Arthroscopic Subchondral Drilling Followed by Injection of Peripheral Blood Stem Cells and Hyaluronic Acid Showed Improved Outcome Compared to Hyaluronic Acid and Physiotherapy for Massive Knee Chondral Defects: A Randomized Controlled Trial

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Purpose: The purpose of this study was to evaluate the safety and efficacy of intra-articular injections of autologous peripheral blood stem cells (PBSCs) plus hyaluronic acid (HA) after arthroscopic subchondral drilling into massive chondral defects of the knee joint and to determine whether PBSC therapy can improve functional outcome and reduce pain of the knee joint better than HA plus physiotherapy. **Methods:** This is a dual-center randomized controlled trial (RCT). Sixty-nine patients aged 18 to 55 years with International Cartilage Repair Society grade 3 and 4 chondral lesions (size $\geq$3 cm^2) of the knee joint were randomized equally into (1) a control group receiving intra-articular injections of HA plus physiotherapy and (2) an intervention group receiving arthroscopic subchondral drilling into chondral defects and postoperative intra-articular injections of PBSCs plus HA. The coprimary efficacy endpoints were subjective International Knee Documentation Committee (IKDC) and Knee Injury and Osteoarthritis Outcome Score (KOOS)—pain subdomain measured at month 24. The secondary efficacy endpoints included all other KOOS subdomains, Numeric Rating Scale (NRS), and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores. **Results:** At 24 months, the mean IKDC scores for the control and intervention groups were 48.1 and 65.6, respectively ($P < .0001$). The mean for KOOS-pain subdomain scores were 59.0 (control) and 86.0 (intervention) with $P < .0001$. All other KOOS subdomain, NRS, and MOCART scores were statistically significant ($P < .0001$) at month 24. Moreover, for the intervention group, 70.8% of patients had IKDC and KOOS-pain subdomain scores exceeding the minimal clinically important difference values, indicating clinical significance. There were no notable adverse events that were unexpected and related to the study drug or procedures. **Conclusions:** Arthroscopic marrow stimulation with subchondral drilling into massive chondral defects of the knee joint followed by postoperative intra-articular injections of autologous PBSCs plus HA is safe and showed a significant improvement of clinical and radiologic scores compared with HA plus physiotherapy. **Level of Evidence:** Level I, RCT.

See commentary on page 2518

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The authors report the following potential conflicts of interest or sources of funding: This study is sponsored by KLSMC Stem Cells Inc and supported by grants from City of Gulf Breeze, Florida, and the State of Florida. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

Received July 19, 2020; accepted January 25, 2021.

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0749-8063/201189/$36.00

https://doi.org/10.1016/j.arthro.2021.01.067

Articular cartilage repair technologies continue to evolve, striving to regenerate cartilage to a normal histologic and biochemical state. Patients with large cartilage defects (size $\geq$3 cm^2), bipolar cartilage defects, patellofemoral cartilage defects, and previously failed cartilage procedures represent a difficult clinical scenario, and there is a major unmet medical need in these instances, especially in the younger population.[1-10] In some cases, these "unmet medical need" patients have to wait for an appropriate time for total knee replacement following a period of conservative treatment. Clinicians addressing this group of patients often provide symptomatic treatment, one of the options being intra-articular hyaluronic acid (HA) injections plus physiotherapy.[11,12]

Recent animal and clinical research has focused on the use of stem cells to augment cartilage repair.[13-23] The authors have been developing arthroscopic subchondral drilling and postoperative intra-articular injections of autologous peripheral blood stem cells (PBSCs) plus HA since 2005.[20-23] PBSCs were chosen due to ease of harvest, long-term safety data on apheresis, and lower cost of "production" for the quantity required as compared with other autologous or allogenic adult stem cells such as cells culture-expanded from bone marrow or harvested from adipose tissues. In vitro studies have compared the differentiation and proliferative potential of PBSCs to cells cultured from bone marrow and found similar orthopedic potential.[24-27] Cartilage repair models in both small and large animals have shown that PBSCs improve cartilage healing potential.[27,28]

This clinical study was designed to compare the developed PBSC technique to HA plus physiotherapy in this unmet medical need population. The purpose of this study was to evaluate the safety and efficacy of intra-articular injections of autologous PBSCs plus HA after arthroscopic subchondral drilling into massive chondral defects of the knee joint and to determine whether PBSC therapy can improve functional outcome and reduce pain of the knee joint better than HA plus physiotherapy. On the basis of earlier clinical studies, we hypothesized that this cartilage regeneration technology would be safe and that after arthroscopic subchondral drilling into massive chondral defects, postoperative intra-articular injections of autologous PBSCs plus HA would improve the clinical and radiologic scores of the knee joint as compared with HA plus physiotherapy.

Methods

This is a 24-month dual-center, open-label phase IIB randomized controlled trial (RCT) conducted as part of an Investigational New Drug application reviewed and cleared by the US Food and Drug Administration (IND 15993). Institutional review board approval was obtained from the Medical Research and Ethics Committee (Ministry of Health Malaysia) from the Malaysian site and the Baptist Hospital System of Pensacola, Florida, from the US site.

An independent data safety monitoring committee (DSMC) was established to review all safety reports and study findings, including relevant clinical results and enrollment process.

A sample-sized study was performed prior to the initiation of the trial based on our previous RCT[22] and retrospective review of earlier clinical data. Recruitment of 120 patients total with massive chondral defects of the knee joint was initiated (please refer to statistical analysis section below for further details). Patients were randomized in a 1:1 ratio to either (1) a control group receiving intra-articular injections of HA plus physiotherapy or (2) an intervention group receiving arthroscopic subchondral drilling into chondral defects with postoperative intra-articular injections of PBSCs plus HA. This study methodology is presented in Figure 1. Enrollment commenced from January 2016 to January 2020 from the Malaysian site and from May 2017 to January 2020 from the US site.

Patient Selection

An informed consent was first obtained. The diagnosis of chondral defects was based on clinical and radiologic evaluation. Weightbearing radiographs with standard anteroposterior, lateral, and merchant views of the affected knee joint were taken. An additional weightbearing longitudinal radiograph of the lower limb in the coronal plane was taken to assess the degree of varus or valgus deformity of the knee joint. Magnetic resonance imaging (MRI) with Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring of the affected knee joint was performed to confirm the diagnosis of chondral lesion and to assess the size of the defect. Suitable patients then went through a medical screening process with an internal medicine—trained physician, and pretreatment data were collected. The inclusion criteria included patients aged 18 to 55 years with International Cartilage Repair Society grade 3 and 4 chondral lesions. Patients with single or multiple lesions were included with at least 1 of the lesions $\geq$3 cm^2. Bipolar, patellofemoral, femorotibial lesions and previously failed cartilage repair procedures were allowed and not exclusionary factors. Exclusion criteria were 3 previous surgical interventions, varus or valgus deformity more than 40% into the medial or lateral compartment, preoperation flexion deformity more than 10°, ligament deficiency, and body mass index $\geq$35 kg/m^2.

