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Outcomes of Clinical Scores and Magnetic Resonance Imaging After Microfracture Treatment With and Without Scaffold Augmentation for Focal Chondral Lesions in the Knee: A Systematic Review and Meta-analysis of Randomized Controlled Trials (RCTs)

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2024 and was last updated on 11 May 2024.

INTRODUCTION

Review question / Objective The review objective will be determined by the outcomes of clinical tests and magnetic resonance imaging following microfracture treatment, with or without scaffold augmentation, for focal chondral lesions in the knee.
The PICOT framework was initially introduced in the preliminary stages of the research:
P (Problem): focal chondral lesion in the knee
I (Intervention): one-step surgical procedure
C (Comparison): Microfractures (MFX) versus Autologous Matrix-Induced Chondrogenesis (AMIC) in randomized controlled trials (RCTs)
O (Outcomes): clinical scores, MRI analysis and possible side-effects or complications
T (Timing): at least 12-months follow-up.

Rationale Chondral and osteochondral lesions in the knee joint are widespread and commonly have a significant impact on individuals' overall well-being and functional capacity. If left untreated, these cartilage injuries can progress to osteoarthritis (OA), which greatly affects both individuals and society, leading to substantial impacts on healthcare and workforce productivity. Since human articular cartilage has limited natural healing capabilities, it's unrealistic to expect damaged tissue to heal on its own. Thus, there is an urgent need for innovative treatment options to protect these joints and delay the need for joint replacement. Throughout the years, various approaches to treating this condition have been developed and refined. Surgical options range from simple techniques like microfracture (MF) or subchondral drilling to more advanced regenerative methods, offering a range of interventions for this condition. Currently, the primary surgical standard of care for cartilage lesions involves arthroscopic debridement or microfracture. This involves removing unstable cartilage fragments (debridement) and creating deep perforations in the subchondral bone (microfracture) to stimulate the bone marrow's cellular components to aid in joint surface repair. Another treatment avenue involves implantation techniques such as autologous chondrocyte

implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), and mosaicplasty. While microfracture is considered a standard approach, its use is limited due to well-known constraints. It is most effective in patients under 40 years old, with a lesion size less than 4 cm^2, and a symptom duration of less than 1 year. Additionally, long-term follow-up studies on microfracture outcomes indicate that clinical improvements tend to diminish over time, typically after 2 to 3 years, due to tissue degradation. Consequently, the quality of cartilage repair becomes unpredictable, often resulting in fibrocartilage formation after microfracture. Recently, numerous randomized controlled trials (RCTs) have emerged comparing MF with other cartilage regenerative techniques. However, there's a lack of meta-analyses comparing the effectiveness of thesetechniques.

Condition being studied The objective of this study was to conduct meta-analyses using RCTs to compare the effectiveness of MF with multilayer biomaterials (scaffolds) in treating osteochondral lesions in the knee. This study stands out as the first of its kind, as it uniquely compares publications with the highest strength of evidence (RCTs) and examines their outcomes.

METHODS

Search strategy An extensive systematic exploration of literature was conducted across PubMed and EMBASE databases in pursuit of peer-reviewed articles concerning matrix-induced chondrogenesis with comparison of microfractures alone for the treatment of focal chondral defects in the knee in randomized clinical trials according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines which consist of a 27-points checklist and a flow-diagram. A standardized selective protocol was formulated for data extraction. Both authors (K.P. and M.S.) independently, manually, extracted the data. The inquiry aimed to identify relevant studies published between 1945 and October 2023. This was achieved by employing varied combinations of specific search terms, including: microfracture, MFX, autologous matrix-induced chondrogenesis, AMIC, scaffold, matrix, arthroscopy, knee, chondral defect, randomized clinical trials. After identifying related articles, a thorough review of all references was conducted to seek out further relevant publications. Any disagreements were solved by a third author (M.D.). Only studies which clearly stated one step surgical procedure were eligible.

Participant or population Studies of adult participants with focal chondral lesions in the knee qualified for the one-step arthroscopic procedure.

