Tools for the management of knee osteoarthritis. INNOTEC

Health Technology Assessment

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Conflict of interests

The authors and experts who participated in the development of the document declare that by virtue of the methodology established by the Global Institute of Clinical Excellence - IGEC there is no conflict of interest that prevents or invalidates the development process (financial, intellectual, affiliation, or relative).

Declaration of editorial independence

Keralty Global Institute of Clinical Excellence and the authors declare that its members carried out the development of the scientific technical document in a rigorous, independent, transparent, and impartial manner.

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Thanks to the systematization of the process, the methodological approach allows the issued guidelines to take into account all the important criteria that are based on the best available evidence from research, which go beyond the efficacy and safety of the interventions and include an analysis of context, priority of the problem, values, preferences, experiences, funding and resource implications, equity, feasibility, affordability, stakeholder acceptability, sustainability and efficiency, among others.

Therefore, it is hoped that professionals, interdisciplinary care teams, as well as managers at tactical and strategic levels, take these guidelines into account to make decisions that generate value in health, within the framework of a comprehensive model centered on people, through shared decisions, which implies taking into account the evidence as well as the individual preferences, beliefs and values of the person, ensuring an understanding of the risks, benefits and consequences of different care options through open discussion, empathic and compassionate.

1. Contents

2. Abstract

Background: The need for regeneration of cartilage has become increasingly important in the fields of orthopedic medicine and traumatology. This document will focus on the evaluation of the efficacy and safety of COLTRIX® CartiRegen for the treatment of chondral lesions.

Methodology: This review was conducted based on the Methodology of rapid systematic reviews for decision-making – CEIIDS. It was conducted an evidence search from Clinical Practice Guidelines, Systematic Reviews of Evidence and Randomized Clinical Trials. The search was performed in PubMed with the last 5 years restriction (2018 to 2023).

Results: 178 records were detected, of which 18 publications were included for this evidence synthesis. The quality of evidence in these clinical practice guidelines, as assessed by AGREE domains, varies but generally demonstrates good quality with some variations in specific domains, for systematics reviews with meta-analysis the confidence was critically low and primary studies varies, with some showing low risk in certain domains but inconsistencies and uncertainties in others, including allocation concealment, blinding of the outcome assessor, handling of missing data, and outcome reporting bias. Overall, there is variability in the risk of bias across the primary studies.

Conclusions: According to the evidence included, intra-articular injections of collagen were suggested that reduce pain in patients with knee osteoarthritis in a period of less than 24 months; however, studies with greater methodological support are needed to allow a recommendation to be issued with the confidence of a high level of evidence and not only from cohort studies and systematic reviews without meta-analysis. Intra-articular injections of hyaluronic acid and stem cells are not recommended for the treatment of patients with knee osteoarthritis since they are still in the experimental phase.

Key words: osteoarthritis, knee, collagen type I, hyaluronic acid, stem cells

3.Introducción

The need for regeneration of cartilage has become increasingly important in the fields of orthopedic medicine and traumatology. This is due to the rising prevalence of injuries and degenerative conditions like osteoarthritis, patients dealing with these issues often suffer from pain, a decreased quality of life and significant medical expenses.

At present there exists a treatment gap for individuals who have symptomatic osteoarthritis but haven't responded to conservative treatments yet don't qualify for more invasive surgeries like joint replacement. This gap means that patients endure periods of debilitating pain, quality of life and substantial financial burdens. In the United Kingdom there are now over 7.4 million people aged 45 or above living with osteoarthritis and 10% may find themselves in this treatment gap that could last for more, than two decades. According to Arthritis Research UK, arthritis related workdays lost annually will increase to 25.9 million by 2030 costing the UK economy £3.4 billion each year (1).

The COLTRIX® CartiRegen comes across as a technology, in this situation. It provides a less invasive treatment option. This document will focus on the evaluation of the efficacy and safety of COLTRIX® CartiRegen for the treatment of chondral lesions.

1. PICO Question

What are the effectiveness and safety recommendations on the use of intra-articular hyaluronic acid and stem cells in the treatment of knee osteoarthritis?

Table 1. Research question according to the PICO structure

Population	People with knee osteoarthritis
Intervention	Use of purified type I collagen gel Intra-articular injections of hyaluronic acid, stem cells or any of their combinations
Comparator(s)	Placebo
Outcomes	Cartilage regeneration Functionality Pain Quality of life

2. Technology description

In the field of medicine there is a growing urgency to find solutions for regenerating articular cartilage, conditions like injuries and degenerative diseases such as osteoarthritis pose challenges for patients leading to long term pain diminished quality of life and substantial financial burdens.

COLTRIX® CartiRegen is a gel made of type I collagen that aims to improve the quality of tissue repair using techniques like micro fracture (MF)(1).

The mechanism of action for COLTRIX® revolves around its function as a purified type I collagen scaffold. Its role is to provide support and create an environment for mesenchymal stem cells derived from bone marrow (MSCs). These MSCs can differentiate and generate cartilage tissue to hyaline cartilage. In essence COLTRIX® promotes the regeneration of cartilage by offering a scaffold, for forming new cartilaginous tissue (1,2).