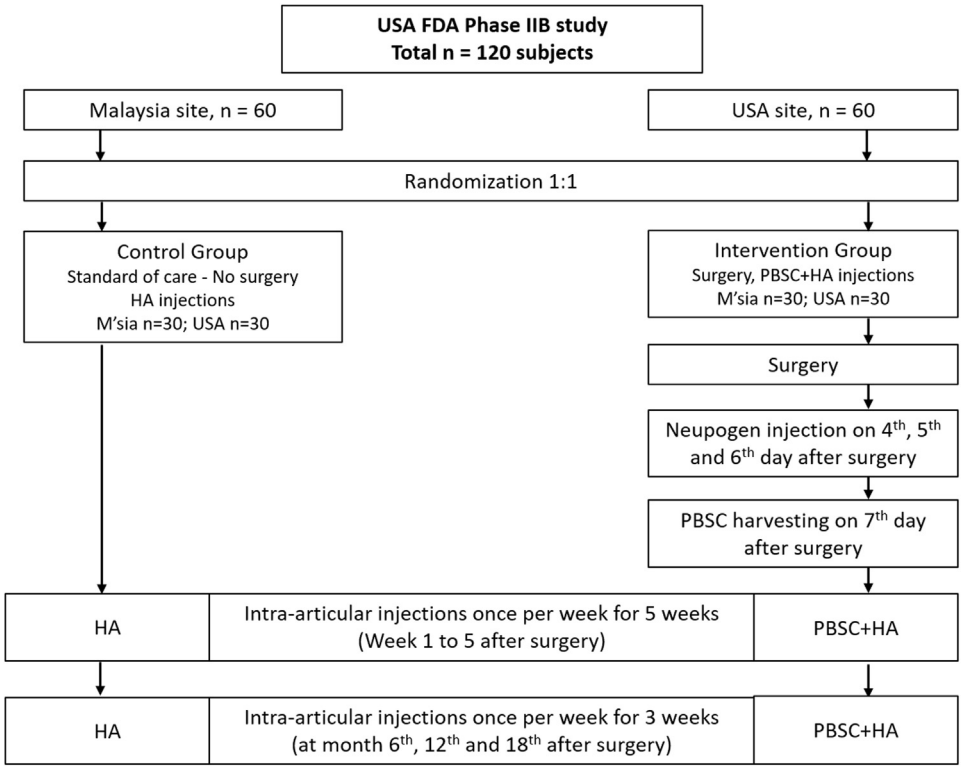


Fig 1. Flowchart of this randomized controlled trial methodology. (FDA, US Food and Drug Administration; HA, hyaluronic acid; PBSC, peripheral blood stem cell.)

Randomization

Patients who met the inclusion and exclusion criteria were randomly allocated to either the controlled group or the intervention group in a 1:1 ratio. Randomization was stratified by center so that each site captured approximately equal numbers of patients in either group, and an interactive online system was accessed after enrollment and used for randomization.

Surgical Procedures

All surgical procedures were performed by the respective principal investigator at each site involving standard arthroscopic techniques. Arthroscopic subchondral drilling of the chondral defects was performed with a recently developed arthroscopic drill (patent number: US 10,702,289 B2) designed to drill with a diameter of 2 mm to a depth of 6 mm (Fig 2). Table 1 lists the additional arthroscopic procedures. The details of the surgical technique with video illustration have previously been published.[21-23]

Filgrastim Administration, Apheresis, and Cryopreservation

On postoperative days 4, 5, and 6, patients in the intervention group were given a morning subcutaneous injection of filgrastim (Neupogen; Amgen, Thousand Oaks, CA), 300 μg daily for patients weighing below 100 kg and 600 μg daily for patients above 100 kg. The details of the harvesting procedure and cell preparation have been outlined in a previous publication.[21]

Intra-articular Injections

All patients received 14 intra-articular injections in total. For the intervention group, on postoperative day 7, immediately after the apheresis process, 8 mL fresh PBPC aliquot was mixed with 2 mL HA (Hyalgan; Fidia Farmaceutici, Abano Terme, Italy) and injected into the operated knee joint under aseptic conditions in the outpatient clinic. This was performed in the supine position via a superolateral approach without the use of ultrasound guidance. Postoperative hemarthrosis was aspirated prior to each injection. At 4 subsequent weekly intervals, an 8-mL aliquot of the frozen PBSCs (cryopreserved as per published methodology[21]) was allowed to thaw to room temperature, mixed with 2 mL HA, and injected into the operated knee joint. At 6, 12, and 18 months following surgery, 3 additional weekly intra-articular injections comprising 4 mL thawed cryopreserved PBSCs and 2 mL HA were given. The control group received 2 mL HA for each intra-articular injection at the same time points as the intervention group, as seen in Figure 1. Any knee effusion was first aspirated prior to the injections.

Physiotherapy

For the control group, each physiotherapy session lasted between 1 to 1.5 hours depending on the patients' condition. Each patient received patellar mobilization in each session. To manage pain and swelling, patients were given ultrasound and transcutaneous electrical nerve stimulation. For leg-strengthening exercises, patients performed

hamstring stretches, various quads strengthening, and stationary bike cycling. All physiotherapy activities were timed and recorded as a compliance measurement.

For the intervention group, in addition to the physiotherapy regime as per control group, postoperative physiotherapy consisted of continuous passive motion on the operated knee 2 hours per day for a period of 1 month, progressing from partial to full weightbearing in 8 weeks. Restrictions to full weightbearing on stairs were advised to patients with drilling over the patellofemoral joint (PFJ) for the first 3 months as to avoid overloading the PFJ.

Study Endpoints

All study outcome measurements were collected at the first visit as baseline prior to any procedures performed after successful screening. The coprimary efficacy endpoints are subjective International Knee Documentation Committee (IKDC) and Knee Injury and Osteoarthritis Outcome Score (KOOS)—pain subdomain measured at month 24. The secondary efficacy endpoints include the following:

1. Subjective IKDC at 6, 12, 18, 36, and 48 months
2. All other KOOS subdomains at 6, 12, 18, 24, 36, and 48 months
3. Numeric Rating Scale (NRS) for pain at 6, 12, 18, 24, 36, and 48 months
4. MOCART scores for the intervention group postsurgery at 6, 12, 18, and 24 months
5. MOCART scores for the control group at 12 and 24 months

MRI Scans

All patients had an MRI scan with MOCART scoring[29] prior to enrollment. The individual study site's radiologist performed the MOCART analysis and reporting of all the MRI scans at each site, respectively. A 3T MRI scanner (Magnetom Spectra; Siemens, Erlangen, Germany) equipped with an 18-channel knee coil was used at the site in Malaysia, and a 3T MRI scanner (Signa HDx; GE Healthcare, Chicago, IL) equipped with an 8-channel knee coil was used at the site in the United States. The MRI protocol included multiplanar proton density weighted with and without fat suppression and T1 weighted at both sites.

