Matrix-associated chondrocyte implantation versus autologous chondrocyte implantation for chondral knee defects: A protocol for a systematic review and updated meta-analysis

DOI: 10.52629/jamsa.v10i1.595

Pratyush Kumar (1), Vishnu B Unnithan (2), Shyam Pandari (3)

1- Intern, Dr. Baba Saheb Ambedkar Medical College and Hospital, Delhi, India

2- House Officer, Department of Nuclear Medicine, Seth GS Medical College and KEM Hospital, Mumbai, India

3- Consultant Orthopaedician, TSRTC Hospital, Telangana, India

Corresponding author: pratyushkumar9958@gmail.com

Abstract:

Background:

Chondrocytes are essential for the smooth functioning of the knee joint. However, derangements of various metabolic processes leads to a high prevalence of insidious chondral defects which may predispose patients to osteoarthritis. This may lead to deterioration of the quality of life in physical, psychological and social domains. Though, autologous chondrocyte implantation (ACI) yields superior results in chondral defects as compared to microfractures, there has been no meta-analysis till date to quantify the clinical efficacy of various chondrocyte implantation techniques as compared to each other. Our review will synthesize current evidence on matrix-associated chondrocyte implantation versus autologous chondrocyte implantation to establish the superior technique for chondral knee defects in terms of clinical outcomes and post-operative quality of life.

Methods:

An exhaustive search will be undertaken on PubMed, Cochrane, Embase, International Clinical Trials Registry Platform (ICTRP), Trip Medical Database and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases to identify relevant studies. Primary human studies comparing matrix-associated chondrocyte implantation and autologous chondrocyte implantation in the context of knee chondral defects would be included. The primary outcome will be postoperative improvement in knee functions assessed clinically or via activity scores like International Knee

Documentation Committee (IKDC) subjective score, Lysholm-Gillquist score and Tegner Activity Score. The secondary outcomes will be radiological scores for monitoring structural improvement like Magnetic Resonance Observation of Cartilage Repair Tissue score and health-related quality of life scores.

Discussion:

This will be the first systematic review and meta-analysis in available literature comparing the clinical outcomes and post-operative quality of life in matrix-associated chondrocyte implantation versus autologous chondrocyte implantation for chondral knee defects. This review can be expected to guide clinical practice as well as research in the treatment of chondral defects of the knee.

Keywords:

Autologous chondrocyte implantation; Chondral defects, MACI, clinical efficacy, postoperative improvement, treatment outcome

Introduction

The knee joint has a very important role in the maintenance of postural stability and is subjected to severe stress frequently. [1] The range of movement coupled with the unique screw-home mechanism makes knee anatomy very complex. [2] The synovial fluid, the joint capsule, ligaments, tendons, muscles and cartilage play key roles in ensuring the maintenance of the knee joint.

Chondrocytes synthesize several cytokines and growth factors which regulate metabolic processes. [3] Derangement of these processes can lead to functional loss and structural damage, manifesting as a myriad of symptoms in patients. Patients may present with pain, joint oedema, impaired range of motion and are at a higher risk of developing osteoarthritis. [4] Self-repair is also restricted due to low cellularity and lack of vascular supply. [5]

Data from knee arthroscopies suggests that there may be a 34-62% prevalence of chondral defects with full thickness lesions being seen in 4.2-6.2% cases below the age of 40. [6, 7] This high prevalence is concerning since untreated chondral defects may lead to the development of osteoarthritis which adversely affects a patient's quality of life, economically burdening patients to the tune of thousands of dollars. [8] Advanced imaging techniques have resulted in enhanced detection of these chondral defects. [7]

However, this increased detection has not necessarily translated to rapidly improved patient outcomes as joint replacement with an artificial prosthesis has remained the go-to option to restore the patient's quality of life in osteoarthritis. Though there are established non-pharmacological, clinical and surgical guidelines, there is no conclusive mention yet on the utility of advanced bioengineering procedures like autologous chondrocyte implantation in the therapy. [9] These modern procedures may offer patients a viable long-term treatment option but more research is needed in this field.