This collagen gel is exceptional because it acts as both a scaffold and a protective membrane creating an environment for Mesenchymal Stem Cells (MSCs) derived from bone marrow and it helps regulate cell differentiation and movement facilitating the formation of repair tissue that shares properties with hyaline cartilage(2,3).

COLTRIX® CartiRegen is a biocompatible solution that minimizes immune responses and inflammation. Moreover, it naturally degrades over time while rapidly solidifying at body temperature (37°C) with pH7(1). Its gel like structure

with small pores enhances permeability making it ideal, for three scaffolds that promote cell growth and migration (2,3).

It is also possible to combine it with living cells bone marrow concentrate (BMC) plasma (PRP) or proteins such as fibrinogen.

The Complete Cartilage Regeneration Kit (CCR) offers a comprehensive and single stage method for regenerating cartilage using bone marrow obtained from the spines. This bone marrow is then centrifuged in the operating room to produce a mixture containing MSCs and growth factors like TGF β1, VEGF, BMP2 and FGF2(1).

The CCR includes acid, thrombin, and fibrinogen prior to application on the chondral/osteocondral defect. This combination creates an environment for regeneration, Hyaluronic acid acts as a scaffold that supports the survival of chondrocytes while promoting the generation of cartilage to hyaline cartilage and enhances cartilage generation by chondrocytes, in laboratory settings and serves as an injectable Carrier (1).

The one step technique using bone marrow concentrate has shown results to matrix induced chondrocyte implantation (MACI) after 3 years of follow up, for knee treatment. Additionally, it has demonstrated outcomes compared to MF at the 5-year mark. Early evidence also indicates its potential as an option for ankle cartilage repair with functional outcome scores and low complication rates observed up to 36 months of follow up (4,5).

3. Methodology

This review was prepared based on the Methodology of rapid systematic reviews for decision-making – CEIIDS.

3.1 Search, screening, selection, and evaluation of evidence

It was conducted an evidence search from Clinical Practice Guidelines, Systematic Reviews of Evidence and Randomized Clinical Trials. The search was performed in PubMed.

The search was conducted on August 11, 2023, considering the following criteria:

- Population, intervention, comparison, outcomes according to the PICO question.
- Type of study: Clinical Practice Guidelines, systematic evidence reviews, and randomized clinical trials.
- Language: English and Spanish

- Publication time: last 5 years (2018 to 2023)
- Publication status: Results published.
- Report of results: studies that reported the outcomes of interest and that were attributable to the comparison of interest.

The search included the following terms "(("Stem Cells"[Mesh]) AND "Osteoarthritis"[Mesh]) AND "Knee"[Mesh]", the results can be found in Annex 1. Language-specific filters were used, date and type of publication. The number of references identified in the search for evidence is summarized in the PRISMA diagram, Annex 2.

A reviewer examined titles and abstracts according to predefined eligibility criteria and screened the total number of references identified in the search. From the group of preselected references, the selection of studies was made, for this; the reviewer verified that each study met the eligibility criteria by reading each publication in full text. Additionally, relevant documents found in other sources were included.

The evaluation of quality and risk of bias of the included documents was carried out using the AGREE II tool for clinical practice guidelines, AMSTAR 2 for systematic reviews, RoB for Clinical trials, and Joanna Briggs for cohort studies.

To evaluate the approval, the presence of COLTRIX® in market and adverse event reporting related to the technology, a search was conducted in several regulatory databases:

- FDA (Food and Drug Administration, United States)
- EMA (European Medicines Agency)
- FDA GUDID (Global Unique Device Identification Database, USA)
- EUDAMED (European Databank on Medical Devices, European Union):
- National Medical Products Administration of China (NMPA).
- INVIMA of Colombia

3.2 Extraction and synthesis of information

The evidence was extracted verbatim from each of the documents included and the findings were summarized narratively.

4. Results

The results of the search, screening, and selection of the evidence for this rapid review are shown in the PRISMA flowchart, Annex 2. Through the search, 178 records were detected, of which 17 publications were included for this evidence synthesis.

4.1 Evidence synthesis

Osteoarthritis disease, specifically in the knee joints, is a complex disease that is not only caused by a wear process but also by inflammatory mediators, in addition to cartilage degradation, ligament and meniscus degeneration. Pain is the characteristic symptom in people with osteoarthritis, which is why it is a clear need to generate treatment strategies that improve the quality of life in these people and delay the progress of the disease(6).

The beginning of stem cell treatment research began more than two decades ago with the injection of stem cells during chemotherapy for breast cancer, it is a promising technology that has shown results in other health conditions (7), in addition, several clinical trials have shown the use of stem cells to regenerate tissues(8). In the same way, intra-articular injections of hyaluronic acid have been created as a promising strategy to improve the properties of synovial fluid in joints with osteoarthritis with the aim of achieving pain reduction and disease progression(9).

