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SYSTEMATIC REVIEWS

Does progress in microfracture techniques necessarily translate into clinical effectiveness?

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Abstract

BACKGROUND

Multitudinous advancements have been made to the traditional microfracture (MFx) technique, which have involved delivery of various acellular 2nd generation MFx and cellular MFx-III components to the area of cartilage defect. The relative benefits and pitfalls of these diverse modifications of MFx technique are still not widely understood.

AIM

To comparatively analyze the functional, radiological, and histological outcomes, and complications of various generations of MFx available for the treatment of cartilage defects.

METHODS

A systematic review was performed using PubMed, EMBASE, Web of Science, Cochrane, and Scopus. Patients of any age and sex with cartilage defects undergoing any form of MFx were considered for analysis. We included only randomized controlled trials (RCTs) reporting functional, radiological, histological outcomes or complications of various generations of MFx for the management of cartilage defects. Network meta-analysis (NMA) was conducted in Stata and

Cochrane's Confidence in NMA approach was utilized for appraisal of evidence.

RESULTS

Forty-four RCTs were included in the analysis with patients of mean age of 39.40 (± 9.46) years. Upon comparing the results of the other generations with MFX-I as a constant comparator, we noted a trend towards better pain control and functional outcome (KOOS, IKDC, and Cincinnati scores) at the end of 1-, 2-, and 5-year time points with MFx-III, although the differences were not statistically significant ($P > 0.05$). We also noted statistically significant Magnetic resonance observation of cartilage repair tissue score in the higher generations of microfracture (weighted mean difference: 17.44, 95% confidence interval: 0.72, 34.16, $P = 0.025$; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. There was a trend towards better defect filling on MRI with the second and third generation MFx, although the difference was not statistically significant ($P > 0.05$).

CONCLUSION

The higher generations of traditional MFx technique utilizing acellular and cellular components to augment its potential in the management of cartilage defects has shown only marginal improvement in the clinical and radiological outcomes.

Key Words: Cartilage injury; Microfracture; Mesenchymal stem cells; Platelet-rich plasma; Bone marrow aspiration concentrates; Clinical outcome; Radiological outcome; Meta-analysis; Network meta-analysis

Core Tip: Chondral lesions have been reported in 60% of patients undergoing arthroscopic procedures of the knee; and such defects are described as one of the leading causes of chronic knee pain. As compared with the other cartilage restoration strategies, microfracture (MFx) is relatively cost-effective, simple, minimally-invasive and may also be performed in a single stage. Nevertheless, recent studies have demonstrated that modifications of the traditional MFx technique, such as the use of synthetic and autologous biological adjuvants may enhance the repair tissue quality, resilience, and overall efficacy of the procedure. Based on the current network meta-analysis we could conclude that the use of acellular and cellular adjuvants has shown only marginal improvement in the clinical (pain and functional scores) and radiological outcome in patients undergoing microfracture for cartilage defects of the knee. The safety and efficacy of the higher generation MFx procedures are also clearly evident from our review. However, there is a substantial potential for further improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques to achieve demonstrable significant outcome improvement.

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INTRODUCTION

Lesions of the articular cartilage of the knee remain a challenging clinical entity in view of the limited capacity of the cartilaginous tissues to heal and potential progression to chronic degenerative arthritis[1]. The deficient endogenous cartilage repair mechanism has been attributed to the poor recruitment of regenerative cells into the area of cartilage defect[2]. Based upon the theory of marrow stimulation by subchondral drilling[1], Steadman *et al*[3] popularized the concept of microfracture (MFx) technique, whereby the migration of the growth factors and mesenchymal stem cells (MSCs) across the subchondral bone stimulates the development of the hyaline-like fibrocartilage. As compared with the other cartilage restoration strategies, MFx is relatively cost-effective, simple, minimally-invasive and may also be performed in a single stage[4]. Despite still being regarded as the gold-standard first-line treatment for cartilage deficiencies of the knee, there are concerns regarding their long-term outcomes and durability of the restored fibrocartilage[5,6]. In this context, alternate cartilage restoration procedures such as autologous chondrocyte implantation (ACI), osteoarticular transfer system and osteochondral allograft transplantation have been advocated as the better treatment strategies in the recent years. In fact, the United Kingdom National Institute for Health and Care Excellence, in a recent assessment, has recommended for the abandonment of MFx in favor of ACI in the management of articular knee defects [7-11].

Nevertheless, recent studies have demonstrated that modifications of the traditional MFx technique, such as the use of synthetic and autologous biological adjuvants may enhance the repair tissue quality, resilience and overall efficacy of the procedure[7,11]. Some researchers have purported that the suboptimal efficacy of the traditional marrow stimulating techniques may be attributed to the insufficient concentrations of MSCs and growth factors getting released from

subchondral marrow. To circumvent this limitation, it has been proposed that supplementation of MFx with intra-articular adjuvants in the form of platelet-rich plasma (PRP) or hyaluronic acid (HA) can improve the outcome[12-18]. In addition, augmentation of defect with scaffolding matrix or cell-free polymer-based implant can provide a bioreactor-like structure, over which the marrow elements get trapped, concentrated and thereby, facilitate the restoration of an effective cartilage layer[19-21]. MFx has also been combined with diverse cellular additives like bone marrow aspiration concentrates (BMAC), MSCs, and peripheral blood stem cells (PBSCs). While individual studies on these biological augmentation [popularly described as "microfracture plus" (MFx+)] techniques have demonstrated encouraging histological and clinical outcomes, our understanding regarding these techniques has been limited by substantial heterogeneity among the study cohorts and paucity of high quality, prospective trials.

The purpose of our study was to consolidate the available evidence; compare the clinical, functional and radiological outcomes of three different generations of MFx techniques (traditional MFx, MFx + acellular additives, and MFx + cellular additives); and to provide the best recommendations on their relative efficacies, advantages, complications and pitfalls in the management of cartilaginous defects of the knee joint.

MATERIALS AND METHODS

PROSPERO (International prospective register of systematic reviews) registration (CRD42022338329) was obtained for the study. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) for Network Meta-analysis (NMA) guidelines[22] were followed for the conduction and reporting of the study.

Search strategy

PubMed, EMBASE, Medline, Cochrane, and Scopus electronic databases were used for literature search. The search was performed by three reviewers independently. The search strategy was built using the MeSH terms and corresponding keywords for knee cartilage defects and their different treatment methods with related complications, employing different boolean operators, as required. The model search strategy is described in Supplementary Table 1 following the PRESS guidelines[23].

The following PICOTS criteria were used for the inclusion of studies: (1) Population: Patients with cartilage defects; (2) Intervention: Treatment methods including various generations of MFx technique; (3) Comparator: Placebo or one of the alternate aforementioned treatment methods; (4) Outcome: Functional, radiological, histological outcome, or complications; (5) Time frame: Inception to 2022; and (6) Study type: Randomized controlled trials (RCTs).

Prospective non-randomized studies, retrospective studies, studies without comparator groups, and pre-clinical or animal model studies were excluded. Disagreements on decisions during the article selection were resolved through discussions among the authors. De-duplication of the articles screened from electronic databases was done using citation manager-Zotero. References of the articles included for the study were screened manually to identify the studies missed during the primary search.