The control group had further MRI scans performed at 12 and 24 months. The intervention group had additional MRI scans performed on postoperative day 1 to document the subchondral drilling as a baseline and to chart chondrogenesis. Additional MRI scans were

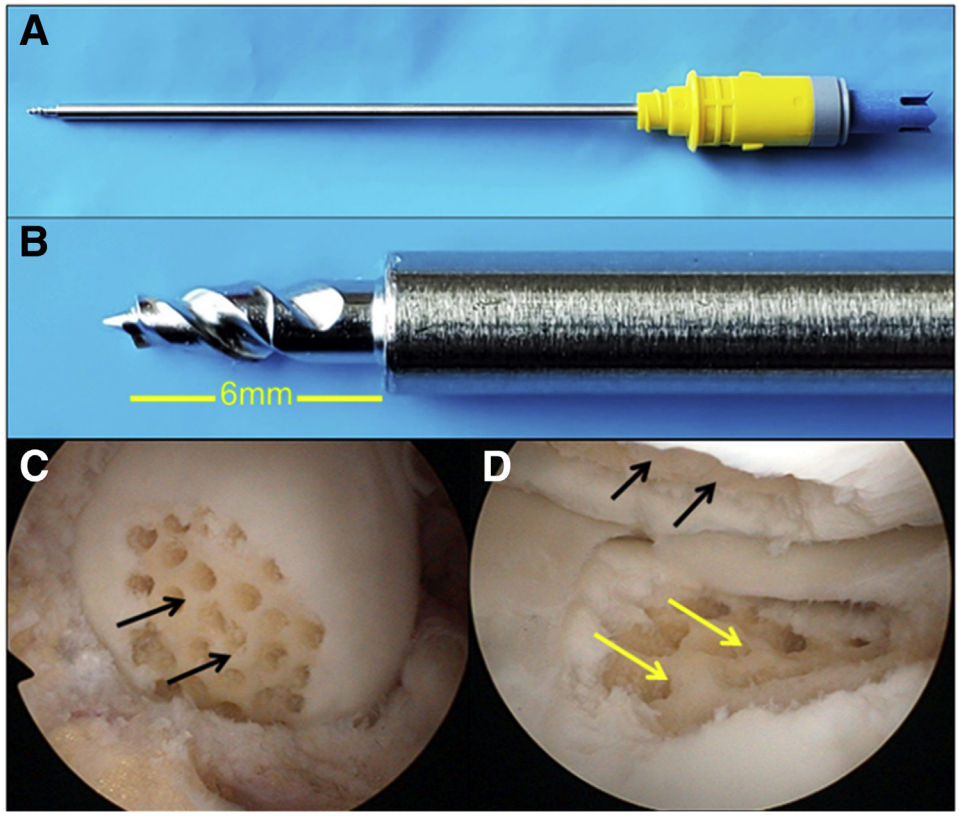


Fig 2. (A) A specially made arthroscopic drill with a pointed tip, with (B) showing a magnified view of the drill end designed to drill with a diameter of 2 mm to a depth of 6 mm. (C, D) Arthroscopic images of the right knee following subchondral drilling using the specially designed arthroscopic drill into the "bone-on-bone" chondral defects at the lateral femoral condyle (black arrows) and lateral tibial plateau (yellow arrows).

Table 1. List of Additional Arthroscopic Procedures Performed in the Intervention Group

Arthroscopic Procedure	No. of Events	% of Patients
Plica resections	28	65
Lateral patellar releases	26	60
Meniscus procedures	11	26
Burring of osteophytes	5	12
Removal of loose bodies	1	2

performed at 6, 12, 18, and 24 months after surgery for the intervention group.

Statistical Analysis

The coprimary endpoints were tested using a group sequential design with 1 interim analysis. The Haybittle-Peto approach was applied to maintain the overall 2-sided $\alpha = .05$, in which at the interim analysis, .025 α was spent at 40% of the total information level. Based on an overall power of at least 80% to detect an effect size of 0.74 for the IKDC and 0.74 for the KOOS-pain subdomain, this study would need a total of 84 randomized patients (42 per arm). This would assume no correlation between the 2 outcomes and was calculated with a *t* test. Any positive correlation between the outcomes and the use of the planned mixed-model repeated-measures analysis would result in smaller effect sizes being observable with the same power. Nevertheless, taking into consideration an estimated withdrawal rate of 30% in the control group (60 patients) and 15% in the intervention group (50 patients) prior to month 24, a total of 110 randomized patients were estimated to be required for the study. For even distribution of patients between the 2 sites, the total number of patients was decided to be 120 with 60 patients in each group.

To measure statistical significance between control and intervention group, the endpoints were tested using a group sequential design with 1 interim analysis. The Haybittle-Peto approach was applied to maintain the overall type I error rate at 2-sided $\alpha = .05$ significance level. The Haybittle-Peto boundary was 0.025 (bilateral) at the interim analysis and 0.032 (bilateral) at the final analysis.

To measure the clinical significance of the treatment outcome applicable only for the intervention group, minimal clinically important differences (MCIDs) were calculated for IKDC and all of the KOOS subdomains. The MCIDs were calculated based on a distribution-based method, in which the MCID value was equal to half of the standard deviation of the outcome measurement at baseline.[30-32] Clinically significant outcome was defined as outcome measurement/score change surpassing the calculated MCID value at follow-up for individual patients.

Results

The protocol-defined interim analysis was performed and the results presented to the DSMC. Early closure of the study was recommended by the DSMC due to overwhelming statistical significance seen at 2 years in the absence of any safety concerns. Enrollment was halted in March 2020, and the study was therefore concluded prior to the recruitment of the 120 patients as originally designed.

At the point of halting study enrollment, the total recruited patients in this study were 81 (control, 38; intervention, 43). Sixty-nine of the 81 patients recruited at both sites reached 2 years' follow-up (control, 33; intervention, 36) at the time of the interim analysis conducted in December 2019. Table 2 shows the demographics of the enrolled patients. There was no statistical significance regarding age, weight, height, or body mass index between the groups.

Subjective IKDC Scores

The subjective IKDC scores reached statistical significance at 18 months ($P = .0045$) and at 24 months ($P < .0001$). Further statistical analysis for the change from baseline of the individual data set at each time point found that statistical significance was achieved from month 18 with $P = .0044$ and at month 24 with $P < .0001$ (Table 3 and Fig 3).

Table 2. Demographics of the Control and Intervention Groups at the Time of Interim Analysis*

Characteristic	Control Group	Intervention Group	*P* Value
Total number	33	36	—
Age, y	44.8 (8.83) [23-55]	44.6 (7.08) [25-55]	.918
Sex, No. (%)			—
Male	17 (51.5)	19 (52.8)	
Female	16 (48.5)	17 (47.2)	
Weight, kg	75.7 (12.49) [49.9-95.4]	78.4 (14.07) [53.2-108.0]	.401
Height, cm	168.8 (9.33) [150.0-188.0]	169.8 (9.43) [154.0-188.0]	.660
Body mass index	26.51 (3.596) [19.7-35.0]	27.07 (3.332) [20.2-34.8]	.509

*Data are presented as mean (SD) [range] unless otherwise indicated.

