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The clinical outcomes of intra-articular injection of human umbilical cord blood-derived mesenchymal stem cells *vs.* bone marrow aspirate concentrate in cartilage regeneration: a systematic review

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Abstract. – OBJECTIVE: This systematic review focuses on which sources of mesenchymal stem cells (MSCs) are more beneficial for cartilage repair, specifically comparing umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) and bone marrow aspirate concentrate (BMAC) in patients treated *via* a high tibial osteotomy (HTO) plus mesenchymal stem cells augmentation.

MATERIALS AND METHODS: PubMed, Scopus, Embase, Cochrane, and Web of Science were searched for literature published in English that compared the effects of hUCB-MSC amplification and BMAC transplantation in articular cartilage lesions of the human knee with at least 1 year of follow-up after surgery. The risk of bias in the included retrospective studies was assessed *via* the Coleman Methodology Score. The clinical prognosis was assessed based on the total clinical score, pain, function, and degree of cartilage repair.

RESULTS: The risk of bias in the included retrospective cohort studies was evaluated as fair. A formal meta-analysis of outcomes was not possible as the low evidence level and the nature of pooled retrospective studies introduced considerable heterogeneity. At an average of 1 year after surgery, two included studies reported that the ratio of normal and nearly normal cartilage repair assessed by International Cartilage Repair Society grading system (ICRS) grading in the second arthroscopy was higher in the hUCB-MSC group (Lee: 71.2% and 81.3%; Yang: 77.3%) than in the BMAC group (Lee: 45% and 40.5%; Yang: 56.8%). Ryu et al reported no significant difference between groups in the ICRS grade at 1-year post-operation ($p = 0.655$). Overall clinical outcome, pain and function were significantly improved at the last follow-up in both the BMAC group and the hUCB-MSC group, and there were no significant differences in these measures between groups.

CONCLUSIONS: This systematic review presents evidence that compared with BMAC injection, intra-articular hUCB-MSCs can induce significantly better tissue repair at 1 year after surgery, as assessed by the ICRS grade. Although there is only short-term follow-up evidence and a lack of histochemical evidence, our systematic review supports the recommendation to use hUCB-MSCs as the source of pluripotent stem cells for treating ICRS III cartilage lesions.

Key Words:
Systemic review, BMAC, HUCB-MSCs, Articular cartilage lesion.

Introduction

Articular cartilage deterioration is one of the major issues in osteoarthritis that, unfortunately, represents a challenge in orthopedics due to the limited healing ability of damaged cartilage. Most attempts to repair cartilage, either through natural repair processes or surgical intervention (e.g., *via* autologous chondrocyte implantation, microfracture, stem cell transplantation[1], and high tibial osteotomy), result in the development of fibrocartilage, which has poor mechanical properties compared to those of hyaline cartilage and results in poor long-term clinical outcomes for patients[2].

Microfracture and subchondral bone drilling are notable surgical methods for cartilage repair as they stimulate the bone marrow. However, poor clinical outcomes after long-term follow-up were previously reported in literature. Kraeutler et al[3] reviewed the effects of bone marrow stimulation techniques. They pooled 7 related studies and found that subchondral drilling resulted in better cartilage repair, evidenced by increased mineralized bone and hyaline cartilage regeneration, but overall, the repaired tissue did not achieve the quality of normal hyaline cartilage. The poor outcomes may be attributed to insufficient stimulation of the function of the mesenchymal stem cells (MSCs)[4] and the lower number of recruited MSCs[5].