Extraction of data

Cochrane Consumers and Communication Group recommendations were followed for data extraction from the included studies. The following were extracted, and a master chart was prepared: (1) Study characteristics: Author name, country, publication year, number of patients in the study; (2) Baseline characteristics: Age for the individual treatment arms, gender proportions, cartilage defect size, interventions analyzed, and duration of follow-up; (3) Functional outcomes: Visual Analog Scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index score, Tegner score, Lysholm score, International Knee Documentation Committee (IKDC) score, Cincinnati score, and Knee Osteoarthritis Outcome Scale (KOOS) score; (4) Radiological outcomes: Magnetic resonance observation of cartilage repair tissue (MOCART) score, and successful magnetic resonance imaging (MRI)-based defect filling (≥ 2/3rd of the defect); and (5) Complications: Adverse events and failures (patient requiring revision surgeries).

Data extraction was performed independently by two reviewers. The different generations of MFx techniques, described in accordance with the ORG classification, include: First-generation MFx (MFX-I) representing the traditional MFx technique; second-generation MFx (MFX-II) involving MFX-I combined with acellular additives [such as PRP, HA, collagen, and procedures such as autologous matrix-induced chondrogenesis (AMIC)]; and third-generation MFx (MFX-III) involves combining MFX-I with cellular additives such as MSCs, BMAC, PBSCs, and stromal vascular fraction (SVF) [24].

We anticipated heterogeneity among the diverse studies in the duration of follow-up for the analysis of outcome measures. Therefore, we analyzed individual outcomes at short-term (1 years and 2 years), intermediate-term (5 years), and if available long-term (≥ 10 years), based on the available data at individual time points for the outcome concerned. The risk of bias of included studies was analyzed RoB2 tool from Cochrane group[25]. It was agreed upon that studies with a high risk of bias would be excluded from the study.

Statistical analysis

Relative effects of various treatment methods used in the management of cartilage defects were compared using NMA. Any bias in the outcome reporting of pairwise meta-analyses was reduced by employing multi-variate meta-analytic strategy[26]. Stata (16.1, Stata Corp LLC) was employed for the analysis. The outcomes, adjusted for the number of studies and number of subjects involved in the individual arms, were plotted into a network map. The difference between the direct effect (obtained by head-to-head comparisons) and the indirect effect estimates for the outcomes was used to

assess the global inconsistency in the network. If a treatment belonged to a closed loop of evidence in the network (with both direct and indirect effects available), their difference was calculated along with their 95% confidence intervals (95%CI) and *P* values. The *P* values estimated the likelihood of conflict to be attributable to chance. A $P \leq 0.05$ was considered to be suggestive of inconsistency; and the inconsistency model of NMA was utilized. The inconsistency was further explored with sensitivity analysis using the network side-split method[27]. If $P > 0.05$, a consistency model of NMA was employed.

Forest plot, using the pooled log odds ratio (OR) or weighted mean difference (WMD), was constructed for reporting the events and continuous outcomes (along with their 95%CI) for the individual arms in the network in order to demonstrate their effect on the outcome analysed (as compared to a constant comparator). We also described an individual pairwise comparison within the network. Random effects model of analysis using the common variance approach was employed in view of the heterogenicity in involved treatment arms[28]. Funnel plot for the outcomes in the included studies was employed for assessing the publication bias. CINeMA approach[29] using CINeMA app[30] was employed to analyse the confidence of the evidence generated.

RESULTS

Overall, 9416 articles were shortlisted for initial screening. De-duplication resulted in 3584 articles. Title and abstract screening excluded 3231 articles. Among them, 353 articles qualified for full-text review; and 44 eligible RCTs[4,9,13,15,19,20,31-68] with 2629 included patients qualified for inclusion in the study. PRISMA flow diagram for the inclusion of studies is shown in Figure 1.

The included studies reported at least one of the generations of MFx employed in cartilage defect management. The baseline characteristics of the studies included in the network are presented in Table 1. Norway ($n = 6$), Germany ($n = 5$), and United States ($n = 5$) were the leading countries reporting the highest number of RCTs in the field. The network plot has been presented in Figure 1. The network had 36 possible pair-wise comparisons, among which, 14 had direct evidence data. The network had 42 two-armed studies and 2 multi-armed studies. We did not find significant variability among the characteristics of the included patients in the network concerning age and gender proportions. The mean age of the patients included in the trials was 39.40 (± 9.46) years. The mean follow-up in the included trials ranged between 1 and 15 years.

Quality assessment

None of the included studies demonstrated high risk of bias to warrant exclusion from the study. The risk of bias in the pairwise comparisons is presented in Supplementary Figure 1. We did not find any significant publication bias using the funnel plot for most of the outcome measures analyzed. When publication bias was noted, we adjusted using the "trim and fill" method to identify the missing studies and their effects on the overall estimate. We did not find any significant impact of the missing studies on the overall outcomes, as shown in Supplementary Figure 2.

Network analysis results

We performed a pooled NMA using a frequentist approach to every outcome of interest. Among all the treatment arms in the network, MFX-I had high data strength as compared with all the other comparators (as shown in the network plots in Supplementary Figure 3). Therefore, MFX-I is taken as the constant comparator and all the outcomes have been reported in comparison to the performance of MFX-I. The outcomes have been analyzed in terms of pain, functional outcomes, radiological outcomes, adverse effects, and failures.

Pain: Inference from the VAS score is taken into consideration for pain outcomes. VAS score was reported at one year in 13 studies[4,15,33,38,41,44,45,49,53,55-58] involving 676 patients, at two years in 10 studies[4,15,33,38,41,45,50,53,57,68] involving 690 patients and at 5 years in 3 studies[39,41,54] involving 297 patients. The pooled forest plot of the VAS score outcome based on the aforementioned follow-up time points is presented in Figures 2, 4, and 5 respectively. Although we did not note a statistically significant improvement in the pain reduction with the advancements to the traditional MFx, the SUCRA ranking of the interventions were consistent in favouring the higher generations in the following order MFX-III > MFX-II > MFX-I as shown in Table 2.

Functional outcomes: The functional outcomes were reported using KOOS, Lysholm score, IKDC score, and Cincinnati score. Figure 2 shows the pooled forest plot of various scores. KOOS score was reported at one year in 8 studies[32,33,44,46,51,55-57] involving 569 patients, and at 2 years in 4 studies[32,33,51,57] involving 361 patients. Lysholm score was reported at 1 year in 10 studies[4,33,35,41,44,47,48,53,59,65] involving 499 patients, and at 2 years in 8 studies[4,15,33,39,41,47,53,59] involving 516 patients. IKDC score was reported at 1 year in 15 studies[15,35,37,43-45,56-60,64,66,67] involving 631 patients, at 2 years in 13 studies[15,37,39,43,45,50,57-59,64,66-68] involving 782 patients, and at 5 years in 4 studies[39,54,58,59] involving 295 patients. Cincinnati score was reported at 1 year in 3 studies[31,38,65] involving 117 patients, and at 2 years in 4 studies[31,38,39,50] involving 349 patients.

The functional outcomes reported at 1, 2, and 5-year time points using the aforementioned scores were clubbed together for the sake of understanding (despite the limitation of such an approach), in view of the heterogenicity in the reporting of functional outcomes among the reviewed studies.

