



# Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study

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## Abstract

**Background** Despite being a common cause of quality-of-life impairment, there are no efficacious therapies that could prevent the progression of knee osteoarthritis (KOA). We conducted an open-label trial of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and hyaluronic acid (HA) for treating KOA.

**Methods** This open-label study was conducted from July 2015 to December 2018 at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Patients diagnosed with KOA were injected three times, comprising of  $10 \times 10^6$  units of hUC-MSCs in 2-ml secretome implantation and 2-ml hyaluronic acid (HA) injection in the first week, followed with 2-ml HA injection twice in the second and third week.

**Results** Twenty-nine subjects (57 knees) were recruited. Seventeen (58.6%) subjects were male, and the mean age was  $58.3 \pm 9.6$  years. Thirty-three (57.9%) knees were classified into Kellgren–Lawrence grade I–II KOA (mild OA). hUC-MSCs significantly decreased pain measured by visual analogue scale in severe KOA from initial to 6th month follow-up [ $5 \pm 2.97$  to  $3.38 \pm 2.44$  ( $p = 0.035$ )]. The International Knee Documentation Committee score significantly increased at 6th month follow-up ( $53.26 \pm 16.66$  to  $65.49 \pm 13.01$ ,  $p < 0.001$ , in subjects with grade I–II and  $48.84 \pm 18.41$  to  $61.83 \pm 18.83$ ,  $p = 0.008$ , in subjects with severe KOA). The Western Ontario and McMaster Universities Osteoarthritis decreased significantly in both groups from initial to 6th month follow-up (from  $22.55 \pm 15.94$  to  $13.23 \pm 10.29$ ,  $p = 0.003$ , and from  $27.57 \pm 15.99$  to  $17.92 \pm 19.1$ ,  $p = 0.003$ , in those with mild and severe KOA, respectively).

**Conclusions** hUC-MSCs could be a potentially new regenerative treatment for KOA. The maximum effect of hUC-MSCs was achieved after 6 months of injection.

**Level of evidence** Therapeutic level II.

**Keywords** Umbilical cord · Mesenchymal stem cells · Osteoarthritis

## Introduction

Musculoskeletal disorders are the most common cause of severe long-term pain and physical disability affecting hundreds of millions of patients worldwide. Among these diseases, osteoarthritis (OA), defined as a chronic degenerative joint disorder involving articular cartilage and many of its surrounding tissues, is the most common; it is [1–5]. OA is estimated to affect 250 million people worldwide [6], and it mainly affects the weight-bearing joints, such as hips and knees [2]. The knee is the most frequent site for OA, and

those presenting with disorder often suffer from progressive loss of function, pain and stiffness, thereby having decreased quality of life of [7].

Despite its consequences, no effective therapy or procedure prevents the progressive destruction of OA [2, 8]. All current treatments, without exception, are more symptomatic than preventive, which further may lead to joint replacement [8–10]. Although generally successful, joint replacement is associated with numerous complications and high financial burden [11]. Moreover, it is not as attractive for younger patients because of prosthesis lifespan approximately 15 years [1, 12–15]. There is, therefore, a crucial need for the development of new treatments for this debilitating condition.

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Although intra-articular injection of hyaluronic acid (HA) has been employed in OA treatment, its effect on chondroprotection and the prevention of OA progression of the knee remain controversial [16, 17]. Many preclinical and clinical treatment protocols involving cell-based therapy use HA as a vehicle [18, 19]. The use of HA as a vehicle may have an added benefit of ensuring delivery of MSCs to the articular surface given that is localised to the articular surface after intra-articular infusion [20]. MSCs have been used for cartilage repair. Bone marrow stem cells (BM-MSCs) are the most common source of MSCs and can prompt cartilage regeneration at certain levels [21, 22]. However, collecting BM-MSCs from donors is invasive and inconvenient [23]. In recent years, human umbilical cord MSCs (hUC-MSCs) have received much attention as a potential cell source for tissue engineering and regenerative medicine, because they are easy to obtain and store [24–26]. However, the role of hUC-MSCs for treating knee OA remains unclear. Several preclinical studies demonstrated that hUC-MSCs decreased osteogenic genes and inflammatory factors, and promoted chondrocyte proliferation [27–31]. Previously, there were several clinical studies that have investigated the effect of hUC-MSCs in subjects with knee OA [9, 32–34]. However, these studies enrolled a few numbers of subjects, with each study consisting of only one to six subjects. Therefore, we try to conduct a larger open-label trial of hUC-MSCs and HA for treating subjects with knee OA.

