these two is that those were not recruited non-responders patients.

Moreover, despite the small number of participants, this is the first study conducted in Italy aimed to evaluate the efficacy of a single intra-articular CM-C injection for the treatment of patients with advanced and symptomatic knee OA unresponsive to HA treatment.

In our innovative study, we aimed to evaluate the efficacy of a single intra-articular CM-C injection for the treatment of patients with advanced and symptomatic knee OA unresponsive to HA treatment.

After data analysis, CM-C seems to show a clear efficacy one month after treatment (T1). Patients reported a significant reduction in pain and a significant increase in knee function (mobility and swelling), independence in ADL, and general QoL at T1 as evidenced by the changes in the Pain, Symptoms, ADL, and QoL KOOS domains plus VAS. In the following months, though, these indicators showed a trend of gradual worsening: at the following study time-points patients reported ascent of pain

and descent of KOOS functional outcomes. These results are not in line with the other two available studies on this topic which showed a clear efficacy, although the population difference between the studies should be considered. Emans et al. found clear improvement in pain and functional outcomes up to 6 months post-injection.[26,40] In our case, it is important to note that at T2 several scores retained better raw values than T0, albeit without reaching statistical significance. Even at T3, almost all variables returned to raw values that still showed a small improvement though being roughly similar to those observed before treatment. Patients thus on average reported a positive trend in the first few months after treatment, and probably the small sample size prevented greater statistical evidence.

Limitations

This study has several limitations such as a small sample size, a short follow-up period, the absence of a control group and its retrospective design. These limitations did not allow a more in-depth statistical analysis.

Conclusions

This is the first study conducted in Italy to evaluate the effects of a single intra-articular CM-C injection for the treatment of patients with knee OA unresponsive to HA.

This retrospective study suggests a short-lasting overall efficacy of CM-C for the treatment of patients with advanced knee OA (KL≥3) non-responders to intra-articular HA injection. Reduction in pain and increase in functional outcomes were observed clearly at one month after CM-C injections but lasted only as a small improvement in the next study time-points up to 6 months.

CM-C could then appear as a treatment option for this population to extend the time to surgery and make the decision more informed. The albeit small improvement in QoL in people who have few or no alternatives for treatment of a disabling condition such as advanced knee OA should not be neglected.

Abbreviations

ADL, Activities of Daily Living

CM-C, Carboxymethyl-chitosan

HA, hyaluronic acid

KL, Kellgren-Lawrence

KOOS, Knee Injury and Osteoarthritis Outcome Score

NSAIDs, Non-Steroidal Anti-Inflammatories Drugs

OA, Osteoarthritis

QoL, Quality of Life

SD, Standard Deviation

VAS, Visual Analogue Scale

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Conflict of interest: all authors have read and approved this manuscript. The authors declare no conflicts of interest.

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Ethics approval: the Territorial Ethics Committee "Lazio Area 2" approved this study (173.24). The study conforms with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent: all patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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Table 1. Anthropometric data of the sample.

	N	Mean	SD	Min.	Max.
Age (Yrs)	10	74.5	4.8	68	83
Weight (kgs)	10	80.6	15.2	56	98
Height (cms)	10	167.9	8.7	159	178
BMI ((kg/m^2)	10	28.66	5.60	21.88	38.28
KL	10	3.6	0.5	3	4

Table 2. Descriptive analysis of the variables over time.

		T0	T1	T3	T6
	N	10	10	10	10
VAS	**Mean**	72	38.5	58.5	70.6
	SD	19.9	21.6	26.1	21.9
	Min	40	20	10	30
	Max	90	70	85	100
KOOS_PAIN	**Mean**	38.6	60.2	51.7	44.1
	SD	17.9	18.1	21.4	17.4
	Min	11.1	25	11.1	22
	Max	63.9	86.1	88.8	83.3
KOOS_SYM	**Mean**	48.6	63.5	56.7	47.8
	SD	14.1	15.7	16.4	17.8
	Min	28.6	28.6	25	25
	Max	71.4	85.7	85.7	89.3
KOOS_ADL	**Mean**	37.2	63	51.3	47.9
	SD	17.6	22.7	15.6	14.5
	Min	7.4	8.8	25	30.9
	Max	58.8	88.2	79.4	83.4
	Mean	14.5	35	29.4	15