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Throughout the development of cell-based technology, combination surgery [bone marrow stimulation or high tibial osteotomy (HTO) plus MSC augmentation or autologous chondrocyte implantation (ACI) with or without a scaffold] and ACI6 have shown[7,8] better cartilage repair than bone marrow-stimulating techniques or HTO. Although ACI produces satisfactory outcomes in long-term follow-up, the application of this technique is limited by the two-stage procedure[9], damage to the donor site, and the decreasing chondrogenic potential with age[10]. Furthermore, a meta-analysis[11] that pooled published RCTs that included the outcomes of cell populations containing MSCs for the treatment of knee osteoarthritis demonstrated that concomitant treatment with the recommended concentration of MSCs could be considered a useful surgical method for treating knee osteoarthritis that produces acceptable outcomes; however, there is a lack of evidence supporting the improvement in cartilage repair. More than this, Maric et al[12] reported that autologous bone marrow aspirate concentrate (BMAC) transplantation improved motor and cognitive functions in children with cerebral palsy (CP) by activating the regenerative capacity of stem cells. Another systematic review[13] showed that the efficacy of bone marrow-derived MSCs (BM-MSCs), adipose-derived stromal vascular faction (AD-SVF), and human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) in terms of clinical outcomes and cartilage repair were not significantly different in patients with osteoarthritis after short-term follow-up[14]. Nevertheless, only BMAC and hUCB-MSCs were approved by the US Food and Drug Administration (FDA) for production as drug products. However, joint cartilage regeneration certainly represents the future of orthopedics, at the moment, there is a lack of studies comparing the clinical outcomes and cartilage repair between these treatments. The studies included are few, and the number of patients is insufficient to determine with certainty which is the best treatment. Therefore, the hypothesis of this review is that hUCB-MSCs may achieve better clinical outcomes and cartilage repair than BMAC.

Materials and Methods

Data and Literature Sources

This systematic review was designed and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.

Five databases, PubMed, Scopus, Embase, Cochrane, and Web of Science, were searched for published literature using a similar search strategy without limiting the publication year; for example, the search strategy for Web of Science was as follows: [(ALL=(umbilical cord blood OR fetal bloods) AND ALL=(mesenchymal stem cells OR mesenchymal stromal cells OR Multipotent Stem Cells OR progenitor cells)] OR (ALL=hUCB-MSCs) AND [ALL=(bone marrow aspirate concentrate) OR ALL=(BMAC)] AND ALL=(articular cartilage injury OR osteoarthritis OR cartilage defect OR cartilage lesion OR cartilage repair OR cartilage regeneration OR cartilage damage).

Study Selection

The level of evidence of the included studies was Level I to IV based on criteria established by the Oxford Centre for Evidence-Based Medicine[15]. The included studies published in English compared the effects of hUCB-MSC amplification and BMAC transplantation in articular cartilage lesions of the human knee with at least 1 year of follow-up after surgery. Furthermore, retrospective studies and randomized controlled trials that reported quantitative clinical outcomes (e.g., clinical score, pain score or knee function score) and the level of cartilage repair (e.g., International Cartilage Repair Society grading system) at the second arthroscopic evaluation or upon radiographic evaluation (e.g., hip-knee-ankle axis angle) after patients underwent hUCB-MSC amplification or BMAC transplantation were eligible. Articles were excluded for the following reasons: (1) the wrong research model (e.g., animal research or *in vitro* research), (2) wrong publication type (e.g., review, comment, case report, meeting proceeding or personal communication), (3) wrong study design, or (4) no interesting quantitative outcome.

Data Extraction

Two authors independently extracted data from the included studies according to the following data extraction form: first author; publication year; study design; intervention method; number of cases; length of follow-up; patient age, sex, and body mass index (BMI); cartilage lesion characteristics (e.g., number, size, and location); source of stem cells; volume of injection solution or number of cells in injection solution; and composition of the injection solution. The recorded outcomes for each study included clinical outcomes such as the overall clinical score, pain score and function score; radiographic evaluations such as the hip-knee-ankle

angle and posterior tibial slope; and the level of cartilage repair, for example, determined using the International Cartilage Repair Society grading system (ICRS). The following clinical outcomes were recorded: Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) score and Knee Society Score (KSS). The ICRS grading system was used to evaluate the level of cartilage repair in each study. The hip-knee-ankle angle and posterior tibial slope were measured by Magnetic Resonance Imaging (MRI).

Assessment of Heterogeneity

The heterogeneous nature of the pooled literature was assessed by two independent observers *via* the Coleman Methodology Score (CMS)[16], which ranges from 0 to 100 (excellent, score ≥85; good, 70≤ score ≤84; fair, 55≤ score ≤69; poor, score ≤54). Two authors independently appraised the included studies. If there were disputed results, the data were assessed by a third author. The differences in systems for assessing clinical outcomes caused considerable heterogeneity among the included studies that precluded a formal meta-analysis. This work was performed and reported following PRISMA guidelines.