Within the included evidence, three clinical practice guidelines issued recommendations on the use of these interventions in people with osteoarthritis of the knee. NICE, in 2022, published the diagnosis and treatment guideline for people over 16 years of age with osteoarthritis, making recommendations against injections of hyaluronic acid and stem cells specifically in knee osteoarthritis, arguing that these are technologies that, although they have shown certain benefits (from very small clinical trials), are still in the experimental phase, so they should not be used. On the other hand, there is no evidence that demonstrates an improvement in the quality of life of people who have received intra-articular injections of hyaluronic acid and no long-term benefits for corticosteroid injections(10). In fact, the update carried out for the same guidelines in 2023 does not include changes in the direction of the recommendations regarding these treatments(11).

Meta-analyses carried out by NICE comparing the effectiveness of stem cell injections versus other interventions such as hyaluronic acid, corticosteroids and placebo, in outcomes such as pain, quality of life, functionality, and adverse events show that there are few significant differences in some outcomes as shown in Table 2, such as quality of life for 3 months, decrease in pain for 3 months or more, and improvement

in physical function in different comparisons that took hyaluronic acid into account, and on the other hand, decrease in pain in stem cell therapy. However, it must be considered that these meta-analyses were carried out with one or few studies and there are some comparisons with high heterogeneity or with too wide confidence intervals(12).

Additionally, the guidelines of the American Academy of Orthopedic Surgeons in 2021 make the recommendation not to routinely use intra-articular hyaluronic acid for the symptomatic treatment of knee osteoarthritis (Strength of recommendation: moderate)(13), as well as the guidelines of the American College of Rheumatology/Arthritis Foundation of the year 2020 in which they report that from the available evidence the benefit cannot be established, in addition, the source evidence resulted in a high risk of bias, for which reason they issue the recommendation against the use of this treatment(14).

Regarding stem cells, this latest guide exposes the lack of standardization in the technique, the preparations available and the techniques used, for which reason they also advise against their use for the treatment of people with osteoarthritis of the knee or hip(14).

Table 2. NICE meta-analysis

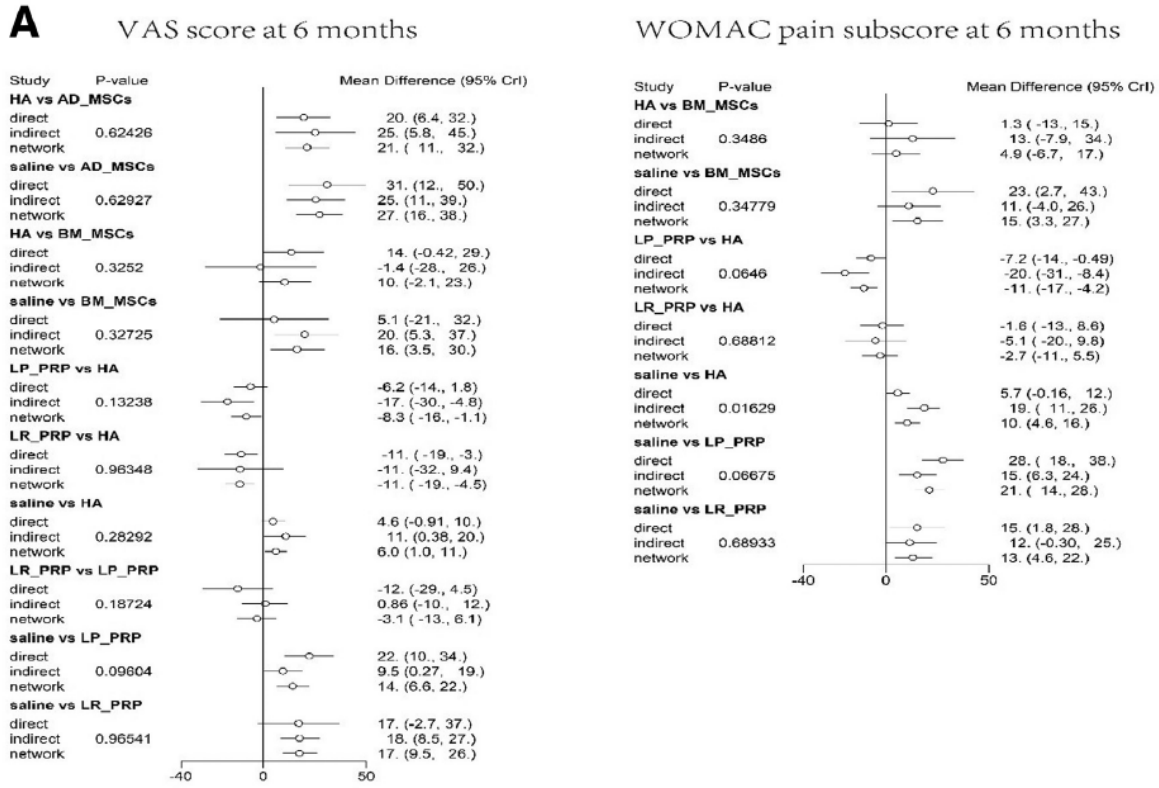
COMPARISON	OUTCOME	ESTIMATOR	95% CI	I2
HYALURONIC ACID				
Intra-articular hyaluronic acid (non-image guided) compared to intra-articular corticosteroids (non-image guided)	Quality of life (SF-36, 0-100, high is good, final values) at ≤3 months	8.00	[3.39, 12.61]	1 study
	Quality of life (SF-36, 0-100, high is good, final values) at >3 months	2.70	[-1.57, 6.97]	1 study
	Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	-0.24	[-0.86, 0.37]	96%
	Pain (KSS pain, VAS, 0-100, high is poor, final values) at >3 months	2.39	[-3.64, 8.42]	83%
	Pain (WOMAC, 0-20, high is poor, final values and change scores) at >3 months	-2.21	[-6.67, 2.25]	99%
	Physical function (WOMAC physical function, Knee society score function subscale [different scale ranges], high is poor, final values) at ≤3 months	-0.05	[-0.79, 0.68]	93%
	Physical function (WOMAC physical function, KSS function subscale [different scale ranges], high is poor, final values) at >3 months	-1.77	[-4.10, 0.56]	98%
	Serious adverse events at ≤3 months	-0.03	[-0.14, 0.07]	68%
	Serious adverse events at >3 months	0.02	[-0.02, 0.07]	87%
Intra-articular hyaluronic acid (non-image guided) compared to placebo	Quality of life (KOOS, 0-100, high is poor) at >3 months	-2.21	[-6.51, 2.10]	0%
	Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	-0.33	[-0.51, -0.15]	31%
	Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months	-0.24	[-0.42, -0.05]	68%
	Pain (VAS [different scale ranges], high is poor, final values) at ≤3 months	0.13	[-0.02, 0.28]	33%
	Pain (VAS, 0-100, high is poor, final values and change scores) at >3 months	-2.25	[-4.44, -0.06]	0%
	Pain (WOMAC, 0-20, high is poor, final values) at >3 months	-0.39	[-0.85, 0.07]	0%

	Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months	-0.15	[-0.32, 0.03]	60%
	Physical function (WOMAC-VAS disability and physical function subscale, 0-10, high is poor, final values) at ≤3 months	-1.01	[-1.54, -0.48]	0%
	Physical function (WOMAC, 0-68, high is poor, change scores and final values) at ≤3 months	-0.21	[-1.85, 1.43]	10%
	Physical function (WOMAC, 0-100, high is poor, final values) at ≤3 months	-7.00	[-12.29, -1.71]	1 study
	Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months	-0.22	[-0.45, 0.00]	70%
	Physical function (WOMAC, 0-68, high is poor, final values) at >3 months	-1.77	[-4.29, 0.75]	0%
	Physical function (KOOS activities subscale, WOMAC, 0-100, high is poor) at >3 months	-3.06	[-6.09, -0.03]	0%
	Osteoarthritis flare-up at >3 months	0.00	[-0.05, 0.05]	0%
	Serious adverse events at .3 months	0.01	[-0.02, 0.03]	0%
	Serious adverse events at >3 months	0.01	[-0.00, 0.02]	0%
STEM CELLS				
Intra-articular stem cell therapy (image guided) compared to placebo	Pain (WOMAC, 0-20, high is poor, change score) at >3 months	-1.63	[-4.23, 0.97]	1 study
	Serious adverse events at >3 months	0.00	[-0.16, 0.16]	0%
Intra-articular stem cell therapy (non-image guided) compared to intra-articular hyaluronic acid (non-image guided)	Quality of life (SF-12 physical component, 0-100, high is good, final value) at ≤3 months	4.00	[-2.88, 10.88]	1 study
	Quality of life (SF-12 mental component, 0-100, high is good, final value) at ≤3 months	-3.00	-3.00 [-10.16, 4.16]	1 study
	Quality of life (SF-12 physical component, 0-100, high is good, final value) at >3 months	5.00	[-1.88, 11.88]	1 study
	Quality of life (SF-12 mental component, 0-100, high is good, final value) at >3 months	-5.00	-11.88, 1.88]	1 study
	Pain (WOMAC [different scale ranges], high is poor, final values) at >3months	-0.65	[-1.20, -0.10]	0%
	Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	-3.10	[-9.94, 3.74]	1 study
	Serious adverse events at >3 months	0.09	[-0.12, 0.31]	79%