One-year functional outcomes: The pooled forest plot of the functional outcomes, sub-grouped based on the individual scores at 1 year, is presented in Figure 2. We observed statistically significant outcome in the higher generations of MFx

Table 1 Characteristics of included studies in the network meta-analysis, each row depicts the individual comparator arm in the studies included

Ref.	Country	Study design	Sample size		Treatment		Mean age		Female		Mean defect size		Follow-up (months)
			Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	
Volz *et al*[31], 2017	Germany	RCT	34	13	AMIC	Microfracture	40.0	36.5	7	3	3.9	2.9	60
Niemeyer *et al* [32], 2019	Germany	RCT	52	50	MACI	Microfracture	36.0	37.0	19	22	2.7	2.4	24
Fossum *et al* [33], 2019	Norway	RCT	21	20	ACI-C	AMIC	37.2	38.3	7	12	4.9	5.2	24
Ulstein *et al*[34], 2014	Norway	RCT	11	14	Microfracture	AOT	31.7	32.7	11	9	2.6	3.0	120
Visna *et al*[35], 2004	Czech Republic	RCT	25	25	Autologous chondrograft transplantation	Microfracture	29.4	32.2	7	9	4	3.3	12
Assche *et al*[36], 2010	Belgium	RCT	33	34	ACI-P	Microfracture	34.0	34.0	11	10	2.5	2.3	24
Saw *et al*[37], 2013	United States	RCT	24	25	Microfracture with HA	Microfracture with PBSC	42.0	38.0	17	15	NA	NA	18
Anders *et al*[38], 2013	Germany	RCT	22	8	AMIC	Microfracture	41.0	38.0	17	15	3.7	3.5	24
Lee *et al*[15], 2013	Republic of Korea	RCT	25	24	Microfracture	Microfracture with PRP	46.0	46.0	10	10	3.0	3.0	24
Brittberg *et al* [39], 2018	Sweden	RCT	65	63	MACI	Microfracture	38.0	34.0	23	20	5.1	4.9	60
Lim *et al*[40], 2012	South Korea	RCT	30	22	Microfracture	AOT	32.9	30.4	12	10	2.7	2.7	60
				18		ACI-P		25.1		8		2.8	60
Knutsen *et al* [41], 2007	Norway	RCT	40	40	ACI-P	Microfracture	33.3	31.1			5.0	5.0	60
Knutsen *et al* [42], 2016	Norway	RCT	40	40	ACI-P	Microfracture	33.3	31.1			5.0	5.0	180
Liu *et al*[43], 2021	Taiwan	RCT	10	5	Kartigen	Microfracture	54.8	67.8	5	3	2.9	1.0	24
Yoon *et al*[44], 2020	Republic of Korea	RCT	20	10	ACI-CCP	Microfracture	41.5	47.2	6	7	3.5	2.5	12

Kon *et al*[45], 2018	Italy	RCT	51	49	Collagen HA	Microfracture	34.0	35.2	15	18	3.4	3.4	24
Vanlauwe *et al* [46], 2011	Belgium	RCT	51	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	60
Stanish *et al*[20], 2013	Canada	RCT	41	39	Microfracture with BST-CarGel	Microfracture	35.1	37.2	18	14	NA	NA	12
Basad *et al*[47], 2010	Germany	RCT	40	20	MACI	Microfracture	33.0	37.5	15	3	7.0	7.0	24
Solheim *et al* [48], 2018	Norway	RCT	20	20	Microfracture	Mosaicplasty	35.0	31.0	6	6	4.0	4.0	180
Bisicchia *et al* [49], 2020	Italy	RCT	20	20	Microfracture with SVF	Microfracture	49.8	46.1	8	7	3.2	3.1	12
Saris *et al*[50], 2014	Netherlands	RCT	72	72	MACI	Microfracture	34.8	32.9	27	24	4.9	4.7	24
Saris *et al*[51], 2008	Netherlands	RCT	57	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	12
Saris *et al*[9], 2009	Netherlands	RCT	57	61	ACI-P	Microfracture	33.9	33.9	22	20	2.6	2.4	36
Qiao *et al*[52], 2020	China	RCT	10	10	Microfracture	Microfracture with HA	62.3	59.7	7	5	4.0	4.0	12
				10		Microfracture with MSC		62.0		7		4.0	12
Nguyen *et al* [53], 2017	Vietnam	RCT	15	15	Microfracture with SVF	Microfracture	58.6	58.2	12	12	NA	NA	18
Lim *et al*[54], 2021	Republic of Korea	RCT	43	46	Microfracture with MSC	Microfracture	55.3	54.4	28	30	4.9	4.0	60
Venosa *et al*[55], 2022	Italy	RCT	19	19	Microfracture with PRP	Microfracture with MSC	56.4	55.8	7	10	1.0	1.0	12
Shive *et al*[19], 2015	Canada	RCT	34	26	Microfracture with BST-CarGel	Microfracture	34.3	40.1	12	12	2.4	2.0	60
Koh *et al*[13], 2016	Republic of Korea	RCT	40	40	Microfracture with MSC	Microfracture	39.1	38.4	24	26	4.8	4.6	24
Knutsen *et al*[4], 2004	Norway	RCT	40	40	ACI-P	Microfracture	33.0	31.1	16	16	5.1	4.5	24
Kim *et al*[56], 2017	South Korea	RCT	14	14	Microfracture	Microfracture with Collagen	55.7	55.4	0	1	2.9	3.6	12
Kim *et al*[57],	South Korea	RCT	48	52	Microfracture	Microfracture	51.7	48.9	9	12	4.6	3.9	24

2020						with Collagen							
Kane *et al*[58], 2018	United States	RCT	21	9	Neocart	Microfracture	41.4	38.8	2	3	2.2	1.7	60
Ibarra *et al*[59], 2021	United States	RCT	24	24	MACI	Microfracture	33.7	35.8	7	10	1.9	1.7	72
Hashimoto *et al* [60], 2019	Japan	RCT	7	4	Microfracture with MSC	Microfracture	42.6	46.3	4	0	3.0	4.4	12
Gudas *et al*[61], 2006	Lithuania	RCT	28	29	AOT	Microfracture	24.6	24.3	10	12	2.8	2.7	36
Gudas *et al*[62], 2013	Lithuania	RCT	28	29	AOT	Microfracture	24.6	24.3	10	12	2.7	2.8	120
Gudas *et al*[63], 2005	Lithuania	RCT	29	28	Microfracture	AOT	24.3	24.6	12	10	2.8	2.7	36
Glasbrenner *et al* [64], 2020	Germany	RCT	12	12	Microfracture	Microfracture with BMAC	36.7	47.9	3	6	1.7	1.7	12
Dasar *et al*[65], 2016	Turkey	RCT	20	20	Microfracture	Carbon fibre rod	36.4	38.5	15	15	3.5	4.0.	24
Crawford *et al* [66], 2012	United States	RCT	21	9	NeoCart	Microfracture	41.0	39.0	2	3	2.8	2.5	24
Cole *et al*[67], 2011	United States	RCT	9	20	Microfracture	MACI	33.0	32.7	4	6	3.4	2.7	24
Chung *et al*[68], 2014	South Korea	RCT	24	12	Microfracture with BMAC	Microfracture	47.4	44.3	10	10	1.3	1.5	24

ACI: Autologous chondrocyte implantation; ACI-C: ACI with collagen cover; ACI-P: ACI with periosteal cover; AMIC: Autologous matrix induced chondrogenesis; BMAC: Bone marrow aspiration concentrate; CCP: Cultured chondrocyte pellet; HA: Hyaluronic acid; MACI: Matrix-induced autologous chondrocyte implantation; MFx: Microfracture; MSC: Mesenchymal stromal cell; NA: Not available; OAT: Osteochondral autograft/allograft transfer; PRP: Platelet-rich plasma; RCT: Randomized controlled trial; SVF: Stromal vascular fraction.

evaluated with IDKC score (WMD = 3.40; 95%CI: 0.65, 6.16; P = 0.045; without significant heterogeneity). However, the difference was not clinically relevant; and less than the minimum clinical difference for the outcome concerned. Although we did not note a statistically significant improvement in most of the functional outcomes with the advancements to the traditional MFx; we observed that (with the exception of Lysholm score) the SUCRA ranking of the interventions consistently favoured the higher generations in the following order: MFX-III > MFX-II > MFX-I (Table 2).