Table 3. *P* Values of All Endpoints at Months 0 (Baseline), 6, 12, 18, and 24*

Outcome Score	Time Points, mo	*P* Value of Mean	*P* Value of Change From Baseline
Subjective IKDC	0	.8842	NA
	6	.6600	.7599
	12	.2443	.1951
	18	.0045	.0044
	24	<.0001	<.0001
KOOS-pain	0	.1965	NA
	6	.5497	.6086
	12	.0047	.0106
	18	<.0001	<.0001
	24	<.0001	<.0001
KOOS—other symptoms	0	.4712	NA
	6	.0705	.1034
	12	.0008	.0024
	18	<.0001	<.0001
	24	<.0001	<.0001
KOOS-ADL	0	.4873	NA
	6	.3306	.3914
	12	.0447	.0516
	18	.0002	.0003
	24	<.0001	<.0001
KOOS-sports/recreational	0	.5000	NA
	6	.0778	.1406
	12	.5481	.4946
	18	.0991	.0753
	24	<.0001	<.0001
KOOS-QoL	0	.8014	NA
	6	.5867	.6762
	12	.4090	.3512
	18	.0219	.0213
	24	<.0001	<.0001
NRS pain	0	.1736	NA
	6	.0001	.0533
	12	<.0001	.0003
	18	<.0001	.0002
	24	<.0001	<.0001
MOCART	0	.8486	NA
	12	<.0001	<.0001
	24	<.0001	<.0001

ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; NA, not applicable; NRS, Numeric Rating Scale; QoL, quality of life.
*Exceptions are the MOCART scores showing only months 0, 12, and 24.

KOOS Subdomains

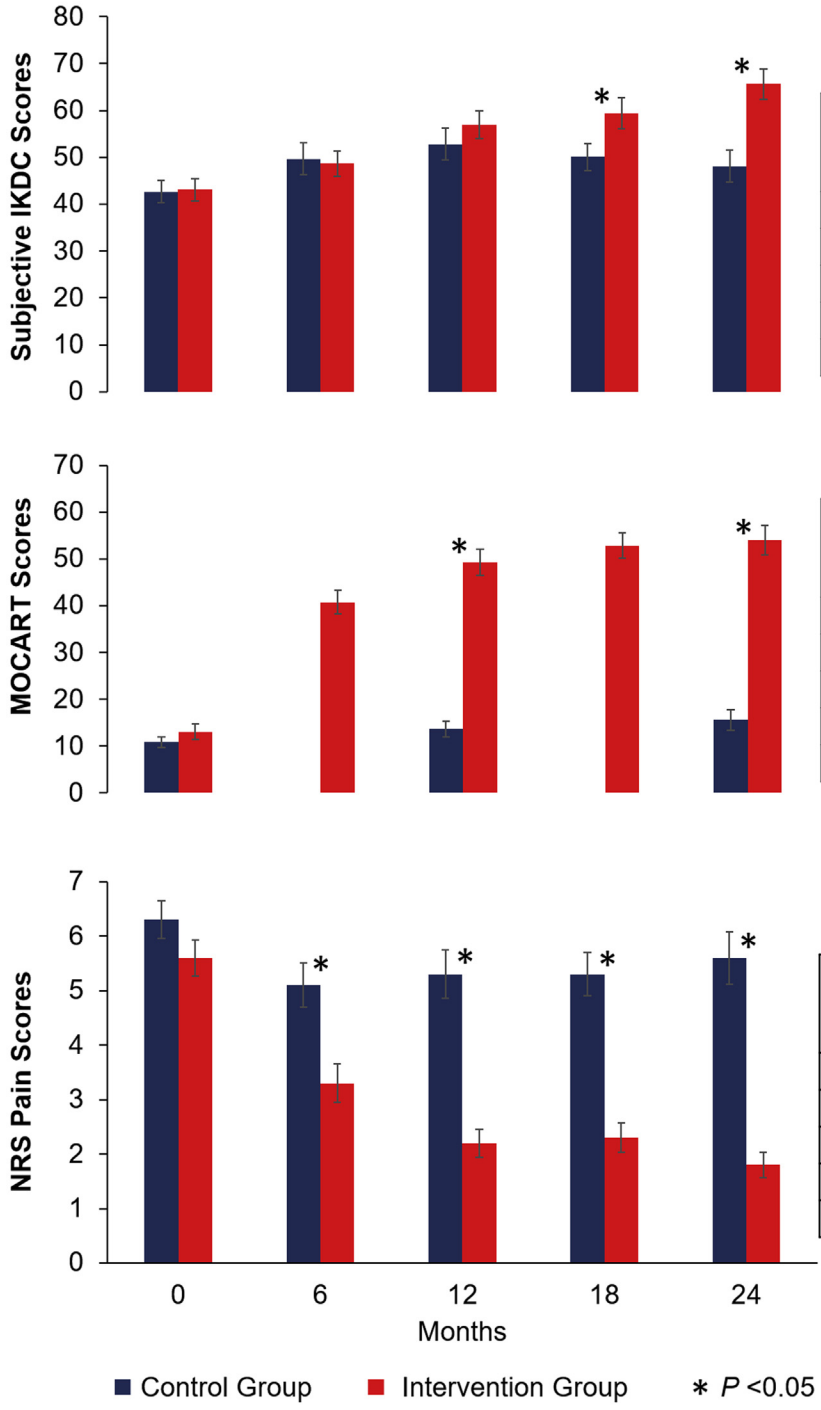
KOOS-pain subdomain as a coprimary endpoint showed statistical significance at 12 months for both the mean and the mean of change from baseline with *P* values of .0047 and .0106, respectively. The bar graphs of the KOOS-pain subdomain are presented in Figure 4. The remaining KOOS subdomains, other secondary endpoints, showed similar results. KOOS—other symptoms, KOOS—activities of daily living, and KOOS—quality of life achieved statistical significance prior to month 24 with KOOS—sports/recreational scores reaching statistical significance only at 24 months. All *P* values are presented in Table 3.

NRS Pain Scores

The NRS pain scores showed progressive improvement in the intervention group with statistical significance ($P = .0001$) as early as 6 months compared with the control group (Table 3 and Fig 3). The NRS pain score for the control group did not change significantly ($P = .1012$) from baseline to 24 months.

MRI Results

Figures 5 and 6 show an example of chondrogenesis in the intervention group. A female patient aged 50 years had right knee multiple chondral defects with varying sizes at the patellar (1.8 cm^2), trochlear (5.1 cm^2), and medial femoral (3.4 cm^2) condyle, including "bone-on-bone" defects at the lateral femoral condyle (2.9 cm^2) and lateral tibial plateau (2.1 cm^2). Figure 2 shows the arthroscopic view with corresponding MRI images (Fig 6 C and D) following subchondral drilling of the lateral femoral condyle and lateral tibial plateau, using a specially designed arthroscopic drill.



Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	42.7	2.37	43.1	2.31
6	49.7	3.39	48.7	2.66
12	52.8	3.43	57.0	2.99
18	50.1	2.88	59.4	3.26
24	48.1	3.34	65.6	3.31

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	10.9	1.11	13.1	1.721
6	N/A	N/A	40.8	0.683
12	13.7	1.62	49.3	2.558
18	N/A	N/A	52.9	2.825
24	15.6	2.20	54.0	2.646

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	6.3	0.34	5.6	0.33
6	5.1	0.41	3.3	0.36
12	5.3	0.44	2.2	0.25
18	5.3	0.40	2.3	0.27
24	5.6	0.48	1.8	0.23

Fig 3. Bar graphs of subjective International Knee Documentation Committee (IKDC), Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART), and Numeric Rating Scale (NRS) pain scores against time (months). Note that statistical significance ($P < .05$) is achieved at time points marked with an asterisk. NRS pain score shows greater pain when the number is higher. Improvement of pain is indicated by lower numbers.

MOCART Scores

The MOCART scores are presented in Table 3 and Figure 3, with statistical significance seen at 12 and 24 months after surgery ($P < .0001$ at both time points) and progressive improvement up to month 24 in the intervention group.

Clinical Significance for the Intervention Group

The MCID values of IKDC and all KOOS subdomains are shown in Table 4. At month 24, 70.8% of patients achieved clinical significance for the IKDC, KOOS-pain, KOOS−other symptoms, and KOOS−quality of life scores, whereby for

Table 4. MCID Values of IKDC and All KOOS Subdomains for the Intervention Group

		% of Patients Achieving Clinically Significant Outcome			
Outcome Measurement	MCID	Month 6	Month 12	Month 18	Month 24
IKDC	6.94	48.39	53.57	60.00	70.83
KOOS-pain	11.45	35.48	50.00	48.00	70.83
KOOS−other symptoms	9.70	54.84	75.00	64.00	70.83
KOOS-ADL	10.59	41.94	53.57	72.00	79.17
KOOS-sports/recreational	9.61	29.03	57.14	64.00	79.17
KOOS-QoL	8.78	35.48	50.00	60.00	70.83

ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MCID, minimal clinically important difference; QoL, quality of life.

KOOS−sports/recreational and KOOS−activities of daily living, 79.2% of patients reached clinical significance.

Complications and Adverse Events

No unexpected and related adverse or serious adverse events were observed. There were no postoperative infections and no cases of deep venous thrombosis diagnosed by the routinely performed duplex ultrasonography done 1 day after surgery in the intervention group. Two deep venous thrombosis adverse events were recorded at approximately 2 weeks after surgery. There were 11 reported adverse event incidents as cartilage injury, which were due to pain in the knee, and further investigation revealed that these were actually due to progression of the osteoarthritis (OA) process mainly in the control group.

Discussion

The results of this RCT evaluating intra-articular injections of autologous PBSCs plus HA after arthroscopic subchondral drilling into massive chondral defects of the knee joint showed that this cartilage repair technique is safe and effective, with improved knee function and pain reduction better than HA plus physiotherapy. Improvements for the intervention group in the subjective IKDC ($P < .0001$) and KOOS-pain subdomain scores ($P < .0001$) were statistically significant at 24 months compared with the control group. Moreover, more than 70% of the patients in the intervention group achieved the MCID value (Table 4) showing clinical significance for these primary outcome measurements, indicating that the treatment is effective.

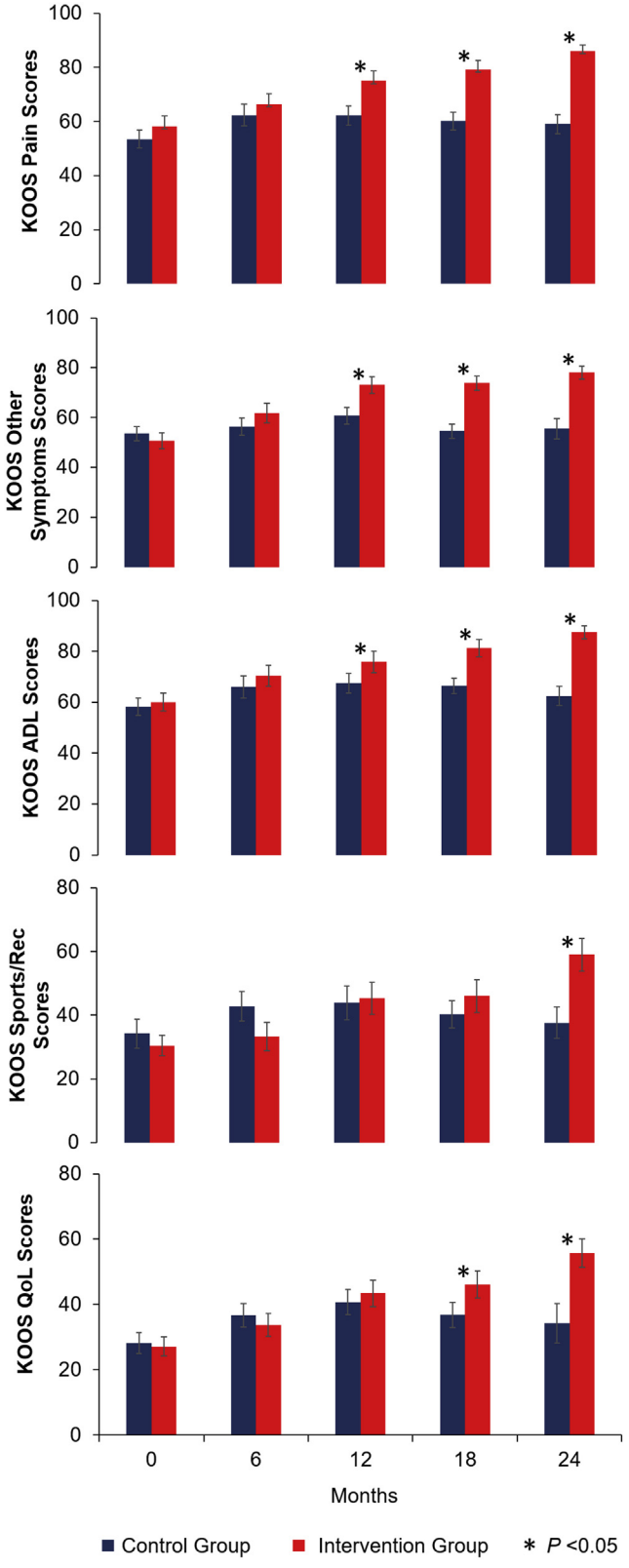
The MOCART score is an objective way of charting chondrogenesis. Statistical significance was observed for the intervention group ($P < .0001$) as early as 12 months after surgery when compared with the control group (Fig 3). As chondrogenesis progressed, evident by the increasing MOCART scores (Fig 3), the deleterious effects of OA regressed with time, resulting in statistical clinical improvement of knee function (IKDC scores) and pain reduction (KOOS-pain subdomain) in the intervention group at 2 years (Table 3, Figs 3 and 4).