Therapy by microfracture of the chondral defect was very common initially but the incidence of long-term complications leaves a lot to be desired. [10] Microfracture is based on the principle of migration of mesenchymal stem cells to stimulate growth of hyaline-like fibrocartilage. [11] It has been argued that supplementing

microfracture with intra-articular injections may enhance efficacy of the procedure. [12-14] However, randomized clinical trials have shown that autologous chondrocyte implantation (ACI) yields superior results in the treatment chondral defects as compared to microfracture. [15-16]

Autologous chondrocyte implantation was a novel procedure that was developed in 1994 by Brittberg et al. [17] A periosteal tibial flap was used to cover the defect using a fibrin glue. However, this commonly caused hypertrophy. Subsequently, porcine collagen was used which eliminated the need for a procedure at tibia and reduced the incidence of post-op complications. [17, 18] With the advent of latest bio-technological advancements, matrix-associated chondrocyte implantation (mACI) has been developed. [19] Autologous osteochondral transplantation, autologous matrix-induced chondrogenesis and osteochondral allograft transplantation are some other procedures which have been implemented in the treatment of chondral defects. [5]

Interestingly, though many reviews have advocated the suitability of chondrocyte implantation over microfracture, there has been no meta-analysis till date to statistically quantify the clinical efficacy of these various chondrocyte implantation techniques as compared to each other. [20] An extensive search will be undertaken in PubMed, Cochrane, Embase, International Clinical Trials Registry Platform (ICTRP), Trip Medical Database and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases to identify studies on mACI and ACI. Our review will overcome this lacuna and shall provide robust evidence on the relative superiority of these various chondrocyte implantation techniques and will guide clinical practice as well as research in the treatment of chondral knee defects.

Methodology:

This protocol adheres to Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines for new systematic reviews which included searches of databases, registries and other sources. [1] The PRISMA checklist has been supplemented in the appendix.

The studies identified in this review will be subject to inclusion based on the following criterias:

Type of Study

Only Randomized controlled trials (RCTs) or controlled clinical trials comparing the two techniques of matrix-induced autologous chondrocyte implantation (MACI) versus the original periosteum cover technique of autologous chondrocyte implantation (ACI) for treatment of symptomatic chondral or osteochondral defects of knee shall qualify to be included in the review. These eligible studies will yield us clinical (functional), radiological and health-related quality of life scores recorded on postoperative follow ups. We shall be excluding any trial which is non-randomised and possesses a threat to the quality of evidence. Literature from conference abstracts, unpublished RCTs or clinical registries shall be included if the required data needed for analysis is either available open-access or can be obtained from authors with due permission.

Type of Population

Eligible participants shall be broad to consider the relevancy of surgical procedures in various clinical settings. Patients aged equal or more than 16 years, without gender or ethnic distinction with symptomatic isolated full-thickness chondral or osteochondral defects of knee irrespective of center of study & concomitant etiology. Exclusion criteria will be extended cartilage erosion, restricted mobility, extended meniscal defect, untreated cruciate or collateral ligament laxity, untreated varus or valgus alignment, inflammation, any history of interventional procedures in the respective knee less than 1 year ago, hyaluronan injection less than 6 months ago. Incase of a heterogenous group, we will try to obtain separate data but will not categorically exclude the study if otherwise eligible. An orthopedician shall approve the final inclusion decision at these instances.

Type of Intervention

Patients who underwent a Matrix-associated autologous chondrocyte implantation (MACI) where a bioscaffold "matrix" is implanted with fibrin glue and embedded with autologous chondrocytes. It is based on ACI's good long-term track record, but a clear cut clinical superiority is yet to be demonstrated. MACI therefore is based on a membrane that acts as a cell transporter to more equally

distribute the cells with a density of 500,000 to 1,000,000 cells per cm2. Patients on concomitant non-surgical treatment modalities shall only be included if provided to both the groups or the contrast between the arms allow to delineate the net effect.

Type of Comparator

Patients who underwent an Autologous Chondrocyte Implantation With Periosteal Flap (ACI-P): ACI of the First Generation. Here a periosteal flap is excised from the tibia covering the cartilage defect (ACI-P). Fibrin glue is used to seal the bioactive chamber after it has been filled. Eligible controls in multi-arm studies will be included as well.

Type of Outcome

The primary outcome will be postoperative improvement in clinical or knee function or activity scores like subjective International Knee Documentation Committee (IKDC) score, Lysholm and Gillquist score or Tegner Activity Scores. Secondary outcomes will be radiological scores for monitoring structural improvement like Magnetic Resonance Observation of Cartilage Repair Tissue score or health-related quality of life scores. The frequency of common follow-ups will outlay the possibility of making multiple forest plots to analyze short term and long term improvement of these surgical procedures or doing a multivariate analysis if found feasible.