Two-year functional outcome: The pooled forest plot of the functional outcomes, sub-grouped based on the individual scores at 2 years, is presented in Figure 4. We did not note statistically significant difference with the higher generations of MFx with regard to the functional scores such as KOOS, Lysholm score, IDKC score, and Cincinnati score. Nevertheless, similar to the functional outcome at 1-year time point; SUCRA rankings of interventions were consistent in

Table 2 Network meta-analysis summary and ranking of interventions based on the SUCRA scores

Follow-up	Outcome	Intervention	Coeffecient	Standard error	SUCRA ranking
1 yr	VAS	mFX-II	0.139	0.296	MFX-III > MFX-II > MFX-I[1]
		mFX-III	0.023	0.457	
	KOOS	mFX-II	-2.296	2.835	MFX-III > MFX-II > MFX-I[1]
		mFX-III	-2.296	5.775	
	Lysholm score	mFX-II	-17.008	11.160	MFX-I > MFX-III > MFX-II[3]
		mFX-III	-5.660	4.427	
	IKDC score	mFX-II	2.782	1.811	MFX-III > MFX-II > MFX-I[1]
		mFX-III	4.339	2.228	
	Cincinnati score	mFX-II	4.257	4.543	MFX-II > MFX-I[1]
	MRI filling	mFX-II	0.383	0.312	MFX-III > MFX-II > MFX-I[1]
		mFX-III	1.860	1.770	
	MOCART score	mFX-II	11.950	7.419	MFX-III > MFX-II > MFX-I[1]
		mFX-III	30.700	14.168	
	Adverse events	mFX-II	-0.529	0.373	MFX-III > MFX-II > MFX-I[1]
		mFX-III	-0.138	0.546	
	Failure events	mFX-II	-0.520	0.777	MFX-II > MFX-I[1]
2 yr	VAS	mFX-II	0.377	0.452	MFX-III > MFX-II > MFX-I[1]
		mFX-III	0.690	0.795	
	KOOS	mFX-II	1.899	2.971	MFX-II > MFX-I[1]
	Lysholm score	mFX-II	0.550	6.952	MFX-II > MFX-I > MFX-III[3]
		mFX-III	-19.560	9.814	
	IKDC score	mFX-II	4.548	4.545	MFX-III > MFX-II > MFX-I[1]
		mFX-III	7.947	9.405	
	Cincinnati score	mFX-II	-6.227	3.775	MFX-II = MFX-I[2]
	MRI filling	mFX-II	0.840	0.468	MFX-II > MFX-III > MFX-I[3]
		mFX-III	0.418	0.508	
	MOCART	mFX-III	10.600	9.281	MFX-III > MFX-I[1]
5 yr	VAS	mFX-III	1.900	1.917	MFX-III > MFX-I[1]
	IKDC score	mFX-III	3.000	2.121	MFX-III > MFX-I[1]

[1]Newer generations better than older generations.
[2]Newer generations equal to older generations.
[3]Newer generations worse than older generations.
VAS: Visual Analog Scale; mFX: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue.

favouring the higher generations in the following order MFX-III > MFX-II > MFX-I (for all outcome measures except the Lysholm score (Table 2).

Five-year functional outcomes: We did not have sufficient data points to evaluate mid-term and long-term functional outcomes. However, based on the available data, there was no significant change in the functional outcome with the higher generations of MFx, as compared to the traditional technique (based on IKDC score; Figure 5). Nevertheless, as with the earlier time points, the SUCRA ranking of interventions favoured the higher generations (in the order MFX-III > MFX-I; Table 2).

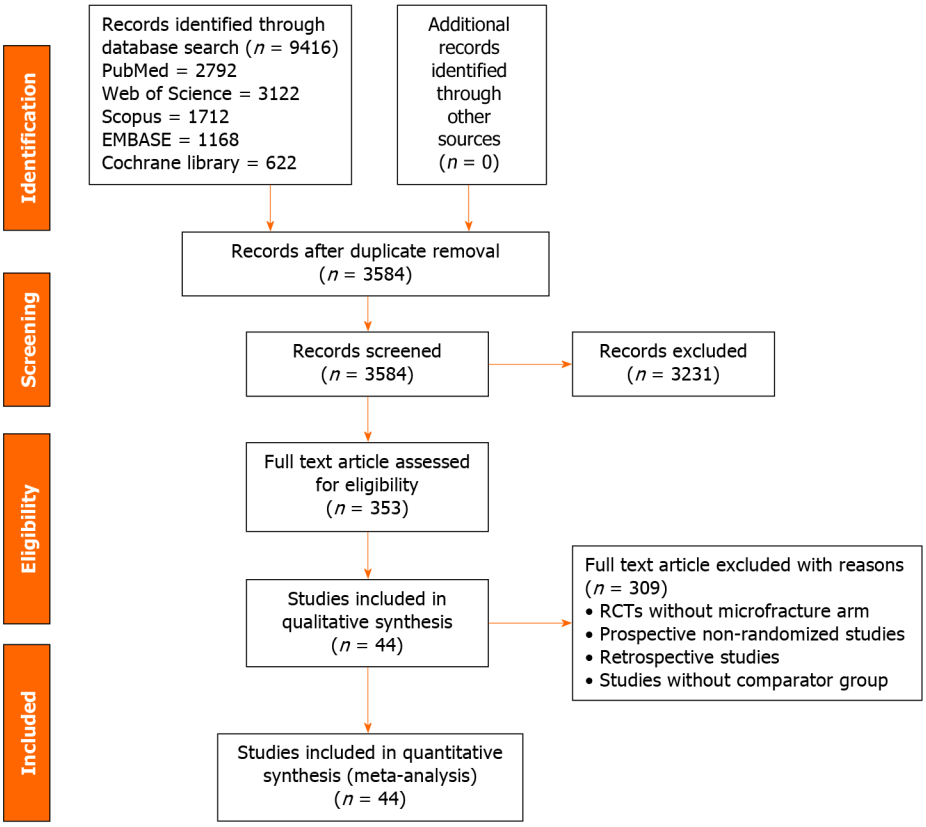

Figure 1 Preferred Reporting Items for Systematic Review and Meta-analysis flow diagram of selection of studies included in the analysis. RCT: Randomized controlled trial.

Radiological outcomes

The MOCART (magnetic resonance observation of cartilage repair tissue) Score and MRI defect filling (> 2/3rd) have been used to report the radiological outcomes in the included studies. The MOCART score was reported at 1 year in 8 studies [4,32,44,56,57,59,60,65] involving 439 patients, and at 2 years in 3 studies[13,32,59] involving 230 patients. The MRI-based defect filling was reported at 1 year in 17 studies[19,20,31,37,38,40,43-45,47,56,57,60,62-64,67] involving 847 patients, and at 2 years in 10 studies[13,19,31,38,45,47,50,64,67,68] involving 610 patients.