Results

The literature selection process is presented in Figure 1. A total of 165 studies were identified using the electronic literature search strategy described above. Of these, 23 papers were excluded as duplicates. A total of 142 articles were screened based on the exclusion criteria, and 87 were excluded because they were reviews or books; the remaining articles were assessed and underwent a full-text review. Sixty-nine publications were excluded for the following reasons (1) not human research; (2) no hUCB-MSC-treated group; (3) no BMAC-treated group; or (4) technical guidance. Ultimately, three retrospective cohort studies[17-19] met the eligibility criteria.

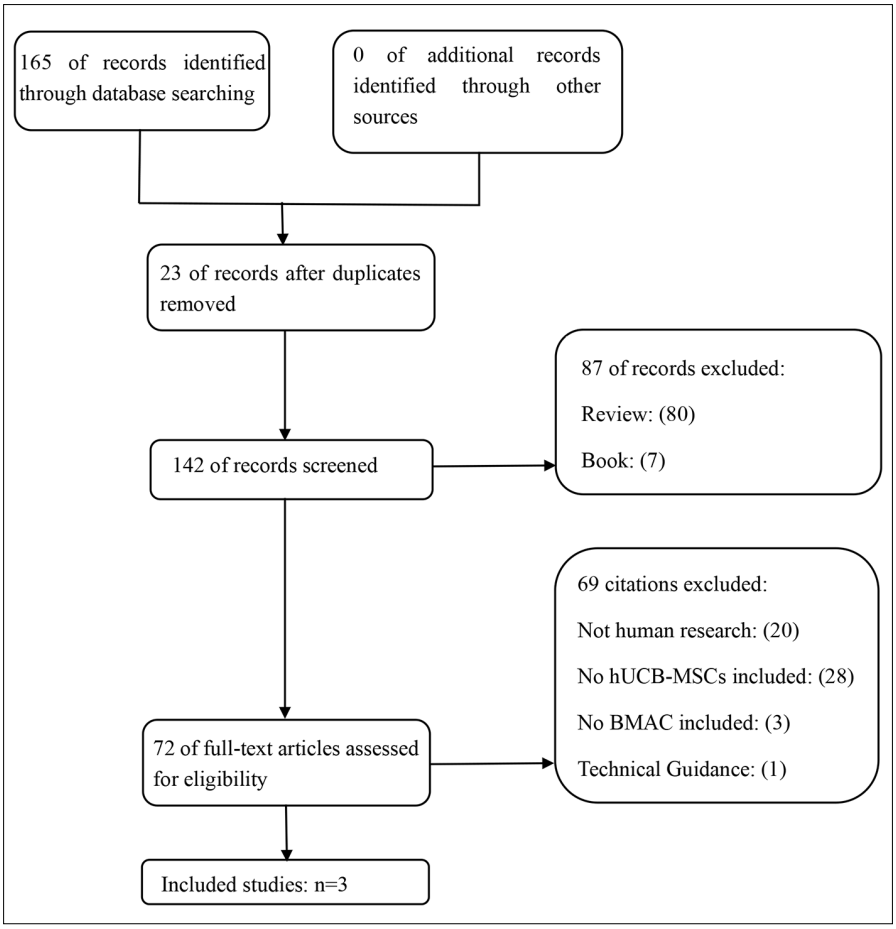

Figure 1. Flowchart of the study selection process.

Risk of Bias

The selected studies[17-19] enrolled 236 patients who were treated by different interventions (BMAC: n=114; hUCB-MSCs: n=122) with concomitant surgery (e.g., HTO+Microfracture). A total of 183 patients underwent second-look arthroscopy at least 1 year after surgery; 91 of these patients were included in the BMAC group, and 92 were treated with hUCB-MSCs. The basic characteristics of the included studies are summarized in Table I, and the outcomes, including the clinical outcomes, radiographic evaluations and ICRS grades, of the included articles are summarized in Tables II and III.