## Methods

This single-arm, open-label study was conducted from July 2015 to December 2018 at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. We included subjects aged 50 years diagnosed with primary OA of one or both knees based on American College of Rheumatology (AC). Osteoarthritis was diagnosed based on history, physical

examination, and radiographic evidence of joint change based on Kellgren–Lawrence grade I–IV 6 months before the initiation of the study.

The study was prospectively registered in ClinicalTrials.gov (reference NCT03800810). After an IRB approval (no. 659/UN2.F1/ETIK/2015), signed informed consent was obtained in accordance with the latest version of the Helsinki Declaration. Knee OA staging was done in accordance with the Kellgren and Lawrence classification [35] using standard knee X-ray imaging of standing anteroposterior and horizontal lateral projection. Image interpretation and staging were independently done by one radiologist. The inclusion and exclusion criteria are listed in Table 1.

## MRI

Knee MRI scans were performed with GE Optima MR450W (wide bore) 1.5 T (GE Healthcare, GE Healthcare, Waukesha, WI). Scans were further analysed using Advance Workstation 4.6 (AW 4.6) and processed to achieve a colourised T2 map using the CartiGram software (GE Healthcare, Waukesha, WI). The T2 mapping sequence was obtained using the following parameters: coronal orientation, 256×256 matrix, 16×16 cm field of view, 4 mm slice thickness, 1.5 mm slice gap, 62.5 kHz receiver bandwidth, 4 min acquisition time, TR of 1000 ms, TE of 8.3, 16.6, 24.9, 33.2, 41.4, 49.7, 58, 66.3 ms and colour range of 25–75 ms.

MRI scans were performed at baseline, 6 and 12 months. Standard knee MRI imaging protocol was obtained in axial, coronal and sagittal planes, in addition to using a specific cartilage sequence which is T1-weighted FS spoiled 3D gradient echo in axial and sagittal planes. Detailed measurements were taken from each compartment from three points: anterior, central and posterior. The mean thickness was calculated. Identical sequences and measurement sites were done on the follow-up scans.

**Table 1** Inclusion and exclusion criteria of this study

Inclusion criteria	Exclusion criteria
Diagnosed with primary OA in one or both knees based on American College of Rheumatology criteria	Secondary OA due to trauma, infection, rheumatoid arthritis, congenital disease or other inflammatory disorders of the knee joint
Evidence of radiographic changes of knee joint according to the Kellgren–Lawrence criteria	Diagnosed with systemic autoimmune disorder, immunodeficiency or coagulation disorder
Joint pain $\geq$ 20 mm measured by visual analogue scale	Had knee joint infection or skin/soft tissue infection around the knee
Failure of nonpharmacological treatment or analgesics	Had sensitivity history to hyaluronan products
Willing to participate the study	Had history of malignancy
Failure of nonpharmacological treatment or analgesics	Had undergone immunosuppressive, anticoagulation or adrenocorticosteroid therapy
Willing to participate the study	Had steroidal injection or viscosupplementation within 6 and 12 months before the study, respectively
	Women who had pregnancy

## Treatment

In our study, subjects diagnosed with OA of the knee were injected three times in total. In the first session, the subjects were injected with  $10 \times 10^6$  units of hUC-MSC in 2 ml secretome and 2 ml hyaluronic acid (HA). In both the second and third week, the subjects were injected with 2 ml HA. The dose was in line with that used in a caprine model of OA in a study conducted by Murphy et al. [36]. Using that dose, the authors found that local delivery of adult MSCs to injured joints stimulates meniscal tissue regeneration. Moreover, such cells also retard the progressive destruction normally seen in OA. hUC-MSCs were isolated by multiple harvest explant method [37], and culture in in-house developed 10% platelet lysate containing xeno-free media as previously described in our study [38]. Subjects were subsequently followed up on the 1st and 3rd, then every 3 months until 1 year. Outcome measures include the International Knee Documentation Committee (IKDC) score, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the visual analogue score (VAS).  $T_2$  map values of the knee cartilage were performed before implantation and then on the 6th and 12th month after the implantation.