The pooled forest plots of the radiological outcomes, sub-grouped based on the individual scores at 1- and 2-year time points, are presented in Figures 3 and 4, respectively. We observed statistically better MOCART score in the higher generations of MFx (WMD = 17.44; 95%CI: 0.72, 34.16; P = 0.025; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. Although we did not note a statistically significant improvement in the MRI-filling with the advancements to the traditional MFx, the SUCRA ranking of the interventions were consistent in favouring the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2).

Complications

Adverse events: The adverse events following the compared interventions were reported in 32 studies[9,19,20,31-33,37-39,43,44,46-48,50-55,57,58,60-63,65-67,69-75] involving 1752 patients. Figure 3 shows the pooled forest plot of the reported complications for the analyzed interventions. In comparison with MFX-I, there was no statistically significant difference in the reported rates of adverse events in the higher generations. On the other hand, the SUCRA ranking of the interventions favoured the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2); thereby, highlighting the safety of the higher generations in comparison with the traditional technique.

Failures: The need for subsequent procedures following the interventions was considered as treatment failure, and the same was reported in 31 studies[4,31,33,34,38-42,46,48,57,59,61,63-65,69,72,73,76,77] involving 1059 patients. Figure 3 shows the pooled forest plot of the failure events for the reported interventions. In comparison with MFX-I, there was no statistically significant difference in the failure events among the higher generations of MFx techniques. Moreover, the SUCRA ranking of the interventions favoured the higher generations in the following order MFX-III > MFX-II > MFX-I (Table 2); thus, highlighting the reliability of the higher generations in comparison to the traditional technique.

Sensitivity & subgroup analysis

We did not observe significant heterogeneity across various outcomes analyzed in the network (based upon the heterogeneity values in the corresponding individual forest plots of pairwise comparisons of interventions). We sub-grouped and analyzed the studies based on the outcome measures and follow-up time point in order to avoid any heterogeneity in

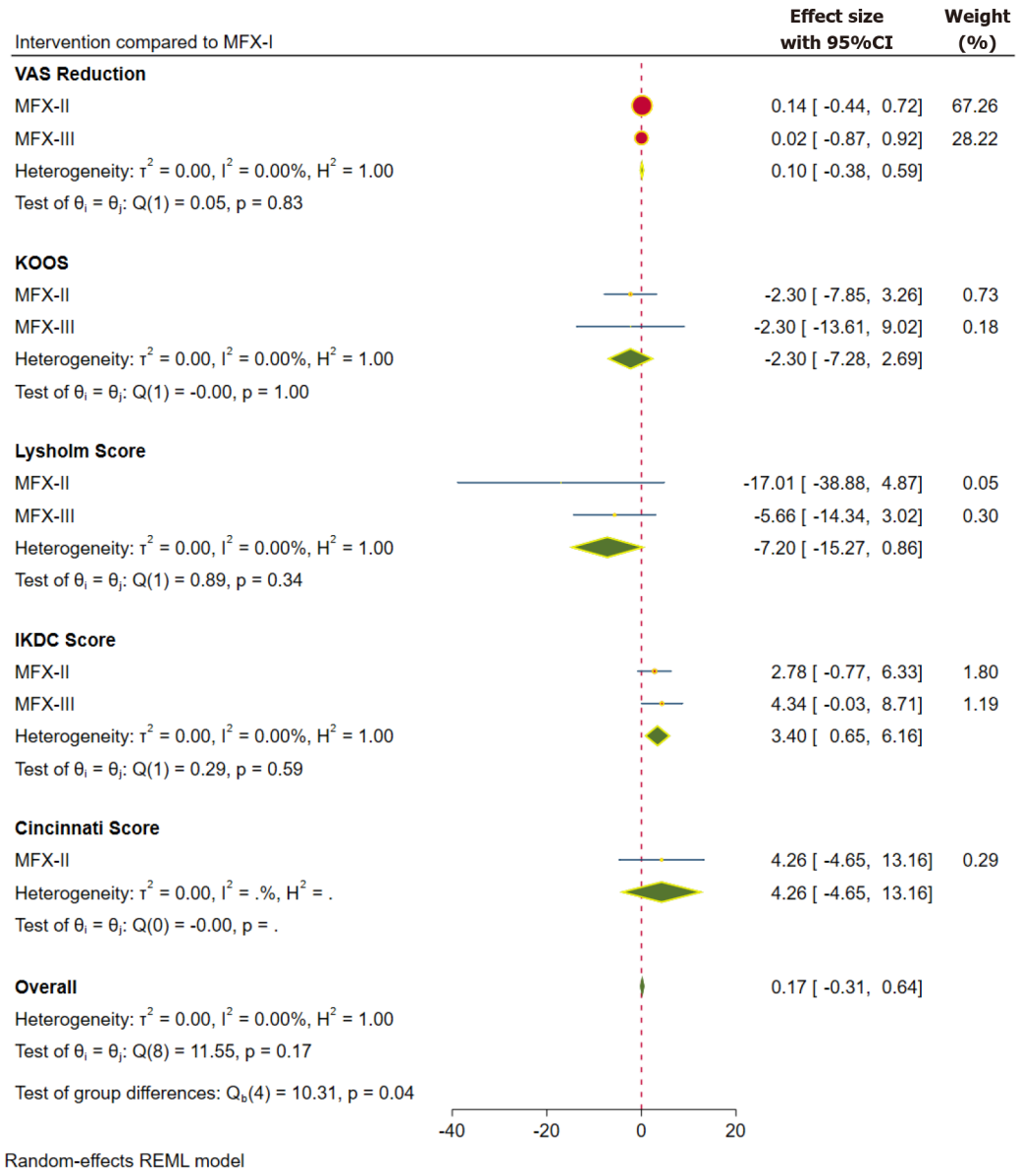

Figure 2 Forest plot comparing the generations of microfracture for the functional outcomes reported at 1 year among the included studies in the network. 95%CI: 95% confidence interval; VAS: Visual Analog Scale; MFx: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; REML: Restricted maximum likelihood.

the pooled results.

Consistency

We did not observe any significant evidence of global inconsistency, which could have affected the transivity of the network results. The consistency analysis was performed for the individual outcomes; and the chi-square values in the corresponding pair-wise comparison forest plots were presented. We noted the indirect pooled estimates to have wider CI compared to direct estimates in some of the paired networks analysed (although without any evidence of systematic differences concerning the potential effect modifiers). We considered these apparent inconsistencies to be the effect of true differences between the direct and indirect estimates. The indirect estimates were considered to reflect a more precise estimate, since they were from a network involving a larger number of studies.

Confidence in evidence

Upon grading the paired comparisons in the network using the CINeMA approach, a "high" confidence was noted across a majority of the paired comparisons (Table 3). However, some of the comparison pairs demonstrated "moderate" confidence. The lack of precision was the most common reason, which downgraded the quality of evidence in the indirect estimates, in view of wider CIs extending on either side of the axes. We also observed some concerns due to certain "within-study bias", following selective reporting of some of the outcome measures.