The heterogeneity of the included studies[17-19] was assessed by two independent observers *via* the Coleman Methodology Score (CMS). We evaluated the risk of bias introduced by the ICRS grading system and the clinical outcome scoring system, as these systems have differences in the number of patients and the follow-up duration. In the included literature, the clinical outcome scoring system was assessed as fair, and the details are presented in Table IV-A. Ryu et al[19], Yang et al[18] and Lee et al[17] did not describe the subjects recruited or the recruitment rate and did not report details regarding selection bias, so the corresponding publications were scored 0 for those items. The included studies[17-19] also received a score of 0 because they were retrospective studies. In Category 7, all the included studies reported details of only postoperative rehabilitation, but they did not report patient compliance; therefore, all the studies scored 6 in this category. Ryu et al[19] reported fewer included patients and a short follow-up, so this publication scored 7 and 3 in Category 1 and Category 2, respectively. Lee et al[17] obtained the lowest score in Category 2, as they reported the shortest follow-up. For the risk of bias of the ICRS grading system (Table IV-B), none of the included studies obtained a score in Category 4 due to issues with subject recruitment and selection bias. In Category 2, the studies scored 2 as they reported 2 years of follow-up. Six points were given for Category 7 because the studies did not describe patient compliance. Therefore, all the included studies were assessed as fair in the ICRS grading system. Together, the differences in systems for assessing clinical outcomes and the ICRS grading system caused considerable heterogeneity among the included studies that precluded a formal meta-analysis.

All the included studies were retrospective studies of BMAC or hUCB-MSC injection with HTO and microfracture in patients with damaged articular cartilage evaluated as at least ICRS grade 3 (Table I). The BMAC was siphoned from the contralateral anterior superior iliac spine[17,18] or ipsilateral iliac crest[19]. hUCB-MSCs in CARTISTEM were purchased from Medipost Co., Ltd (Seongnam-si, Gyeonggi-do, Korea)[13].

Clinical Score

Ryu et al[19] recorded improvements in the overall clinical score based on the IKDC grade preoperatively and at 6 months, 1 year, and 2 years post-operation. The IKDC and Western Ontario and McMaster Universities Arthritis Index (WOMAC) grading systems were used to calculate the overall clinical score preoperatively and at the last follow-up in the studies published by Yang et al[18] and Lee et al[17], respectively. The follow-up duration in the included studies ranged from 1-2 years. Details regarding overall clinical outcomes reported in the included publications are presented in Table II. There were no significant differences between the BMAC group and the hUCB-MSC group in the total clinical outcome score at the last follow-up in the included studies. However, the overall clinical scores were significantly improved in both groups after surgery compared with before surgery in all the published studies.

Pain and Function Scores

Pain and function were evaluated by the KOOS at each time point mentioned above in the studies published by Ryu et al[19], Yang et al[18] and Lee et al[17]. Pain and function are subgroups of the total clinical outcome scoring system. The same results were obtained for the pain and function scores as for the total clinical outcomes score.

Radiologic Outcomes

Details of the radiologic outcomes are presented in Table III. The hip-knee-ankle (HKA) and posterior tibial slope (PTS) were measured by anteroposterior and lateral X-rays, respectively. The study by Ryu et al[19] was excluded because they used MRI to evaluate cartilage repair tissue with the modified Magnetic Resonance Observation of Cartilage Repair Tissue (M-MOCART) scoring system rather than recording the HKA and PTS measurements. Yang et al[18] and Lee et al[17] reported no significant differences between the BMAC group and the hUCB-MSC group in the post-surgery HKA or the post-surgery PTS (Table III). However, the post-surgery HKA reported by Yang et al[18] seemed to be different from

Table I. Details of the pooled studies.