### Multiple harvest explant method [34]

Umbilical cord from at-term healthy delivery was dissected, and the umbilical artery and vein discarded and minced into small pieces. The pieces were put into wells of 24-well plates, one piece per well, and immersed in a small amount of medium, just to make them wet and to prevent floating of the pieces. The pieces were cultured in an incubator at 37 °C and with 5% CO<sub>2</sub>. The cultures were observed every day for cell outgrowth and dryness. A small amount of medium was added when necessary, and when cell outgrowth was observed, more medium was added, and cultures were harvested at 80–90% confluence. Harvested cells were recultured to obtain enough cells to be delivered to the patients.

### Data analysis

Statistical analyses were performed using SPSS 23 for Mac. Paired *t* test or Wilcoxon's test was used to analyse numerical variables between baseline and both 6 and 12 months after implantation.

## Results

### Patients demographics

A total of 29 subjects were enrolled in this study. Seventeen (58.6%) subjects were male, and the mean age was  $58.3 \pm 9.6$  years. The mean BMI was  $27.12 \pm 4.4$ . A total of 57 knees received stem cells implantation. Based on the Kellgren–Lawrence system, 33 (57.8%) knees were classified into grade I–II osteoarthritis, and 24 knees (42.1%) were classified into grade III–IV. Characteristics of the subjects are presented in Table 2.

### Clinical outcome

Tables 3 and 4 summarise the distribution of disability indices and knee pain throughout the observation period. Tables 3 and 4 divide the subjects into subjects with Kellgren–Lawrence grade I–II and III–IV (mild and severe OA), respectively. No complication was observed.

VAS between subjects with Kellgren–Lawrence grade I–II and III–IV showed similarity when patients were observed within 6 and 12 months. VAS in both groups showed mean reduction during 6th and 12th month follow-up even though only one period of follow-up reached statistical significance (6th month follow-up in group Kellgren–Lawrence grade III–IV), from  $5 \pm 2.97$  to  $3.38 \pm 2.44$  ( $p = .035$ ).

Assessment of knee pain with IKDC Knee Forms also showed similar result between both groups, in which the mean IKDC score significantly increased over 6th month follow-up ( $53.26 \pm 16.66$  to  $65.49 \pm 13.01$ ,  $p < .001$ , in subjects with grade I–II; and  $48.84 \pm 18.41$  to  $61.83 \pm 18.83$ ,  $p = .008$ , in subjects with grade III–IV). In WOMAC, similarity also found in 6th month follow-up. In this period, mean reduction was found statistically significant in both groups (from  $22.55 \pm 15.94$  to  $13.23 \pm 10.29$ ,  $p = .003$ , and

**Table 2** Demographic characteristics of subjects

	Value
No. of patients	
Patients	29
Samples	57
Gender	
Male	17 (58.6%)
Female	12 (41.4%)
Age	$58.3 \pm 9.68$
BMI	$27.12 \pm 4.38$
Kellgren–Lawrence grade	
I–II	33 (57.8%)
III–IV	24 (42.1%)

**Table 3** Outcome of the mild osteoarthritis group at baseline, 6th month follow-up, 12th month follow-up

	Baseline	6th month follow-up	12th month follow-up	<i>p</i>
VAS				Initial—6 months <i>p</i> = 0.145 <sup>b</sup>
<i>n</i>	33	33	33	Initial—12 months <i>p</i> = 0.158 <sup>b</sup>
Mean ± SD	4.19 ± 2.09	3.17 ± 2.25	2.57 ± 2.42	6–12 months <i>p</i> = 0.217 <sup>b</sup>
Median	4	4	3	
Range	(1–9)	(0–7)	(0–7)	
IKDC				Initial—6 months <i>p</i> < 0.001 <sup>a</sup>
<i>n</i>	33	33	33	Initial—12 months <i>p</i> = 0.038 <sup>b</sup>
Mean ± SD	53.26 ± 16.66	65.49 ± 13.01	60.43 ± 16.69	6–12 months <i>p</i> = 0.242 <sup>b</sup>
Median	56.3	70.65	59.77	
Range	(28.7–82.7)	(44.8–85.19)	(36.87–89.66)	
WOMAC				Initial—6 months <i>p</i> = 0.003 <sup>b</sup>
<i>n</i>	33	33	33	Initial—12 months <i>p</i> = 0.071 <sup>b</sup>
Mean ± SD	22.55 ± 15.94	13.23 ± 10.29	13.46 ± 11.08	6–12 months <i>p</i> = 0.911 <sup>a</sup>
Median	13.54	11.45	10.93	
Range	(6.25–52.1)	(2.08–34.37)	(0–37.5)	
T2 map				
Medial				Initial—6 months <i>p</i> = 0.767 <sup>b</sup>
<i>n</i>	33	33	33	Initial—12 months <i>p</i> = 0.627 <sup>b</sup>
Mean ± SD	58.72 ± 60.73	45.18 ± 8.23	62.58 ± 82.55	6–12 months <i>p</i> = 0.569 <sup>b</sup>
Median	43.45	43.5	48.12	
Range	(30.9–361.36)	(27.0–70.0)	(30.84–481.5)	
Lateral				Initial—6 months <i>p</i> = 0.065 <sup>b</sup>
<i>n</i>	33	33	33	Initial—12 months <i>p</i> = 0.663 <sup>a</sup>
Mean ± SD	41.66 ± 9.53	47.78 ± 15.10	44.72 ± 10.23	6–12 months <i>p</i> = 0.486 <sup>b</sup>
Median	39.67	43.7	61.67	
Range	20.5–68	32.8–104	30.84–70.	