Table 3 Risk of bias for all the pairwise comparisons for functional outcome from the network assessed with Cochrane's Confidence in network meta-analysis approach

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reasons for downgrading
MFx-I: MFx-II	7	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results
MFx-I: MFx - III	1	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results
MFx-II: MFx - III	1	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	No concerns	Moderate	Imprecision in results

MFx: Microfracture.

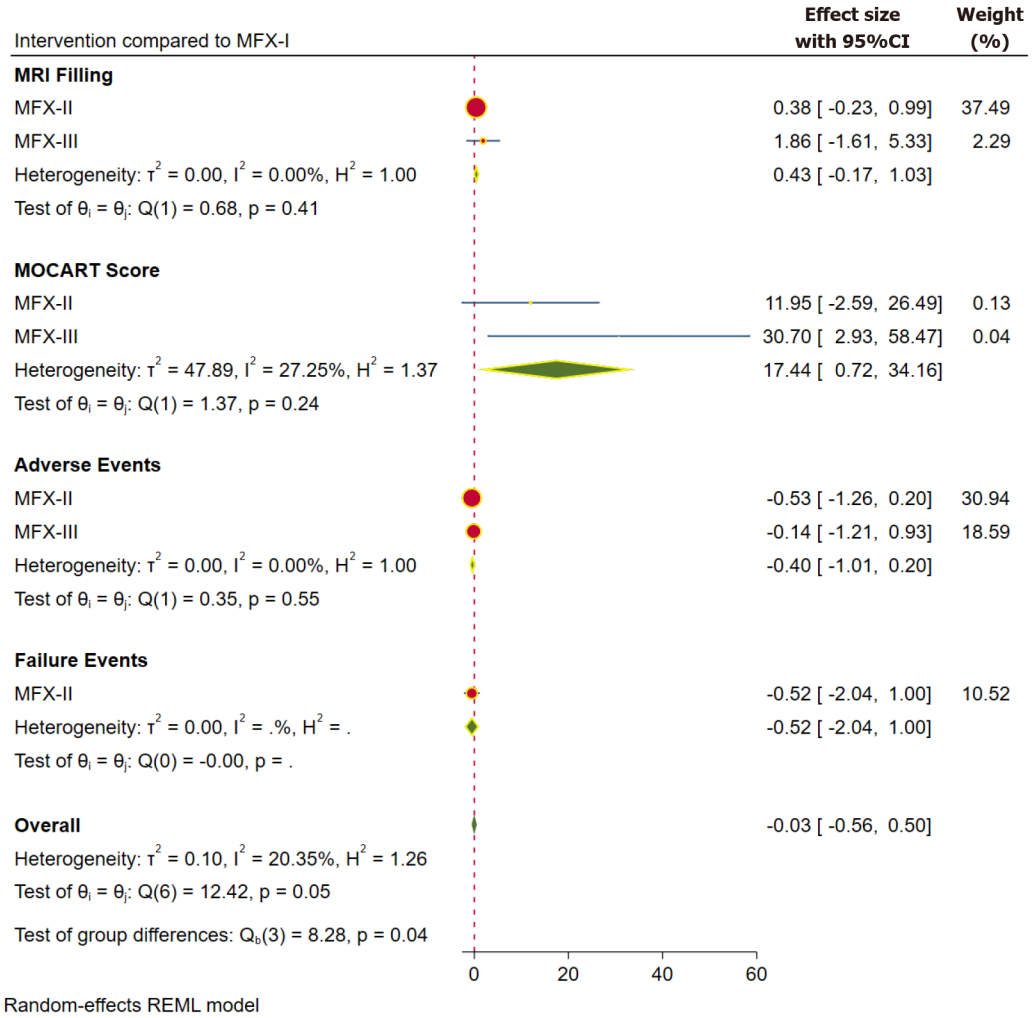

Figure 3 Forest plot comparing the generations of microfracture for the radiological outcomes reported at 1 year among the included studies in the network. 95%CI: 95% confidence interval; MFx: Microfracture; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue; REML: Restricted maximum likelihood.

DISCUSSION

Chondral lesions have been reported in 60% of patients undergoing arthroscopic procedures of the knee; and such defects are described as one of the leading causes of chronic pain[78-81]. These defects may result from acute trauma, repetitive microtrauma, osteochondritis dessicans or early osteoarthritis; and can produce symptoms like pain, swelling, catching, stiffness and locking[33]. Hunter *et al*[82,83] described the challenge of cartilaginous injury by stating that, "once the cartilage is destroyed, it never recovers". These observations still hold true; and the avascular as well as aneural nature of