When introducing a cartilage repair technique to address massive chondral defects, safety is of paramount concern. The expected and related adverse events are mainly secondary to the surgical procedures, apheresis process, and associated intra-articular injections. There were no unexpected and related adverse or serious adverse events. The MRI scans performed during this study allow assessing the entire repair area, charting chondrogenesis, and imaging the whole knee joint in a noninvasive manner. The scans revealed no evidence of adverse synovial or osseous changes.

We named our cartilage repair technique the KART procedure, an abbreviation for KLSMC (Kuala Lumpur Sports Medicine Centre) Articular Regeneration Technology. Kuala Lumpur Sports Medicine Centre has been developing this articular cartilage regeneration method since 2005.[15,21-23] The development of this method for chondrogenesis is guided by best available clinical and histologic evidence. KART has the ability to repair and regenerate massive chondral defects in the knee and other joints,[22,33,34] provided that the 3 main components of this chondrogenesis methodology are adhered to, namely, (1) specialized surgical technique, (2) multiple PBSCs plus HA intra-articular injections, and (3) physiotherapy with a tailored weightbearing regime.

Surgical Technique

In 2011, we published[21] our concept of drilling closer and deeper together as opposed to what was recommended for microfracture surgery, as seen in Figure 7. As a result, our surgical technique has subsequently evolved so that a goal of 1 mm between drill holes is now preferred based on the results of second-look arthroscopy. This enhanced method of arthroscopic subchondral drilling is further simplified with the development of a recently designed arthroscopic drill, as seen in Figure 2. It is not crucial that the subchondral drilling be performed perpendicular to the bone surface because a lesser angle of drilling capable of penetrating into the subchondral bone is sufficient. The important



Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	53.5	3.33	58.2	3.82
6	62.4	3.99	66.5	3.83
12	62.2	3.57	75.0	3.81
18	60.2	3.35	79.2	3.28
24	59.0	3.49	86.0	2.34

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	53.6	2.85	50.7	3.23
6	56.4	3.48	61.7	3.93
12	60.7	3.42	73.1	3.29
18	54.5	2.89	73.9	2.85
24	55.5	4.03	78.0	2.53

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	58.2	3.36	60.1	3.53
6	66.0	4.29	70.3	4.13
12	67.5	3.96	75.9	4.20
18	66.5	3.05	81.2	3.39
24	62.5	3.69	87.5	2.47

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	34.2	4.61	30.4	3.20
6	42.8	4.73	33.3	4.39
12	43.9	5.34	45.3	5.13
18	40.2	4.29	46.0	5.16
24	37.6	4.96	59.0	5.18

Months	Control Group		Intervention Group	
	Mean	SEM	Mean	SEM
0	28.2	3.25	27.1	2.93
6	36.7	3.66	33.7	3.48
12	40.7	3.87	43.4	4.07
18	36.8	3.92	46.1	4.15
24	34.2	5.99	55.8	4.37

Fig 4. Bar graphs of all Knee Injury and Osteoarthritis Outcome Score (KOOS) subdomains scores. Note that statistical significance ($P < .05$) is achieved at time points marked with an asterisk. (ADL, activities of daily living; QoL, quality of life.)

aspect of this chondrogenesis methodology is that each drill hole creates a turf of cartilage (Fig 7B). A sufficient depth of drilling is therefore required to have an adequate volume of blood clot scaffold to differentiate into protruding cartilage into the joint surface. The clinical relevance is that there is no limitation to the size

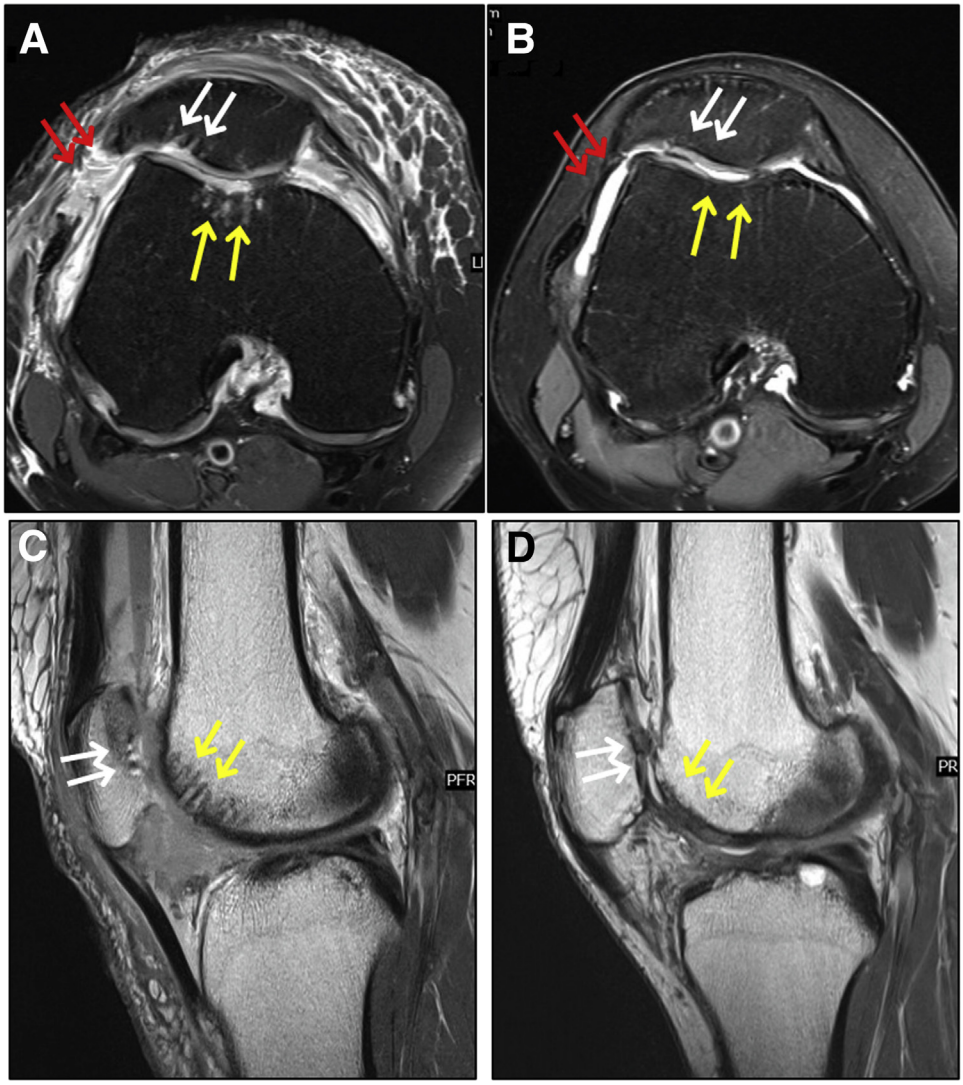


Fig 5. Magnetic resonance (MR) images of the right knee. (A) An axial image of full-thickness chondral defects of the patella (white arrows) and trochlear (yellow arrows) following subchondral drilling and lateral patellar release (red arrows). (B) An axial image of the same knee at 2 years after surgery showing full-thickness articular cartilage regeneration of the same lesions (white and yellow arrows) with healing of the previously performed lateral patellar release (red arrows). (C) A sagittal image of the same defects (white and yellow arrows) following subchondral drilling. (D) A sagittal image of the same lesions (white and yellow arrows) 2 years after surgery showing satisfactory chondrogenesis. (A, B) Axial fat-suppressed proton density-weighted MR images. (C, D) Sagittal proton density-weighted MR images.