Search Strategy

Electronic search shall be run on PubMed, Cochrane, Embase, ICTRP, Trip Medical Database, CINHAL, Scopus with the broad spectrum keywords (to increase the possibility of least exclusion) of [(matrix-induced autologous chondrocyte implantation) OR matrix-associated autologous chondrocyte implantation) OR MACI OR mACI OR m-ACI OR (matrix AND chondrocyte implantation)] to identify studies from inception till 31st January, 2022 without any publication or language restriction. Manual searches on references of included articles and previous reviews as well as clinical trial registries shall be thoroughly searched. For Grey literature: MedRxiv, BioRxiv, AiXiv and other preprint servers will be searched.

Study Selection

Articles identified from the search results will be imported to Endnote X9 and duplicates will be removed. Eligibility screening will be done by

title and abstract of the articles by two independent reviewers. Any disagreement between the two reviewers shall be solved either by consensus or involving the third reviewer (faculty expert). All potential articles selected by screening will be sent for full-text review by both the independent reviewers and the same strategy will be followed upon disagreement. Finally, a third review will also be done by faculty experts of all included studies in consensus with the independent reviewers.

Data Extraction

Data shall be extracted to an excel sheet by a reviewer whereas the other reviewer will cross-check the entry from the original manuscript. Any disagreement between the two reviewers shall be solved either by consensus or involving the third reviewer (faculty expert). Corresponding authors shall be contacted upon lack of adequate data or in need of additional information.

We shall be extracting the following data:

1. Study Information: first author, year of publication, study location and corresponding author with details.
2. Population: Size with Mean age & sex distribution, type of defect and any concomitant disease/treatment.
3. Intervention and Comparator: m-ACI and ACI with any significant surgical notes if present
4. Outcome: Baseline and postoperative clinical/functional, radiological and quality of life scores.

Data will be obtained as Mean and standard deviation at each time point. If not available, we will try to reliably calculate the data if sufficient information is available or otherwise contact the corresponding author. The following data will be extracted via an objective data extraction form customized from Cochrane Development, Psychosocial and Learning Problems Review Group and therefore complies with Methodological Expectations of Cochrane Intervention Reviews. [20]

Risk of Bias Assessment

The revised Cochrane Risk of Bias instrument (RoB 2) will be used to assess the risk of bias in individual RCTs. For each of the domains of RoB 2, a low, high, or some concerns risk of bias will be determined by two independent

reviewers and a third faculty expert will be involved in disagreement.

Data synthesis

RevMan 5.4 will be used where the heterogeneity assessed by I^2 statistics will lead the way for a random or fixed effect analysis model. Inverse variance analysis will be done for each outcome using Mean and Standard Deviation with 95% confidence interval. Based on the possibility of sufficient power of heterogeneity, additional meta regression models might be implied.

Confidence in evidence

The strength of the evidence is assessed and qualitatively summarized based on the individual risk of bias assessment.

Discussion

Due to the immense epidemiological burden of the condition, it is important for orthopedics to be fully aware of the utility of various therapeutic procedures. The gap in literature necessitates the need for our review which will provide an insight into the efficacy of various ACI procedures. [21] This will in turn serve to improve patient prognosis as well.

We expect the sensitivity of our search to be limited by the lack of MeSH terms. To overcome this, we have used a wide range of word combinations. Also, medical databases in languages other than English would not be covered, so a language bias may exist in our findings. Nevertheless, to our knowledge, this systematic review and meta-analysis would be the first to assess the efficacy of mACI as compared to ACI. The study would also help to identify areas for future research, thus guiding clinical researchers.

References

1. Delafontaine A, Fourcade P, Honeine JL *et al.* Postural adaptations to unilateral knee joint hypomobility induced by orthosis wear during gait initiation. *Sci Rep* **8,** 830 (2018). https://doi.org/10.1038/s41598-018-19151-1

2. Kim HY, Kim KJ, Yang DS *et al.* Screw-Home Movement of the Tibiofemoral Joint during Normal Gait: Three-Dimensional Analysis. Clin Orthop Surg. 2015

Sep;7(3):303-9. https://doi.org/10.4055/cios.2015.7.3.303

3. Akkiraju H, Nohe A. Role of Chondrocytes in Cartilage Formation, Progression of Osteoarthritis and Cartilage Regeneration. *J Dev Biol*. 2015;3(4):177-192. https://doi.org/10.3390/jdb3040177