Study	Study Design	Level of evidence	Inter-vention	No. of cases (n)	Female patients (%)	Age (years)	Follow-up (months)	BMI	Number of lesions (S:M)	Lesion location	Source site	No. of cells	Mixed solution	Concomitant treatment	Lesion size (cm^2)
Ryu et a[l19] (2020)	Retro-spective cohort	III	hUCB-MSCs	27	59.3	53.93±8.6	24	26.38± 3.54	19:5	NA	CARTISTEM	$0.5*10^7$/ ml	HA	HTO+ microfracture	4.77±1.81
			BMAC	25	48	39.64±9.83	24	26.19± 3.74	16:4	NA	Ipsilateral iliac crest	60 ml	HA		4.33±1.66
Yang et al[18] (2021)	Retro-spective cohort	III	hUCB-MSCs	55	23.6	56.4±5.3	31.0±6.0	26.8± 3.2	NA	Medial femoral condyle (MFC)	Medipost	$0.5*10^7$/ ml	HA	HTO+ microfracture	6.2± 2.4
			BMAC	55	30.9	55±7.3	34.2±8.4	27.2± 3.9	NA		Contralateral anterior superior iliac spine	$0.5*10^7$ ml	NA		6.4±3.1
Lee et al[17] (2021)	Retro-spective cohort	III	hUCB-MSCs	32	81.2	58.1±3.6	15.6±2.8	26.6± 3.0	NA	Medial femoral and medial tibial cartilage	CARTISTEM	NA	HA	HTO+	7.0±1.9
			BMAC	42	85.7	60.7±4.1	20.7±6.1	26.1± 2.8	NA		Contralateral anterior superior iliac spine	40 ml	NA		6.5±2.9

hUCB-MSCs: umbilical cord blood-derived mesenchymal stem cells; BMAC: bone marrow aspirate concentrate; M: F: male: female; BMI: body mass index; S:M: Single lesion: Multiple lesions; HA: hyaluronic acid; HTO: high tibial osteotomy; NA: Not available.

Table II. Clinical outcomes of the included studies. KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; IKDC: International Knee Documentation Committee; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; hUCB-MSCs: umbilical cord blood-derived mesenchymal stem cells; BMAC: bone marrow aspirate concentrate.

Author (year)	Intervention	Cases (n)	Follow-up (months)	Scoring system										Scoring system		
				KOOS	Pain		Symptom		Activities of Daily Living		Sports and recreation		Quality of life		IKDC	Pre-operation	6 months post-operation
					Pre-operation	6 months post-operation	Pre-operation	6 months post-operation	Pre-operation	6 months post-operation	Pre-operation	6 months post-operation	Pre-operation	6 months post-operation			
Ryu et al[19] (2020)	BMAC	25	24		50.38±9.11	70.38±7.59	50.89±11.39	69.11±8.61	63.80±6.33	71.65±7.59	37.72±14.43	66.58±11.65	28.61±11.90	58.73±12.91		44.17±12.5	68.63±6.67
	hUCB -MSCs	27	24		50.38±10.13	68.61±11.39	48.86±10.38	66.33±13.42	62.53±7.59	70.89±10.13	33.42±14.43	61.01±16.71	26.08±10.63	54.68±17.47		42.02±13.63	65.49±12.55
						1-year post-operation		1-year post-operation		1-year post-operation		1-year post-operation		1-year post-operation			1-year post-operation
						75.44±9.62		75.95±9.87		81.27±6.33		72.15±13.16		76.46±15.44			77.25±8.63
						77.22±12.15		77.47±12.67		77.72±8.35		67.85±14.94		68.10±14.68			75.29±11.37
						2-years post-operation		2-years post-operation		2-years post-operation		2-years post-operation		2-years post-operation			2-years post-operation
						84.81±10.13		82.03±9.37		86.33±7.34		76.96±13.67		76.2±15.95			80.27±9.48
						82.53±11.14		82.28±12.91		83.54±9.11		74.68±14.43		71.14±13.92			81.35±11.07
					Pre-operation	Last follow-up	Pre-operation	Last follow-up	Pre-operation	Last follow-up	Pre-operation	Last follow-up	Pre-operation	Last follow-up		Pre-operation	Last follow-up
Yang et al[18] (2021)	BMAC	55	34.2±8.4		42.3±3.7	81.7±6.4	40.9±5.1	79.2±7.5	52.0±7.1	82.4±5.0	23.8±7.0	62.0±11.9	31.1±4.8	72.4±6.8		36.2±3.0	72.8±5.8
	hUCB -MSCs	55	31±6		41.4±6.5	83.1±8.3	39.5±6.9	79.4±8.8	51.5±8.4	83.1±5.8	23.7±9.2	63.2±10.7	29.8±6.3	73.8±8.7		35.4±5.5	73.3±9.8
				KSS	Pain						Function				WOMAC		
					Pre-operation	Last follow-up					Pre-operation	Last follow-up				Pre-operation	Last follow-up
Lee et al[17] (2021)	BMAC	42	20.7±6.1		30.8±11.0	40.6±9.1					62.3±11.9	80.1±15.0				43.9±12.7	45.2±8.8
	hUCB -MSCs	32	15.6±2.8		31.6±10.4	42.8±7.9					63.1±11.2	82.4±15.5				23.4±11.6	19.5±15.8

Table III. Radiological indexes of the included studies.