Intra-articular stem cell therapy (non-image guided) compared to intra-articular corticosteroids (non-image guided)	Quality of Life (KOOS quality of life, 0-100, high is good, change score) >3 months	7.60	[-11.66, 26.86]	1 study
	Pain (KOOS pain, 0-100, high is good, change score) at >3 months	3.20	[-15.08, 21.48]	1 study
	Physical function (KOOS function/daily living, 0-100, high is good, change score) >3 months	5.80	[-14.76, 26.36]	1 study
Intra-articular stem cell therapy (non-image guided) compared to placebo	Pain (WOMAC, VAS, 0-100, high is poor, change score) at ≤3 months	-15.19	[-23.44, -6.94]	0%
	Pain (WOMAC, VAS, 0-100, high is poor, change score) at >3 months	-12.83	[-21.88, -3.79]	0%
	Physical function (WOMAC, 0-100, high is poor, change score) at ≤3 months	-9.20	[-19.15, 0.75]	1 study
	Physical function (WOMAC, 0-100, high is poor, change score) at >3 months	-13.40	[-39.40, 12.60]	1 study
	Serious adverse events at >3 months	0.00	[-0.04, 0.04]	0%

Modified from: NICE 2022(12)

According to the evidence from systematic reviews, the first of them, found significant differences in pain relief in less than 6 months, as well as functionality at 6 and 12 months. In fact, considering the results of adverse events, the review authors recommend other therapies such as platelet-rich plasma, although stem cells had better results in pain relief (6-month outcome). However, the width of the confidence intervals prevents issuing a recommendation, and the comparisons included other treatments in combination with them(15).



From: Zhao 2021 (15)

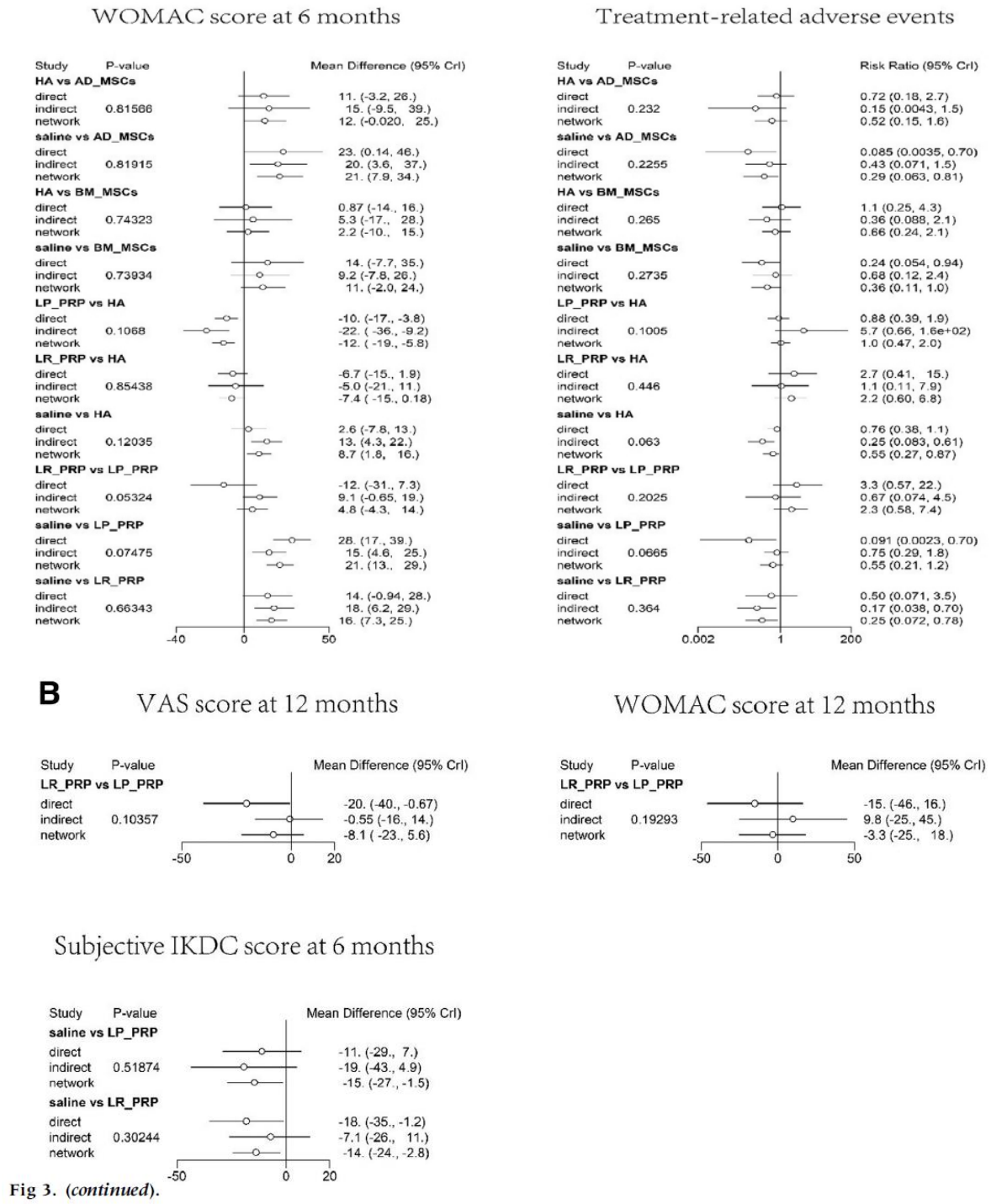


Fig 3. (*continued*).