4. Houck DA, Kraeutler MJ, Belk JW *et al*. Do Focal Chondral Defects of the Knee Increase the Risk for Progression to Osteoarthritis? A Review of the Literature. Orthop J Sports Med. 2018 Oct 18;6(10):2325967118801931. https://doi.org/10.1177/2325967118801931

5. Migliorini F, Eschweiler J, Schenker, H *et al*. Surgical management of focal chondral defects of the knee: a Bayesian network meta-analysis. *J Orthop Surg Res* 16, 543 (2021). https://doi.org/10.1186/s13018-021-02684-z

6. Flanigan DC, Harris JD, Trinh TQ et al. Prevalence of chondral defects in athletes' knees: a systematic review. Med Sci Sports Exerc. 2010 Oct;42(10):1795-801. https://doi.org/10.1249/MSS.0b013e3181d9eea0

7. Camp CL, Stuart MJ, Krych AJ. Current concepts of articular cartilage restoration techniques in the knee *Sports Health*. 2014;6(3):265-273 https://doi.org/10.1177/1941738113508917

8. Xie F, Kovic B, Jin X *et al*. Economic and Humanistic Burden of Osteoarthritis: A Systematic Review of Large Sample Studies. *PharmacoEconomics* **34,** 1087–1100 (2016).

https://doi.org/10.1007/s40273-016-0424-x

9. Fuggle NR, Cooper C, Oreffo ROC, et al. Alternative and complementary therapies in osteoarthritis and cartilage repair. *Aging Clin Exp Res*. 2020;32(4):547-560. https://doi.org/10.1007/s40520-020-01515-1

10. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. Knee Surg Sports Traumatol Arthrosc. 2014 Sep;22(9):1986-96.

https://doi.org/10.10.1007/s00167-013-2676-8

11. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res*. 2001;(391 Suppl):S362-9.

12. Koh Y-G, Kwon O-R, Kim Y-S, Choi Y-J, Tak D-H. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. *Arthroscopy*. 2016;32(1):97-109.

13. Siclari A, Mascaro G, Gentili C, Kaps C, Cancedda R, Boux E. Cartilage repair in the knee with subchondral drilling augmented with a platelet-rich plasma-immersed polymer-based implant. *Knee Surg Sport Traumatol Arthrosc*. 2013;22(6):1225-34.

14. Strauss E, Schachter A, Frenkel S, Rosen J. The efficacy of intra-articular hyaluronan injection after the microfracture technique for the treatment of articular cartilage lesions. *Am J Sports Med*. 2009;37(4):720-6.

15. Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO, Emans P, Podskubka A, Tsuchida A, Kili S, Levine D, Brittberg M; SUMMIT study group. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. Am J Sports Med. 2014 Jun;42(6):1384-94. https://doi.org/10.1177/0363546514528093

16. Bachmann G, Basad E, Lommel D, Steinmeyer J. Die MRT in der Verlaufskontrolle nach matrixgestützer autologer Chondrozytenimplantation (MACI) und Mikrofrakturierung [MRI in the follow-up of matrix-supported autologous chondrocyte transplantation (MACI) and microfracture]. Radiologe. 2004 Aug;44(8):773-82. German. https://doi.org/10.1007/s00117-004-1084-y.

17. Brittberg M, Lindahl A, Nillson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331:889-95.

18. Tuan RS. A second-generation autologous chondrocyte implantation approach to the treatment of focal articular cartilage defects. *Arthritis Res Ther* 2007; **9:**109 https://doi.org/10.1186/ar2310

19. Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi, B, Schmitt, H. (2010). Autologous Chondrocyte

Implantation Using the Original Periosteum-Cover Technique Versus Matrix-Associated Autologous Chondrocyte Implantation: A Randomized Clinical Trial. 38(5), 924–933. https://doi.org/10.1177/0363546509351499

20. The Cochrane Collaboration. Data extraction forms. Cochrane Developmental, Psychosocial and Learning Problems. https://dplp.cochrane.org/data-extraction-forms. Published 2014. Accessed February 6, 2022.

21. Bedi A, Feeley BT, Williams RJ 3rd. Management of articular cartilage defects of the knee. J Bone Joint Surg Am. 2010 Apr;92(4):994-1009. https://doi.org/10.2106/JBJS.I.00895.