VAS visual analogue score, *IKDC* International Knee Documentation Committee, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

<sup>a</sup>Paired *t* test

<sup>b</sup>Wilcoxon

from  $27.57 \pm 15.99$  to  $17.92 \pm 19.1$ ,  $p = 0.003$ , in those with Kellgren–Lawrence grade I–II and III–IV knee OA, respectively).

### Radiographic outcome

Magnetic resonance imaging (MRI) quantitative T2 mapping was used to evaluate the result of stem cells treatment in both medial and lateral cartilage of the knees. The result of T2 mapping showed a varied result with no significant differences during 6th and 12th month follow-up (Tables 2, 3). In grade I–II knee OA, quantitative MRI T2 showed tendency to increase after implantation of stem cells (from 43.45 (30.9–361.36), 39.67 (20.5–68) to 43.5 (27.0–70.0), 43.7 (32.8–104) in 6th month follow-up and 48.12 (30.84–481.5), 61.67 (30.84–70.1) during 12th month follow-up for medial and lateral knee, respectively). On the other hand, quantitative MRI T2 for grade III–IV knee OA showed decreasing

value during 6th and 12th month follow-up, but for medial cartilage, T2 mapping increased again during 12th month follow-up.

### Discussion

Osteoarthritis is a degenerative joint disease characterised by progressive destruction of articular cartilage, which results in limitations of joint motion [3, 39, 40]. However, in this study, we did not measure the limitation of joint movement at baseline and follow-up. This was the limitation of our study. Current treatment options for OA include the use of anti-inflammatory drugs and lubricating supplements, as well as surgeries, such as drilling, microfracture and mosaicplasty. However, these modalities only improve the symptoms transiently [41]. Despite advances in treatment, most therapies do not stop or even reduce the progression

**Table 4** Outcome of the severe osteoarthritis group at baseline, 6th month follow-up, 12th month follow-up

	Baseline	6th month follow-up	12th month follow-up	<i>p</i>
VAS				Initial—6 months <i>p</i> = 0.035 <sup>b</sup>
<i>n</i>	24	24	24	Initial—12 months <i>p</i> = 0.153 <sup>a</sup>
Mean ± SD	5 ± 2.97	3.38 ± 2.44	3 ± 3.06	6–12 months <i>p</i> = 0.866 <sup>a</sup>
Median	5	3	4	
Range	(0–10)	(0–8)	(0–8)	
IKDC				Initial—6 months <i>p</i> = 0.008 <sup>b</sup>
<i>n</i>	24	24	24	Initial—12 months <i>p</i> = 0.28 <sup>a</sup>
Mean ± SD	48.84 ± 18.41	61.83 ± 18.82	54.16 ± 15.46	6–12 months <i>p</i> = 0.136 <sup>a</sup>
Median	49.45	62.07	52.9	
Range	(21.8–87.36)	(26.44–95.4)	(27.59–78.16)	
WOMAC				Initial—6 months <i>p</i> = 0.003 <sup>b</sup>
<i>n</i>	23	24	24	Initial—12 months <i>p</i> = 0.044 <sup>b</sup>
Mean ± SD	27.57 ± 15.99	17.92 ± 19.1	16.42 ± 12.42	6–12 months <i>p</i> = 0.276 <sup>b</sup>
Median	23	11.95	11.46	
Range	(5.21–60.42)	(3.13–72.41)	(2.08–37.5)	
T2 map				Initial—6 months <i>p</i> = 0.52
Medial				Initial—12 months <i>p</i> = 0.363 <sup>b</sup>
<i>n</i>	24	24	24	6–12 months <i>p</i> = 0.691 <sup>b</sup>
Mean ± SD	201.57 ± 310.26	103.66 ± 180.31	68.97 ± 50.14	
Median	65	45.94	47.65	
Range	32–1046	30.9–882.16	40.15–230.78	
Lateral				Initial—6 months <i>p</i> = 0.359 <sup>a</sup>
<i>n</i>	24	24	24	Initial—12 months <i>p</i> = 0.910 <sup>b</sup>
Mean ± SD	46.25 ± 15.02	46.64 ± 12.14	52.21 ± 19.74	6–12 months <i>p</i> = 0.112 <sup>b</sup>
Median	47.37	45.45	44.9	
Range	9–72	23.42–76.83	37.95–122.9	