Author (year)	Inter-vention	Cases (n)	Follow-up (months)	HKA		Posterior tibial slope		Scoring system	Cases (n)	Follow-up (months)	Methods	Normal and nearly normal rate (%)		Normal and nearly normal cases (n)		Compli-cations (n)
				Pre-operation	Last follow-up	Pre-operation	Last follow-up	ICRS			Second-look arthroscopy					
Ryu et al[19] (2020)	BMAC	25	24	NA	NA	NA	NA		12	12		91.6	7	2		
	hUCB - MSCs	27	24	NA	NA	NA	NA		16	12		87.5	14	3		
Yang et al[18] (2021)	BMAC	55	34.2±8.4	7.6±2.9	-1.5±2.3	7.7±2.4	8.5±2.5		37	mean 17		56.8	21	1		
	hUCB - MSCs	55	31±6	7.5±2.7	-1.6±2.2	7.9±2.1	8.2±2.5		44	mean 17		77.3	34	0		
												Medial femoral condyle	Medial tibial condyle	Medial femoral condyle	Medial tibial condyle	
Lee et al[17] (2021)	BMAC	42	20.7±6.1	8.6±3.1	2.8±3.2	8.5±3.9	8.8±4.5		42	20.7±6.1		45	40.5	19	17	NA
	hUCB - MSCs	32	15.6±2.8	7.4±2.6	2.9±1.6	7.6±3.7	7.4±3.8		32	15.6±2.8		71.2	81.3	26	26	NA

HKA: hip-knee-ankle; PTS: posterior tibial slope; hUCB-MSCs: umbilical cord blood-derived mesenchymal stem cells; BMAC: bone marrow aspirate concentrate; ICRS: International Cartilage Repair Society; Normal: ICRS repair score=12; Nearly normal: ICRS repair score=8-11; NA: Not available.

Table IV. CMS for the scoring methods of clinical outcome (**A**) and ICRS grading system (**B**)

A Study	Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	Category 7	Category 8	Category 9	Category 10	Total
Ryu et al (2020)[19]	7	3	10	0	5	5	6	2,2,3,3	0,4,3,3	0,0,5	61
Yang et al (2021)[18]	10	5	10	0	5	5	6	2,2,3,3	0,4,3,3	0,0,5	66
Lee et al (2021)[17]	10	2	10	0	5	5	6	2,2,3,3	0,4,3,3	0,0,5	63
B Study	**Category 1**	**Category 2**	**Category 3**	**Category 4**	**Category 5**	**Category 6**	**Category 7**	**Category 8**	**Category 9**	**Category 10**	**Total**
Ryu et (2020)[19]	4	2	10	0	5	5	6	2,2,3,3	0,4,3,3	0,5,5	62
Yang et al (2021)[18]	10	2	10	0	5	5	6	2,2,3,3	0,4,3,3	0,5,5	68
Lee et al (2021)[17]	10	2	10	0	5	5	6	2,2,3,3	0,4,3,3	0,5,5	68

that published by Lee et al[17] [Table III; BMAC group: -1.5±2.3 (Yang) and 2.8±3.2 (Lee); hUCB-MSCs: -1.6±2.2 (Yang) and 2.9±1.6 (Lee)].

Assessment of Cartilage Repair

Tissue repair was assessed by second arthroscopy at a mean follow-up of 1 year in the studies published by Ryu et al[19], Yang et al[18] and Lee et al[17]. The results of normal and nearly normal cases assessed by ICRS grading for each included study are summarized in Table III. Lee et al[17] assessed cartilage repair in the medial femoral condyle and medial tibial condyle. Yang et al[18] and Ryu et al[19] did not provide the detailed location of the assessment using the ICRS grading system. Ryu et al[19] reported that compared with the hUCB-MSC-treated group, the BMAC group had a similar ratio of normal and nearly normal regenerated cartilage tissue assessed at the second arthroscopy by the ICRS grading system at 1-year post-operation (hUCB-MSC group: 91.6%; BMAC group: 87.5%). Yang et al[18] reported that the hUCB-MSC group had a better ICRS grade at the same time point under the second arthroscopy (hUCB-MSC group: 77.3%; BMAC group: 56.8%). Lee et al[17] presented similar results for the medial femoral condyle (hUCB-MSC group: 71.2%; BMAC group: 45%) and medial tibial condyle (hUCB-MSC group: 81.3%; BMAC group: 40.5%).