From: Zhao 2021(15)

In a complementary way, the review published by Shang et al. in 2023 states that the ineffectiveness of stem cells, the risk of potential complications, and the limited quality of evidence from current studies preclude any recommendation for the use of stem cell products in patients with osteoarthritis of the knee. Therefore, the clinical use of stem cell therapies in the treatment of knee osteoarthritis is not supported by evidence and should be approached with caution until it is out of the clinical investigation phase(16).

It is of great importance to highlight that the publications related to the use of stem cells in the treatment of knee osteoarthritis repeatedly expose the lack of standardization in:

- The source and nature of stem cells(8)
- The quantity, dose, and mixture to apply(8,17)
- The frequency of treatment

Although cell therapy holds promise as a means of restoring local cartilage cell populations that are deficient due to injury or disease. These biologic injectables as a treatment for OA of the knee theoretically have significant potential, but as previously stated they remain investigational, and their long-term effect has not been determined(18).

On the other hand, a narrative review showed that intra-articular injections of type I collagen can stimulate chondrocytes that promote cartilage regeneration and combat the inflammatory response, which facilitates the formation of fibrous tissue, reducing symptoms and improving functionality, thus that it can become not only effective but also safe due to the few adverse events that have been found in different primary studies(19). In the same way, a cohort study published in 2020 showed positive results in the improvement of pain in the follow-up of patients who received intra-articular injections of polymerized type I collagen for at least 60 months together with the improvement of functionality and the decrease in the need for knee replacement surgery(20).

However, the source of evidence for the statements from these two documents is based on cohort studies and follow-ups carried out with pain and quality of life scales that only show improvement in these outcomes.

According to the evidence from clinical trials, one of them compared the intra-articular use of collagen with placebo to evaluate the effectiveness and safety of this intervention, founding significant results in the reduction of pain in a follow-up period of 24 weeks (Scale of VAS pain), however, no significant differences in quality of life or adverse events were found(21). As well as a clinical trial in which the effectiveness of intra-articular injections of stem cells was evaluated, in which an improvement in

the functionality of the knee joints was found without adverse events during 6 months of follow-up(22).

For its part, a clinical trial that evaluated the effectiveness of stem cell injections in 30 patients with knee osteoarthritis reported the absence of serious adverse events with a significant improvement in pain and functionality at 12-month follow-up, so it seems be an effective and safe intervention that can prevent the progression of the disease(23).

It is important to note that the comparisons made in the different trials included are not the same and that despite being injections with hyaluronic acid, stem cells or collagen scaffolds, a standardized dose, quantity, frequency, or technique is not established that allows for a recommendation regarding these interventions. Additionally, the trials are made up of small groups and follow-up times in the short or medium term, as occurs with technologies in the experimental phase, and the effectiveness and safety of these interventions have not yet been established, furthermore, as shown in the clinical practice guidelines and the confidence intervals of the different comparisons are very wide, therefore, trials with a larger sample size and better statistical power are suggested.

4.2 Approval and Adverse Event Reports for COLTRIX

A search was conducted, in both the FDA GUDID (Global Unique Device Identification Database) and the EMAs EUDAMED (European Databank on Medical Devices) to find information about the COLTRIX CartiRegen collagen gel. However, no records or registrations for this gel in those databases was found. It is worth mentioning that this gel might not be categorized as a device in those databases because of its unique nature as a collagen scaffold used for cartilage repair.

During the search the product COLTRIX CartiRegen developed by Ubiosis Co., Ltd. has obtained approval from the China NMPA (National Medical Products Administration), and they will take measures to monitor patient safety after the device is, on the market, This news about COLTRIX approval in China comes from the NMPA (National Medical Products Administration of China) with reference Updated: April 4, 2023, (24).

5. Conclusions

- According to the evidence included, intra-articular injections of collagen appear to reduce pain in patients with knee osteoarthritis in a period of less than 24 months; however, studies with greater methodological support are needed to allow a recommendation to be issued with the confidence of a high level of evidence and not only from cohort studies and narrative reviews.
- Currently available evidence, coming from clinical practice guidelines and systematic reviews, does not support the effective and safe use of intra-articular injections of hyaluronic acid, stem cells or their combinations, since they are still in the experimental phase.
- Recommendations for the rehabilitation of patients with osteoarthritis include physical therapy, guided exercise, and weight reduction. All of this provides a better environment to prevent cartilage loss, reduce pain, and delay the progression of the disease(17).
- Now, pharmacological alternatives continue to be recommended, such as the use of topical or oral medications that have shown benefits in the short and medium term and with proven safety(7,10,11).
- The challenge of the proposed interventions is not only to reduce pain but also to find management strategies that delay the progression of the disease, which is why there are still ongoing clinical trials that aim to modify the recommendations of the current guidelines(7).
- A limitation of this document is the scarcity of evidence with a high level of quality and low risk of bias, as well as the inclusion of systematic reviews without meta-analysis as a source of evidence due to the absence of clinical trials that allow statistical analysis or grading of the evidence to issue a recommendation with a high degree of confidence and with low risk of bias.