Intervention Autologous matrix induced chondrogenesis (AMIC) repair of chondral defects of the knee in a single surgical procedure.

Comparator Microfractures (MFX) for the chondral defects of the knee in a single surgical procedure.

Study designs to be included This review will include only published randomised controlled trials (RCTs) in peer-reviewed journals.

Eligibility criteria Articles were considered for inclusion if they met each of the following criteria:
(1) clinical studies comparing effects of the microfractures alone versus matrix-induced chondrogenesis in the human knee (one step procedures)
(2) randomized clinical trials
(3) publications written in English
(4) publication in peer-reviewed journal

The exclusion criteria were as follows:
(1) retrospective studies, quasi-RCT papers, case reports, letters etc. (Level of Evidence lower than 2)
(2) animal or in vitro studies
(3) trials that containing either the MFx alone or AMIC alone, while comparing them to alternative methods such as ACI, OATs, etc.
(4) papers including non-surgical methods
(5) patients less than 18 years old
Prospero identified 7 ongoing systematic reviews related to diverse aspects of knee cartilage defects. However, none of these reviews include a systematic review of randomized controlled trials (RCTs) similar to the scope of this paper.

Information sources For a comprehensive literature review, the PubMed and EMBASE databases was searched. In addition, the reference lists of studies meeting the inclusion criteria was reviewed to identify further relevant research. Eligibility screening of references was conducted independently by two researchers.

Main outcome(s) The outcome parameters included, depends on the particular RCT, Knee Injury and Osteoarthritis Outcome (KOOS) Score, International Knee Documentation Committee (IKDC) Score, Cincinatti Score, Tegner Activity Scale Score, International Cartilage Repair Society (ICRS) Score, Visual Analog Scale (VAS) Score, MRI analysis and potential complications. The characteristics documented for each eligible study encompassed the first author, publication title,

publication year, intervention, case count, patient gender distribution, average patient age, average patient BMI, follow-up duration, lesion size and scaffold type (AMIC procedure).

Quality assessment / Risk of bias analysis Each RCTs has been analysed for the quality with Jadad scale score and Coleman methodology score. All the data was checked by the third reviewer. (M.K.) This study exclusively involved Randomized Controlled Trials (RCTs), prompting the utilization of the RoB 2 Cochrane critical bias tool. This tool assesses risk across five domains (1) the randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result) and categorizes it as low, high, or indicating some concerns. The critical appraisal process was independently carried out by two reviewers (K.P. and M.S.).

Strategy of data synthesis We will conduct a meta-analysis to combine data from individual studies only when appropriate. Continuous data will be expressed as the mean difference (MD) with a 95% confidence interval (CI), while dichotomous data will undergo analysis using a random effects method to calculate the summary risk ratio (RR) with a 95% CI. If a high level of clinical heterogeneity is anticipated due to variations in study design, including interventions, intervention parameters, outcome measures, and trial settings, we will employ a random effects model. Conversely, a fixed effects model will be utilized otherwise. In situations where conducting a meta-analysis is not feasible, we will provide a narrative description of the results. Statistical significance will be set at $p<0.05$.

Subgroup analysis If we find substantial heterogeneity (I^2 more than 50%), we will investigate the possible causes and carry out subgroup analyses if appropriate.

Sensitivity analysis Sensitivity analysis will be conducted by excluding the included RCTs at high risk of bias for any one or more of selection, attrition, or detection bias. The meta-analysis will be undertaken again after removing the lower-quality studies. The results of syntheses will be compared and discussed according to the pooled effect size.

Language restriction The article published in English will be considered for inclusion.

Country(ies) involved Poland.

Keywords microfracture, MFX, autologous matrix-induced chondrogenesis, AMIC, scaffold, matrix, arthroscopy, knee, chondral defect, randomized clinical trials.

Dissemination plans The article with the results of syntheses is planned to be submitted to an international peer-reviewed journal with an impact factor.

Contributions of each author

Author 1 - Karol Pałka - conceiving the review; designing the review; data collection; data management; analysis of data; interpretation data; writing the protocol.
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