VAS visual analogue score, *IKDC* International Knee Documentation Committee, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

<sup>a</sup>Paired *t* test

<sup>b</sup>Wilcoxon

of the disease and are only symptomatic [42]. Cell-based therapy may hold promise for the repair of articular cartilage defects as transplantation of autologous chondrocytes was effective in treating cartilage defects in the knee [41]. As this approach is limited by the number of healthy chondrocytes in patients, stem cells have emerged as an alternative [20].

Mesenchymal stem cells are an attractive source of cells because of their chondrogenic potential and easy access for isolation and future expansion [1]. MSCs are multipotent, adult stem cells that show clinical promise as therapeutic agents in regenerative medicine [8, 43–46]. MSCs can be easily isolated from many anatomic locations, including from whole marrow aspirate, muscle biopsy, adipose liposuction aspirate and from other tissues [43]. For orthopaedic uses, these sources have been compared by many researchers for their ability to heal bone and cartilage, with differences being noted [47]. Due to a painless collection procedure and self-renewal properties, the human UC

provides a promising source of MSCs, although the use of UC-derived stem cells in other diseases [48–50] and the effect of human UC stem cell for OA treatment have not been reported in the literature. Several studies reported that chondrocytes promoted chondrogenic differentiation of human umbilical cord blood-derived MSCs [51–54].

UC-MSCs can be isolated from various areas within the umbilical cord, including the subendothelial layer, perivascular zone, Wharton's jelly, umbilical cord lining and the whole umbilical cord [55]. UC-MSCs also meet the minimum criteria of plastic adherence, immunological profile and differentiation potential [56]. The many advantages of using UC-MSCs in tissue engineering and regenerative medicine are the avoidance of ethical issues, a painless harvesting process, few embryonic features, high cell proliferation, wide differentiation potential [57], hypoimmunogenicity [25] and nontumorigenicity [58].

In the present study, we found that the subjects had significantly improved IKDC and WOMAC scores. However, there was no significant MRI improvement at both 6th and 12th month follow-up. Therefore, it is now known whether improvement was from HA or hUC-MSCs. This is in line with previous studies; a meta-analysis of the 11 trials with 558 patients using MSCs found a significant improvement in various clinical scores [59]. They also found a significant improvement in clinical symptoms and cartilage morphology [59]. However, one published work using allogeneic bone marrow-derived MSCs in advanced knee OA in humans showed clinical improvement but no significant MRI improvement [60].

The mechanism of how UC-MSCs improve OA symptoms remains unclear. Whether MSCs stimulate the proliferation and differentiation of resident progenitor cells or they differentiate into chondrocytes remains to be clarified [61]. Rabbit and goat models of osteoarthritis suggest that the repair occurs through paracrine effects by stimulation of endogenous repair mechanisms [36]. Van Lent, in his editorial, suggested that the main effect of MSC transplantation in the joint is the suppression of the synovial inflammation [62]. Wang et al. [27] found that human umbilical cord stem cell decreased the osteogenic genes (COX2, COL10A1 and MMP13) and production of some inflammatory factors (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-10). This indicates that human umbilical cord stem cell attenuated inflammatory response of OA. Zhu et al. [28] reported that human umbilical cord blood MSC transplantation suppresses inflammatory responses during the early stage of focal cerebral ischaemia in rabbits, an ischaemia-induced increase in IL-1 $\beta$ , IL-6 and TNF- $\alpha$  levels in the serum and peri-ischaemic brain tissues within 6-h MCAO-reperfusion were markedly suppressed human umbilical cord stem cell transplantation. In another study, human UC-MSCs were reported to decrease expression of MDA, GSSG, TNF- $\alpha$ , IFN- $\gamma$ , TGF- $\beta$ , IL-1, IL-2, IL-6, collagen type 1 mRNA and MMPs [29].