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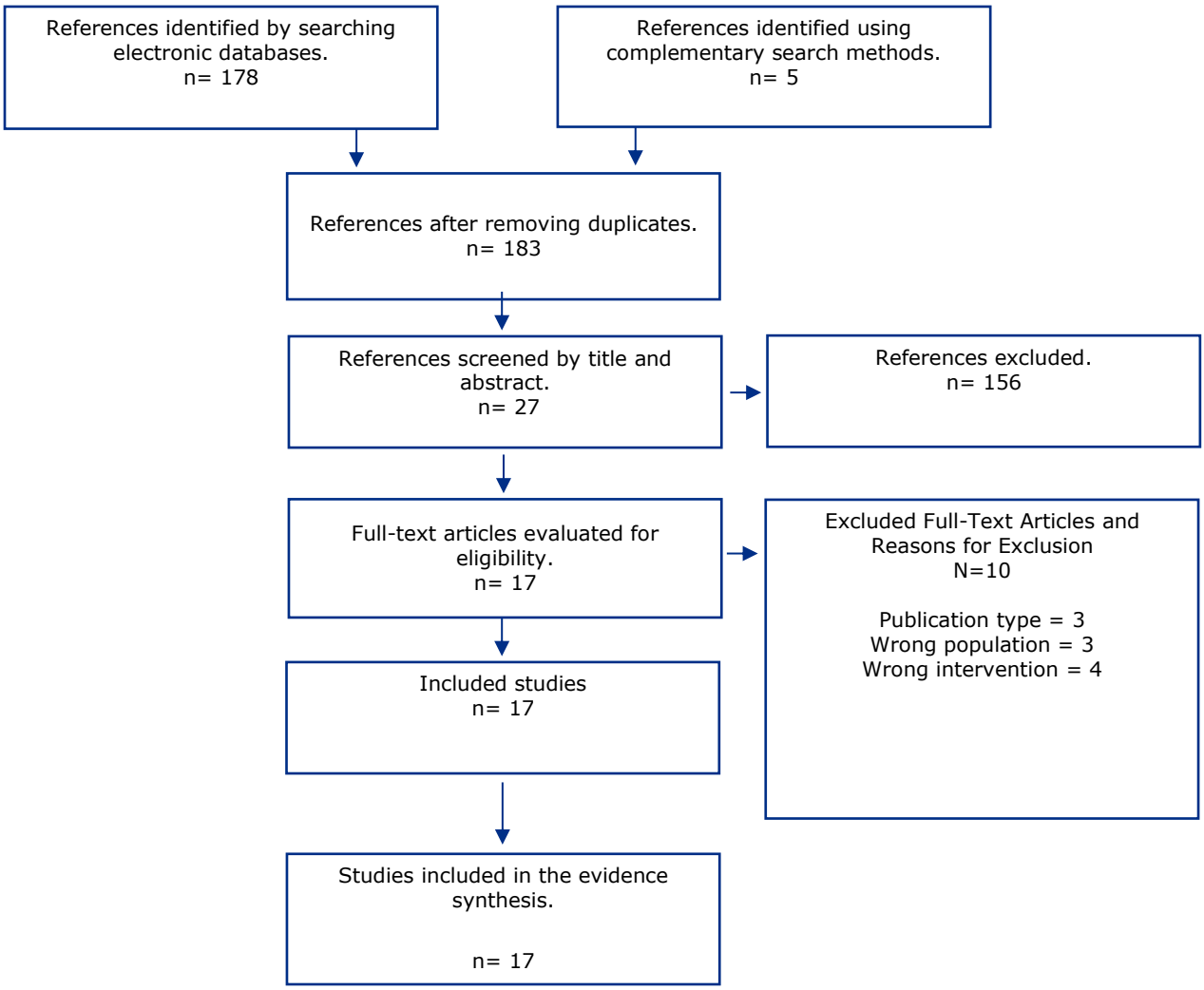
7. Annexes

Annex 1. Evidence search reports in electronic databases.