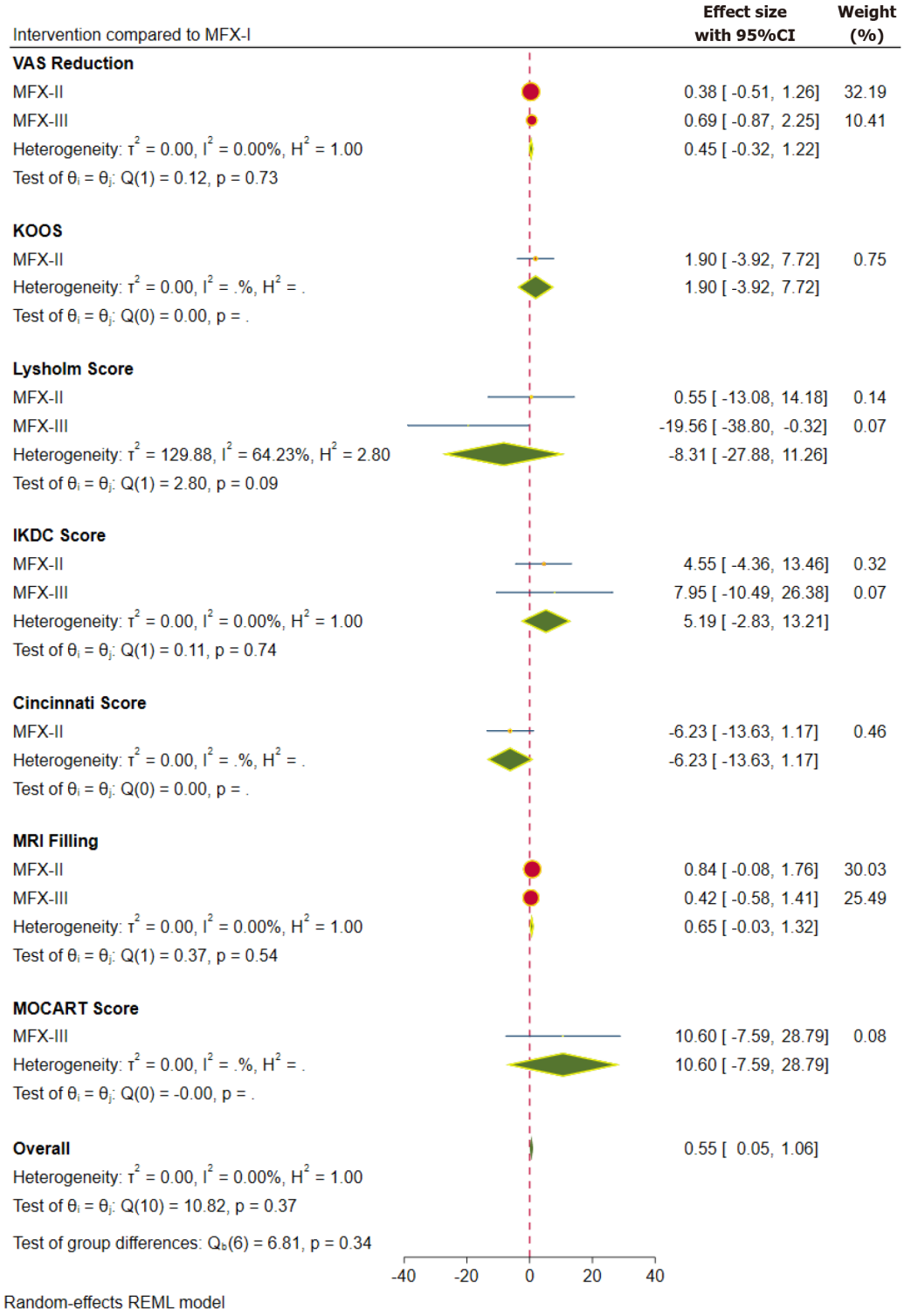

Figure 4 Forest plot comparing the generations of microfracture for the functional and radiological outcomes at 2 years reported among the included studies in the network. 95%CI: 95% confidence interval; VAS: Visual Analog Scale; MFx: Microfracture; KOOS: Knee Osteoarthritis Outcome Scale; IKDC: International Knee Documentation Committee; MRI: Magnetic resonance imaging; MOCART: Magnetic resonance observation of cartilage repair tissue; REML: Restricted maximum likelihood.

cartilage substantially limits its ability to self-regenerate[84]. If left untreated, a transgressed cartilage gradually results in severe osteoarthritis of the joint and ensuing long-standing disability[85].

Superficial cartilage deficiencies do not induce a local inflammatory response; therefore, despite proliferation of matrix molecules and chondrocytes, the surface is not adequately restored[86]. When the cartilage defect penetrates the subchondral plate, the vascularized bone marrow can enable the formation of clot rich in chondroprogenitor cells, fibrin and bioactive molecules; which in turn, facilitates the formation of type I collagen and fibrocartilage[87]. This is the rationale underlying the MFx technique, which has traditionally remained the first-line treatment for small to medium-sized defects[88]. The purported benefits of the procedure include low cost, easy technique and proven improvement in

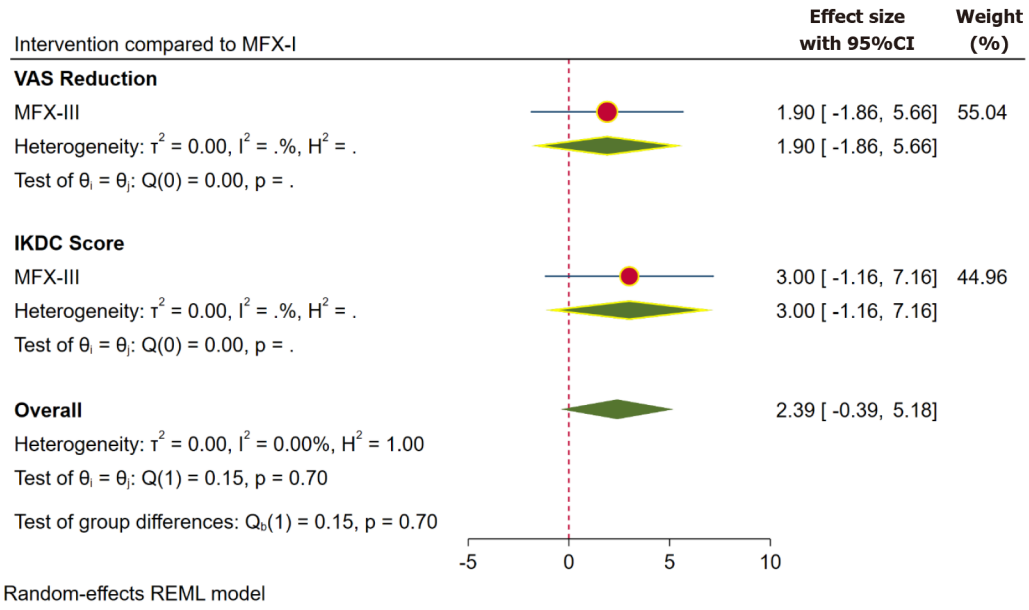

Figure 5 Forest plot comparing the generations of microfracture for the functional outcomes reported at 5 years among the included studies in the network. 95%CI: 95% confidence interval; mFX: Microfracture; IKDC: International Knee Documentation Committee; REML: Restricted maximum likelihood.

short-term outcome[87,88]. Nevertheless, 47% to 80% of patients have been reported to demonstrate substantial functional deterioration at 18 to 36 months post-surgically[10], which may be attributed to the poor viscoelastic properties of the restored fibrocartilage[89]. Since the initial description of MFx technique, multitudinous attempts have been made in the fields of tissue engineering and cartilage repair in an attempt to find the "holy grail", which enables the restoration of hyaline cartilage that can consistently integrate into the deficiency[42].

Evolution of MFx

In the traditional MFx technique described by Steadman *et al*[3], the debridement of the unstable cartilaginous tissues is initially performed arthroscopically; and a well-shouldered vertical wall is created around the periphery of the lesion. Following this, layers of calcified cartilage are removed using a curette. An arthroscopic awl is then utilized in a direction perpendicular to the bone in order to create holes in the subchondral plate around 3-4 mm apart (ascertaining that the interposed subchondral bone between the MFx perforations is maintained intact). Alternately, microdrilling using a 1.5 mm drill may be performed to perforate the subchondral plate to a depth of 1 cm.

While lesions smaller than 2 cm^2 in low-demand individuals are amenable to treatment with traditional MFx technique; lesions larger than 4 cm^2 have been purported to require additional adjuvant modalities too[90]. Diverse acellular biomaterials such as alginate, collagen, tri-copolymer and poly-lactic-glycolic acid have been utilized for engineering of cartilaginous tissues[91]. These tissues serve as carriers for delivery of cells and growth factors; as well as provide an appropriate milieu for tissue regeneration[92].

The cell therapy for cartilage repair was initially proposed in the 1980s using the technology of tissue engineering[93]; and cellular therapeutic innovation was eventually realized in 1994, when Brittberg *et al*[94] described the ACI technique. Further on, scaffold-based ACI (matrix-induced ACI-MACI: FDA-approved in 2016) technique has also been described as a modification of the traditional MFx. The discovery of adult stem cells resulted in a paradigm shift in the field of regenerative medicine[95]. A variety of stem cell-based therapies involving multipotent MSCs implantation (like bone marrow, adipose tissue, synovium, periosteum, peripheral blood, *etc*.) have been employed for cartilage repair. The chondrogenesis and development of neo-cartilaginous tissues from such undifferentiated MSCs can be guided using growth factors, and other biophysical or biomechanical stimuli[96,97].

As an alternative form of cell-based therapy, Gobbi *et al*[10] described the technique of implanting the bone marrow aspirate concentrate delivered *via* HA-based scaffold (HA-BMAC) over the micro-fractured area. Such an approach relies on the presence of MSCs and growth factors at the deficient zone so as to steer chondrogenesis. They concluded that such an approach yielded successful medium-term clinical outcome with restoration of durable cartilage, irrespective of the size and age of the lesion.