Further experiments demonstrated that human UC-MSC significantly promoted chondrocyte proliferation that may be explained by that human umbilical cord stem cell containing many soluble factors, such as G-CSF, PDGF-BB and bFGF [30, 31]. In addition, human umbilical cord stem cell may inhibit apoptosis and then promoted proliferation. Zhang et al. [63] found that human umbilical cord stem cell promoted proliferation and inhibited apoptosis of skin cells after head stress *in vitro* by secreting exosomes.

In this study, we also noted that the greatest improvement in knee function was observed after 6th month follow-up. This finding is in line with previous studies [9, 32–34], which found that the maximum results were achieved at 6th month follow-up but decline afterwards. Davatchi et al. [9] conducted an open-label trial in four subjects with moderate-to-severe OA of both knees. They noticed that at 6 months

the subjects had considerable improvement particularly on major parameters such as walking time, climbing stairs, getting pain, VAS and range of motion. However, at 2-year follow-up, the results were started to decline [9]. Centeno, in 2008, was experimenting with one human subject [32, 33]. It showed good results at 6 months with no side effects. In 2012, Emadedin [34] reported the results of six patients with knee OA, who had an MSC transplantation. The outcomes were good at 6 months; however, the effects declined at 12 months. However, compared to the baseline, the outcomes were much better at 12 months [34].

The reason behind the declining efficacy of MSC after 6 months remains unclear. Perhaps, it may be due to the continuous degradation of the cartilage. Probably, after a while, the transplanted MSCs lose their characteristics and become like the original resident MSCs with chaotic function. If that is what happened, the transplanted MSCs did not have the time to repair the cartilage significantly. However, this is just a presumption and has to be verified scientifically. Feng et al. [64] used an intra-articular injection of allogeneic adipose-derived MSCs combined with HA in a sheep model, and they found that it could efficiently block OA progression and promote cartilage regeneration and allogeneic adipose-derived MSCs combined with HA lasted for 14 weeks after intra-articular injection. Davatchi et al. [9] found that although after a while the improvement started to decline, the transplanted knee joint in their study declined slower than the contralateral nontransplanted knee. This suggests that the repair effect of MSCs probably has not entirely disappeared. However, the lasting effect up to 6 months may also be due to the effect of HA. To get a more lasting effect, repeated MSC injection might be needed [65]. In a systematic review of 18 RCTs regarding the effect of HA in knee OA, O'Hanlon et al. [66] found that the functional outcomes of the subjects were improved by intra-articular HA injection. However, the durability of the effects could be measured beyond 6 months. On the other hand, Feng et al. [64] administered adipose-derived mesenchymal stem cells (AD-MSCs) combined with HA in sheep models with OA. They found that the levels of inflammatory factors (such as TNF- $\alpha$ , IL-6) in synovial fluid of AD-MSCs + HA-treated group were significantly lower than those of saline and HA-alone groups. All of these findings suggest that further RCTs comparing the effect of MSC and HA in longer follow-ups are required to investigate the exact reason behind the declining efficacy of MSC after 6 months.

The present study demonstrates that UC-MSCs could be a potential new treatment for OA. However, our study was limited by its open-label, nonrandomised design as well as the absence of a placebo arm. We hope that further clinical studies with better study design and larger sample size will be conducted in the future to investigate the safety and efficacy of this cell-based therapy for OA.

## Conclusions

The combination of hUC-MSCs and HA implantation could be a potentially new regenerative modality for osteoarthritis of the knee. The most significant effect was achieved after 6 months of injection. However, incorporation of hUC-MSC as a treatment option in knee OA needs more evidence. Further randomised clinical studies are required to investigate the safety and efficacy of these cells for treating osteoarthritis of the knee.

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## Compliance with ethical standards

**Conflict of interest** Ismail Hadisoebroto Dilogo, Anissa Feby Cantitika, Alberto Lastiko Hanitya, Jeanne Adiwinata Pawitan, Isabella Kurnia Liem and Jacub Pandelaki declare that they have no conflict of interests.

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