Search type	Electronic
Database	PubMed-Medline
Search date/ search date range	11/08/23 2018 to 2023
Language restrictions	English and Spanish
Other limits	Clinical Trial, Guideline, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review.
Search strategy	(("Stem Cells"[Mesh]) AND "Osteoarthritis"[Mesh]) AND "Knee"[Mesh]:
Identified references	178

Annex 2. PRISMA diagram: flow of the search, screening, and selection of studies



Annex 3. Assessment of risk of bias

AGREE II for Clinical Practice Guidelines

Clinical Practice Guidelines	domains					
	1	2	3	4	5	6
ACR2019	100%	86%	84%	83%	19%	68%
AAOS GPC 2021	92%	67%	89%	83%	63%	100%
NICE 2022	92%	86%	90%	92%	63%	100%
NICE 2023	92%	86%	90%	92%	71%	93%

AMSTAR 2 for Systematic reviews

Systematic review	AMSTAR-2
Shang,2023	LOW CRITICAL
NICE, 2023	LOW CRITICAL
Zhao,2021	LOW CRITICAL
Giorgino 2023	CRITICALLY HIGH
Tarantino 2023	CRITICALLY HIGH
Wei 2023	CRITICALLY HIGH
Vakharia 2019	CRITICALLY HIGH

ROB Tool for Randomized Clinical Trials

STUDY (Author - Year)	Bastos 2020	Freitag 2019	Kuah 2018	Lee 2019	Lee 2021
Was there adequate generation of the allocation sequence?	LOW RISK	LOW RISK	LOW RISK	HIGH RISK	LOW RISK
DESCRIPTION	randomization schedule was used to specify the allocated treatment group, and the biologist who prepared the material to be injected had restricted access to this schedule	Participants were already randomly allocated to this treatment group and yet to commence the trial were re-randomized to another trial group	The randomization schedule was prepared by a statistician using a block method, and patients were randomized 4:1 via a secure customized central website to receive either PRG or placebo. The allocation of patients to treatment groups was determined by the randomization schedule	Not mentioned	The study states that a computer-generated list of random numbers was used to allocate patients to either the BioCollagen group or the Placebo group
Was there adequate allocation concealment?	LOW RISK	HIGH RISK	LOW RISK	HIGH RISK	UNCLEAR
DESCRIPTION	biologist who prepared the material to be injected had restricted access to the randomization schedule, which specified the allocated treatment group	Participants were aware of their treatment allocation	The allocation of patients to treatment groups was determined by the randomization schedule	Not mentioned	Not mentioned
Was there blinding of the treatment administrator?	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK

DESCRIPTION	The orthopaedic surgeon, patients, and staff directly involved in the study were blinded to group assignment. Only the biologist involved with the preparation of the material to be injected knew the patient allocation	Participants were not blinded to their treatment allocation.	The intra-articular injections were administered by an independent, unblinded radiologist or sports and exercise medicine physician trained in the technique. A screen was used to ensure that the patient remained blinded to the treatment allocation	double-blinded, placebo-controlled study	BioCollagen and Placebo solutions were prepared by a pharmacist who was not involved in the clinical evaluation of the patients. The solutions were then labeled with a code number and provided to the investigator, who administered the treatment to the patients
Was there blinding of the outcome assessor?	UNCLEAR	LOW RISK	UNCLEAR	UNCLEAR	UNCLEAR
DESCRIPTION	Not mentioned for the analysis	The physician performed the analysis using a single-blinded approach, meaning they were unaware of the treatment group assignments	Not mentioned	double-blinded, placebo-controlled study, Not clear who's blinded	not provide specific information about whether there was masking of who did the analysis
Was there blinding of the recipient of the treatment?	LOW RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK
DESCRIPTION	The orthopaedic surgeon, patients, and staff directly involved in the study were blinded to group assignment	participants were not blinded to their treatment allocation	The participants, investigators, study coordinator, and study team remained blinded to the treatment allocation	randomized, double-blinded, placebo-controlled study	BioCollagen and Placebo solutions were labeled with a code number and provided to the investigator, who administered the treatment to the patients
Is there a complete handling of missing data?	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR

DESCRIPTION	unclear if missing data were handled appropriately in the analysis	not mention anything about the complete management of missing data	not mention anything about the complete management of missing data	not mention anything about the complete management of missing data	not mention anything about the complete management of missing data
Is there a risk of outcome reporting bias?	HIGH RISK	UNCLEAR	LOW RISK	UNCLEAR	LOW RISK
DESCRIPTION	The study does not provide a detailed description of all the outcomes that were measured and analyzed. It only mentions the use of the Portuguese version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) as the primary outcome measure	Patients and/or the public were not involved in the development of the research question, choice of outcome measures, design of the trial, recruitment of participants and conduct of the trial. Results of the trial will be disseminated to study participants through direct consultation with a trial clinician at completion of the trial and on publication of results.		intra-articular injection of AD-MSCs was associated with improvement in the WOMAC score and other clinical outcomes -->it does not provide information on whether all outcomes measured in the study were reported	
Is there a risk of other biases?	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

Joanna Briggs Institute for Cohort studies

COHORTE BORJA 2020				
JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES	**YES**	**NO**	**UNCLEAR**	**NOT APPLICABLE**
1. Were the two groups similar and recruited from the same population?	x			
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?				x
3. Was the exposure measured in a valid and reliable way?	x			
4. Were confounding factors identified?	x			
5. Were strategies to deal with confounding factors stated?		x		
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?		X		
7. Were the outcomes measured in a valid and reliable way?	x			
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	x			
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	x			
10. Were strategies to address incomplete follow up utilized?			x	
11. Was appropriate statistical analysis used?	x			