of the chondral defects that can be addressed, so long as subchondral drilling is performed. The absence of chondrogenesis in between the drill holes, as seen in Figure 7C, further emphasizes the need for subchondral drilling. This provides evidence that, in the absence of drilling, intra-articular injection of PBSCs plus HA alone is unable to regenerate cartilage. Further examples can be seen in our previously published book chapter,[33] showing that it is not possible for abrasion chondroplasty on its own to regenerate high-quality repair cartilage. It is important to address other concomitant pathology of the affected knee joint prior to the chondrogenesis process. Common examples are correction of malalignment, ligamentous instability, meniscus procedure, and lateral patellar maltracking.

Multiple PBSCs Plus HA Intra-articular Injections

Our current protocol consists of 5 weekly intra-articular injections (8 mL PBSCs plus 2 mL HA) starting at 1 week after surgery and 3 weekly booster injections at 6, 12, and 18 months (4 mL PBSCs plus 2 mL HA). The rationale for this is that in the first 5 weeks after surgery, the aspirated hemarthrosis before injection is normally between 10 and 50 mL, and therefore a 10-mL intra-articular injection (8 mL PBSCs plus 2 mL HA) does not result in significant discomfort. Beyond 6 months, knee aspiration is usually minimal, and an intra-articular injection of 6 mL (4 mL PBSCs plus 2 mL HA) is generally more comfortable. Histologic analysis of 18- to 24-month biopsy specimens showed that samples with only 1 set of 3-weekly booster injections at 6 months still contain a certain amount of fibrocartilage and a lesser amount of collagen II. This is in contrast to samples that received 3-weekly booster injections at 6, 12, and 18 months, which showed that the regenerated articular cartilage score approached 95% of the normal articular cartilage score histologically.[22,23] The mechanism of action of PBSCs plus HA and the

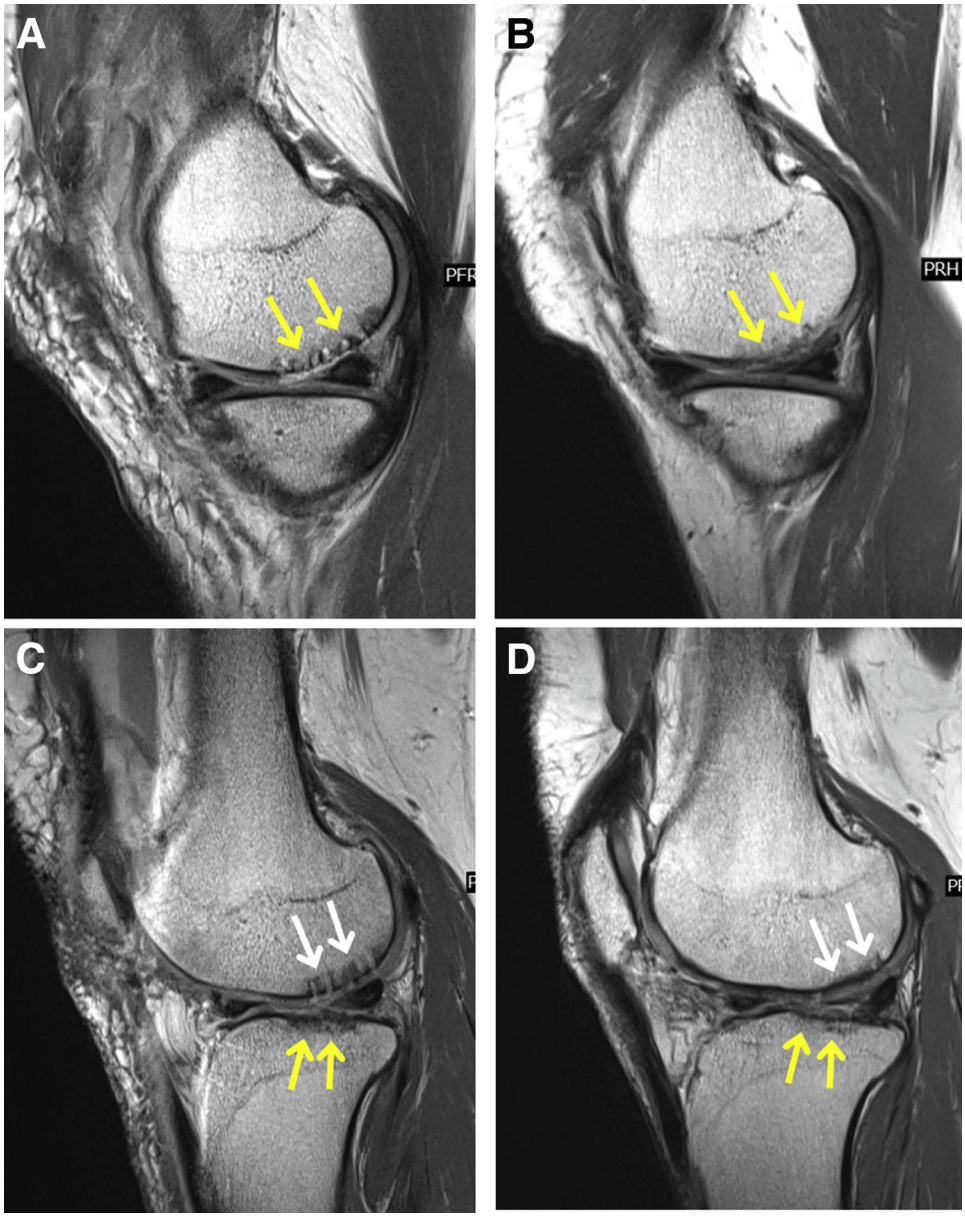


Fig 6. Sagittal proton density-weighted magnetic resonance images of the right knee. (A) Large medial femoral condyle defect (yellow arrows) following subchondral drilling and (B) the same lesion at 2 years after surgery showing full-thickness articular cartilage regeneration (yellow arrows). (C) "Bone-on-bone" chondral defects of the lateral femoral condyle (white arrows) and lateral tibial plateau (yellow arrows) following subchondral drilling, with corresponding arthroscopic images in Figure 2, and (D) the same lesions at 2 years after surgery showing full-thickness articular cartilage regeneration.

rationale for this protocol have been explained in our previous publication.[23] It is important to note that without stem cells, animal and human histologic studies showed no evidence of collagen II formation.[15,20,22] Thus, poorer quality of repair cartilage and in the long term will result in lesser resilience of the treated joint.