Despite such extensive publications, there has been a substantial dearth of large-scale, high-quality RCTs on this subject. In a recent systematic review; among 540 reviewed manuscripts, only 10 studies were found to be methodologically sufficient to be included for final analysis. The current evidence on this subject is therefore, still largely unclear [98]. The purpose of the current NMA was to comprehensively analyse the existing literature on chondral injuries of the knee; and comparatively evaluate the histological, radiological and clinical outcome following 3 different generations of MFx, namely traditional MFx (MFx-I), modified MFx technique using acellular adjuvant (MFx-II); and modified MFx technique using cellular adjuvant (MFX-III).

Observations from our study

Clinical and functional outcome: Overall, in our meta-analysis, we compared the pain scores and functional outcome measures (KOOS, Lysholm score, IKDC score, and Cincinnati scores) among the three generations of MFx. We could clearly observe a trend of improved pain scores and functional outcome scores (KOOS, IKDC and Cincinnati scores) with the use of cellular adjuvants (MFx-III-MSC, BMAC, PBSC, and SVF). Although the difference in the pain and functional scores improved with the use of acellular adjuvants (such as PRP, HA, collagen, and AMIC) too in comparison with traditional MFx, the differences were not as substantial as for cellular adjuvants.

This observation is in concurrence with a majority of the studies, which have demonstrated overall improved clinical outcome with acellular (MFx-II) adjuvants. In a prospective, multicenter clinical trial[31], AMIC with biodegradable type I/III collagen membrane showed significantly improved longer-term radiological (MRI defect filling) and functional outcome (as assessed by Cincinnati and modified ICRS scores) at the 5-year time point, in comparison with MFx-I. In another recent RCT, Shive *et al*[19] concluded that the use of BST-CarGel (soluble polymer scaffold containing polysaccharide chitosan dispersed in uncoagulated blood) following MFx leads to improved cartilage resurfacing and wound healing. On a similar note, various prospective studies have also reported meliorated outcome (clinical and radiological) following the use of diverse cellular components after MFx (MFx-III). Some such cellular components, which have been successfully tried in cartilage defects, include single-stage cell-based therapy using autologous cartilage fragments (cartilage autograft implantation system-CAIS)[67], collagen-covered ACI (ACI-C), AMIC[33], micro-fragmented stromal-vascular fraction (rich in adipose-derived MSCs-ADMSC)[49], and tri-layered collagen hydroxyapatite biomimetic osteochondral scaffold (CHAS) seeded intra-operatively with autologous chondrocytes (AC) or filtered bone marrow stem/stromal cells (fBMSC)[99]. In a prospective series by Liu *et al*[43], it was demonstrated that the application of Kartigen (matrix with autologous bone marrow MSC-derived chondrocyte precursors embedded in atelocollagen) enabled the restoration of columnar surface of articular cartilage, collagen type 2 and glycosaminoglycan in similar composition to native hyaline cartilage (on histology).

Radiological outcome: A majority of the studies reported on MOCART score and MRI filling defect during the follow-up. There was a statistically significant improvement in the MOCART score at the end of 1 year in patients following the use of cellular adjuvants after MFx, indicating a substantially improved cartilage tissue quality and integration. Although the radiological outcome scores at the subsequent follow-up time points were not statistically different; similar to the clinical outcome, there was a definitive trend towards better outcome after the use of cellular and acellular adjuvants following MFx (cellular > acellular).

In a prospective randomized study by Ibarra *et al*[59], it was concluded that structural outcome (as assessed by MRI-T2 mapping and MOCART score) and significantly improved clinical outcome (as evaluated by KOOS subscale and Tegner scale) at 1 to 6 years and 4 to 6 years, respectively in patients undergoing matrix-assisted autologous chondrocyte transplantation, as compared with traditional MFx. Patients undergoing adjuvant cell therapy also demonstrated higher response and lower failure rates in this series. Similar prospective cohort studies have demonstrated improved cartilage fill on T2WI MRI and mean MOCART score following surgical treatment with PRP-loaded scaffold (MFx-II)[100], scaffold augmentation using BMAC (MFx-III)[100] and transplantation of autologous BMSCs (BMSC-MFx-III)[60].

Complications and adverse events: Based on our network analysis, we could also clearly identify mitigated complication and failure rates with the higher generations of MFx (although the differences were not statistically significant. In a prospective series by Martinčič *et al*[99], tri-layered CHAS seeded intra-operatively with AC or fBMSC demonstrated significantly improved outcome, in comparison with MFx. In this study, blood soaking of the scaffold prior to cell seeding substantially reduced early post-operative complications like synovitis and arthrofibrosis.

Limitations: Though our study is one of the most comprehensively-performed reviews of the existing literature on this subject, there are certain limitations. The long-term data on histological and radiological outcomes following recent generations of MFx are limited. There is substantial paucity as well as heterogeneity in the reporting on the diverse functional outcome measures, which prevented uniform comparison of events.

Current status and future directions: Based on our comprehensive review and NMA, we could conclude that the use of acellular and cellular adjuvants (2nd and 3rd generation) marginally improves the overall clinical status (pain and functional scores) and radiological outcome (MOCART score and MRI-filling) in patients undergoing MFx for cartilage defects of the knee. The safety and efficacy of the higher generation MFx procedures are also clearly evident from our review. However, there is a substantial potential for further improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques[6].

CONCLUSION

The use of acellular and cellular adjuvants (2nd and 3rd generation) has shown only marginal improvement in the clinical (pain and functional scores) and radiological outcome (MOCART score and MRI-filling) in patients undergoing MFx for cartilage defects of the knee.

ARTICLE HIGHLIGHTS

Research background

We have noted improvements in the traditional microfracture (MFx) techniques over the decades of its routine use in the management of cartilage defects. The recent generations include the addition of acellular components and cellular components to the cartilage defect. However, the effectiveness of these modifications is not explored further.

Research motivation

To explore the clinical effectiveness of the various generations of the MFx technique to understand their clinical effect in the management of cartilage defects.

Research objectives

To comparatively explore the clinical, radiological and histological outcomes along with the complications reported in the various generations of MFx in the context of the management of cartilage defects.

Research methods

We made a systematic review by utilizing the databases such as PubMed, EMBASE, Web of Science, Cochrane, and Scopus to identify the randomized controlled trials (RCTs) reporting the outcomes of utilization of various generations of MFx in the management of cartilage defects. Network meta-analysis was performed among the three generations for the outcomes analysed using Stata.

Research results

Forty-four RCTs were included in the analysis with patients of mean age of 39.40 (± 9.46) years. Upon comparing the results of the other generations with MFX-I as a constant comparator, we noted a trend towards better pain control and functional outcome (KOOS, IKDC and Cincinnati scores) at the end of 1-, 2-, and 5-year time points with MFx-III, although the differences were not statistically significant ($P > 0.05$). We also noted statistically significant MOCART score in the higher generations of MFx (WMD = 17.44; 95%CI: 0.72, 34.16; $P = 0.025$; without significant heterogeneity) at 1 year. However, the difference was not maintained at 2 years. There was a trend towards better defect filling on MRI with the second and third generation MFx, although the difference was not statistically significant ($P > 0.05$).

Research conclusions

The higher generations of traditional MFx technique utilizing acellular and cellular components to augment its potential in the management of cartilage defects has shown only marginal improvement in the clinical and radiological outcomes.

Research perspectives

Future work could focus on the improvement in the cellular components (chondrocytes over other cellular lineage), culture or processing methodology, delivery modalities (including appropriate scaffolds); as well as better surgical techniques to make the clinical impact with their further advancements.

FOOTNOTES

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