KOOS SPORT	**SD**	23.1	32.3	17.1	18.3
	Min	0	0	5	0
	Max	75	90	55	60
KOOS_QOL	**Mean**	22.5	36.8	31.6	32.8
	SD	11.8	15.4	22.1	17.4
	Min	6.3	0	0	12.5
	Max	43.7	56.3	81.2	75

VAS, Visual Analogue Scale; KOOS PAIN, Pain domain of the KOOS Scale; KOOS SYM, Symptoms domain of the KOOS Scale; KOOS ADL, Activities of Daily Living domain of the KOOS Scale; KOOS SPORT, Sport and Recreational Activities domain of the KOOS Scale; KOOS QOL, Quality of Life domain of the KOOS Scale.

Figure 1. Error-bar of VAS variation during study timeline.

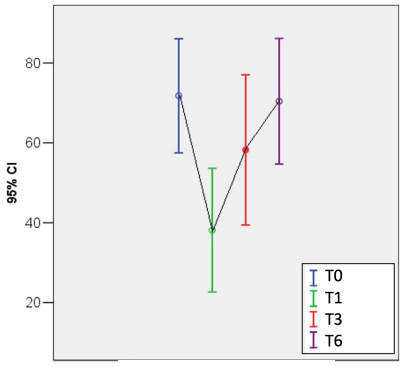


Figure 2. Error-bar of the Symptoms Domain of KOOS variation during study timeline.

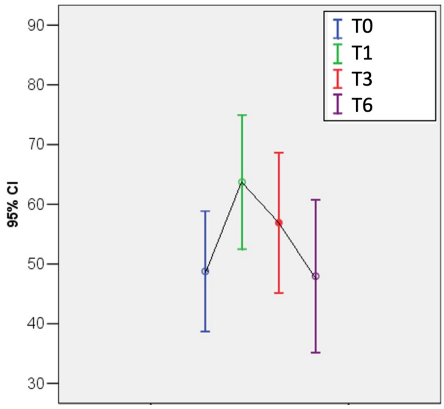


Figure 3. Error-bar of the Pain Domain of KOOS variation during the study timeline.

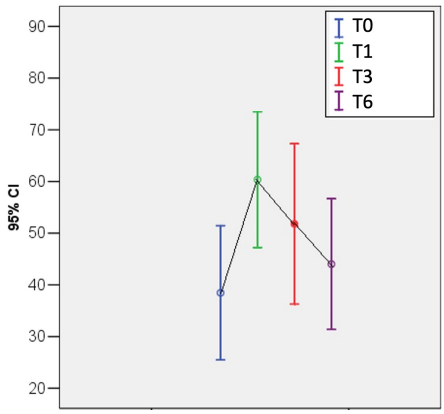


Figure 4. Error-bar of the Sports and Recreational Activities Domain of KOOS.

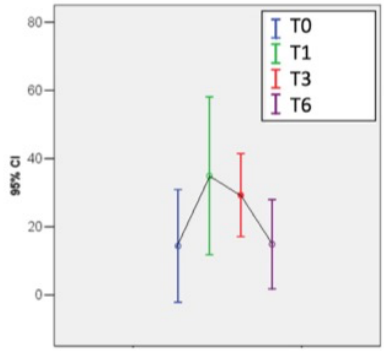


Figure 5. Error-bar of the ADL Domain of KOOS variation during the study timeline.

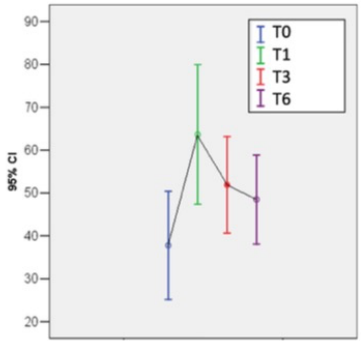
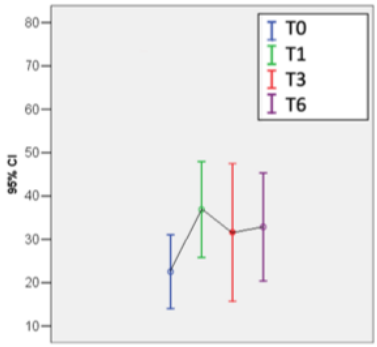


Figure 6. Error-bar of the QoL Domain of KOOS variation during the study timeline.



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