Discussion

Joint surface defects (JSDs) are local lesions on the surface of articular cartilage that are very common, reported in approximately 19% of 1,000 arthroscopic procedures[20]. Regrettably, chronic asymptomatic JSDs can cause unacceptable outcomes, such as joint deformities and osteoarthritis (OA). However, articular cartilage has a relatively poor regenerative capacity, meaning that most attempts to repair this tissue, either through natural repair mechanisms or surgical intervention (e.g., autologous chondrocyte implantation, microfracture, stem cell transplantation), result in the development of hyaline-like cartilage, which has poor mechanical properties compared to those of natural hyaline cartilage and achieves poor clinical outcomes for patients[2]. Therefore, current clinical treatments only relieve joint pain and delay disease progression instead of treating cartilage degradation related to OA or symptomatic articular cartilage defects.

In the clinic, HTO plus stem cell intra-articular injection after microfracture is a successful treatment strategy that significantly improves joint function and relieves pain in the short term[12-14]. However, there is still controversy about which source of stem cells for intra-articular injection is most beneficial for cartilage repair, and best resist deterioration in healing tissue. This systematic review focuses on the clinical effects of the intra-articular injection of stem cells from BMAC or hUCB-MSCs.

In this systematic review, the ICRS scores were greater than III before surgery for all the included patients[12-14]. And the ICRS scores for the patients included in the studies by Lee et al[17] and Ryu et al[19] were greater than IIIB and IV, respectively. Ryu et al[19] described the inclusion criterion as Kellgren-Lawrence grade equal to or less than II, while the inclusion criterion in the research by Yang et al[18] was Kellgren-Lawrence grade III. Lee et al[17] did not describe the Kellgren–Lawrence classification. Nonetheless, the pooled studies[17-19] reported that the included patients did not show significant differences in pre-surgery indicators such as the total clinical score, pain, function, HKA and PTS (Table II, Table III).

These findings indicate that the differences in inclusion criteria, specifically, Kellgren-Lawrence classification or ICRS scoring, did not seem to significantly affect the total clinical score, pain, function, HKA or PTS before surgery. Yang et al[18] and Lee et al[17] presented different postoperative values for the HKA (Table III). However, they reported that the HKA and PTS were not significantly different between the hUCB-MSC group and the BMAC group after surgery, which may mean that standard HTO surgery was performed on each patient[12,13]. However, there is a small difference in the standard HTO surgery reported by Yang et al[18] and Lee et al[17]. The included studies presented similar results: HTO plus stem cell intra-articular injection with microfracture was an effective treatment, as pain, function, and the total clinical score were significantly improved at the last follow-up[12-14]. Moreover, none of the included studies showed significant differences between the BMAC group and the hUCB-MSC group in the total clinical score, pain, or function at the last follow-up (Table II). Previous scholars[21] have shown that increasing levels of inflammatory factors [e.g., interleukin (IL)-1, IL-6, IL-7, Prostacyclin E2] induce exaggerated pain in osteoarthritis, and osteoclasts can accumulate in the knee at the early stage of OA; these cells secrete

Netrin1, which can stimulate sensory nerves in aberrant subchondral bone remodeling *via* deleted in colorectal cancer (DCC). Therefore, the excellent immune regulation, anti-inflammatory function, and cartilage differentiation ability of pluripotent stem cells may contribute to pain relief and functional recovery[22]. He et al[23] revealed that bone marrow mesenchymal stem cells decreased the ability of IL-1 to inhibit the proliferation and migration of chondrocytes, increased Collagen Type II Alpha 1 Chain (*col2A1*) and Aggrecan (*ACAN*) expression, and reduced Matrix Metallopeptidase 13 (*MMP-13*) and A Disintegrin and Metalloproteinase With Thrombospondin 5 (*ADAMTS-5*) expression *via* stem cell-derived exosomes in an IL-1-induced osteoarthritis animal model. A previous study[24] showed that hUCB-MSCs accelerate the differentiation of cartilage progenitor cells by secreting thrombospondin-2.

On average, the ICRS score results showed that the ratio of normal to nearly normal cartilage was significantly higher in the hUCB-MSC group than in the BMAC group at the 1-year follow-up after surgery, as reported by Lee et al[17] and Yang et al[18] (Table III). This finding could be easily explained by the fact that hUCB-MSCs have better proliferative ability and maintain a more stable hyaline cartilage phenotype than stem cell-derived marrow mesenchymal stem cells. Rim et al[22] reviewed the abilities of hUCB-MSCs and bone marrow pluripotent stem cells; the former present better proliferative capacity, more doublings in all passages, and a longer time to replicative senescence that is characterized by the loss of proliferation and the original morphology *in vitro* than bone marrow-derived mesenchymal stem cells, while hUCB-MSCs are more difficult to obtain. Wang et al[25] determined the characteristics of chondrocytes differentiated from hUCB-MSCs and BM-MSCs and found that after 6 weeks, chondrocytes differentiated from hUCB-MSCs maintained more glycosaminoglycans (GAGs) than those differentiated from BM-MSCs, and the levels of GAGs secreted by chondrocytes differentiated from BM-MSCs declined during weeks 3-6 *in vitro*. However, chondrocytes induced by MSCs undergo mineralization and hypertrophy over time. Pelttari et al[26] induced MSCs to differentiate into cartilage *in vitro* and revealed that hyaline cartilage-related genes such as *col2A1* were upregulated, while hypertrophy-related genes such as *MMP-13* and Collagen Type X (Col X) were upregulated. *In vivo*, proteoglycan and type II collagen were detected continuously at the subcutaneous MSC transplantation site in severe combined immunodeficiency (SCID) mice, and this site also showed mineralization. However, in the hyaline chondrocyte control group, hypertrophy-related genes were not detected *in vitro*, and limited mineralization was observed *In vivo*.

Ryu et al[19] showed that there were no significant differences in the ratio of normal to nearly normal cartilage between the hUCB-MSC group and the BMAC group at 1-year post-operation (Table III). It is worth noting that the patients in the BMAC group were significantly younger than those in the hUCB-MSC group. Therefore, the authors performed a subgroup study based on age. The results were similar to those described above but were unconvincing as less than 3 patients were included in each subgroup. Furthermore, cartilage injuries in younger patients have a better clinical prognosis. Messner et al[27] followed 28 young athletes who were diagnosed with isolated cartilage defects by arthroscopic procedures in the bearing area of the joint for 14 years. Three of these athletes were treated by cartilage drilling or cartilage scraping, and the others did not receive any treatment for cartilage defects. It is exciting that 22 of these athletes showed great joint function after 14 years.

Limitations

There remains a lack of long-term clinical studies of cartilage lesions treated by HTO plus stem cell transplantation. We are still not sure which source contains stem cells that can differentiate more chondrocytes, maintain stable hyaline cartilage, and resist hypertrophy and mineralization of the repaired tissue in long-term clinical follow-up.

Conclusions

This systematic review presents evidence that hUCB-MSCs generate more stable cartilage with better coverage than BMAC at 1-year post-surgery. Regrettably, the repaired tissue was evaluated by the ICRS scoring system, which is a macro scoring system under arthroscopy rather than a system based on immunohistochemistry or histochemistry. Based on the evidence collected for this systematic review, we recommend hUCB-MSCs as the source of pluripotent stem cells for treating patients with cartilage lesions greater than ICRS III.

Informed Consent
Not applicable.

Conflict of Interest
All authors declare no relevant financial or non-financial interests and no conflicts of interest relevant to the article content.

Data Availability
Data are available upon reasonable request upon contact with the corresponding authors.

Authors' Contributions
Pengfei Wang performed the study, draft the manuscript and designed the study. Jian Xing summarized previous literature, reviewed the manuscript and designed the study. All authors read and approved the final manuscript.

Ethics Approval
Not applicable.

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