Physiotherapy With a Tailored Weightbearing Regime

Our previous publication[21] looking into regenerated cartilage biopsy specimens from a nonweightbearing area to those from a weightbearing area has led us to believe that early partial to full weightbearing is essential for the regeneration and remodeling of the collagen fibrils with alignment along the axis of weight transmission. After surgery, continuous passive motion is used on the operated knee 2 hours per day for a period of 1 month. Passive motion aids synovial movement, as well as provides chemical and cellular signals for the stem cells to differentiate into chondrocytes and hence regenerate cartilage.[35,36] Patients with subchondral drilling to the weightbearing femorotibial joint (FTJ) are instructed on crutch-assisted partial weightbearing (15-20 kg) commencing on the first postoperative day for the first 6 weeks. This progresses to full weight-bearing in 6 to 8 weeks.

Patients with drilling limited to the patellofemoral joint (PFJ) are allowed partial to full weightbearing of the FTJ as tolerated in the first 6 to 8 weeks. An example of this is mobilizing with a pair of crutches

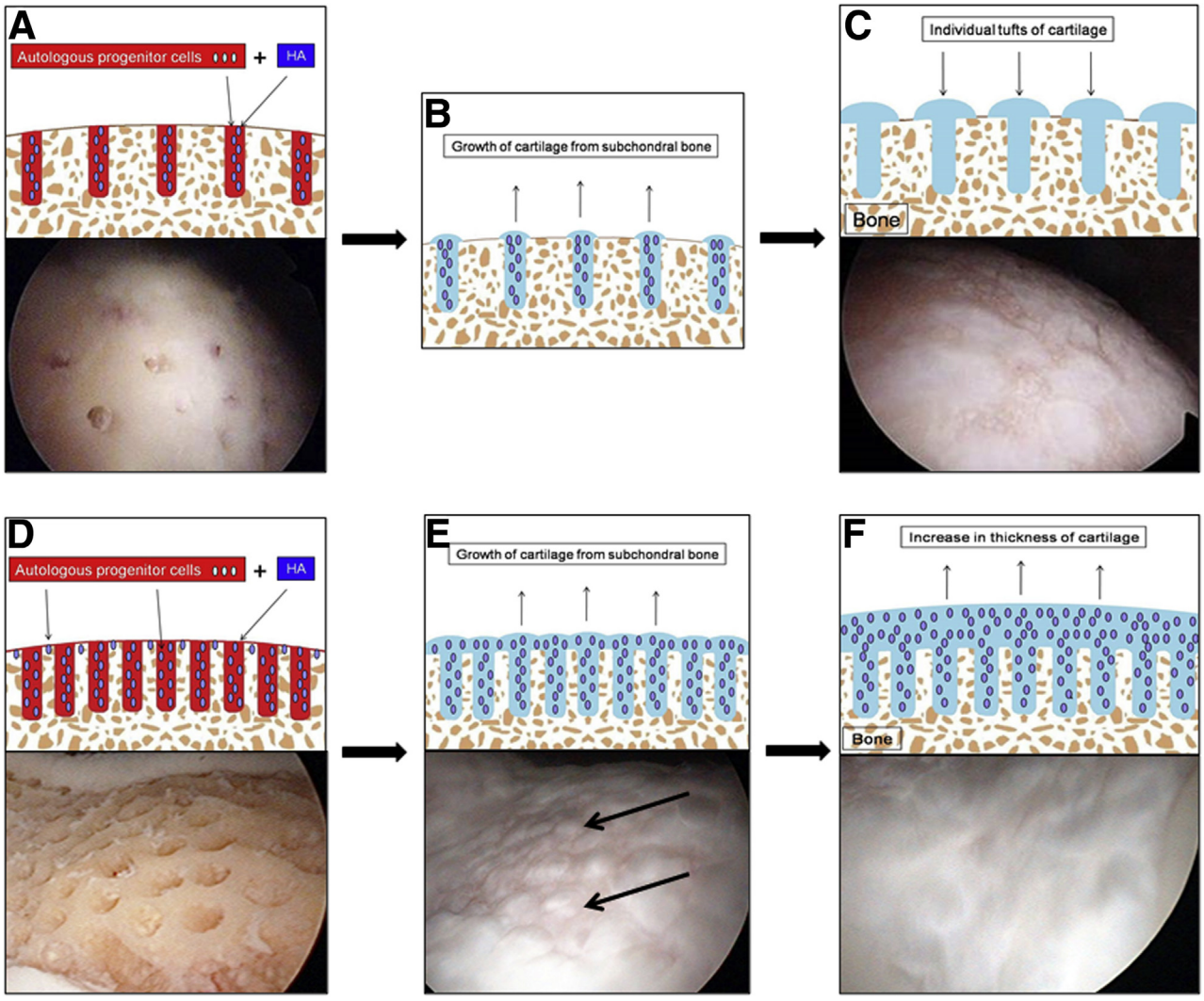


Fig 7. Chondrogenesis on uncontained lesion with sparse drilling, showing (A) in large chondral defects with areas of bare bone, the only available blood clot scaffold is from the areas after subchondral drilling. Injection of autologous peripheral blood stem cells (PBSCs) plus hyaluronic acid (HA) will result in the homing of the PBSCs into the subchondral blood clot scaffold, initiating the chondrogenesis process. (B) Due to the absence of blood clot scaffold superficial to the subchondral bone, chondrogenesis can only be achieved by the protruding tufts of cartilage from the subchondral bone drilling. Each individual "drill hole" produces one tuft of cartilage. (C) If the subchondral drill holes are placed too far apart, the end result is the incomplete coverage of the subchondral bone with individual tufts of cartilage seen between areas devoid of cartilage. The lower parts of A and C are arthroscopic pictures to further illustrate this process. Chondrogenesis on an uncontained lesion with ideal drilling, showing (D) ideally placed subchondral drilling (1 mm apart) and abrasion chondroplasty between the drill holes increase the available bony areas for the homing of the PBSCs and HA, enabling a larger surface area of raw bone to initiate the process of chondrogenesis. (E) Individual tufts of cartilage arise from the subchondral bone and coalesce to cover the bony defect, initially with a "cobblestone" appearance (lower image, black arrows). (F) Progressive chondrogenesis results in an increase in thickness of the regenerated cartilage covering the entire defect. The images shown below D, E, and F are arthroscopic pictures for further illustrations. (Images adapted from Saw et al.[21])

with the knee in extension. However, there is a significant distinction between postoperative weightbearing for the FTJ as opposed to the PFJ, as seen in Figure 8. During normal walking gait, the FTJ naturally provides weightbearing on both the femoral and tibial components. This is not the case with the PFJ as normal gait on heel strike with the knee in full extension does not engage the loading surfaces of the PFJ to provide enough loading of the patellar and trochlear components. To achieve this, patients with PFJ subchondral drilling need to have a tailored program of loadbearing over the range of the drilling areas with a variable degree of knee flexion to provide sufficient loading across the patellar and trochlear components (Fig 8C). It is important to start with static loading (10-20 kg) in the sitting position from the first postoperative day with a

variable knee flexion for the first 6 weeks and then progress to full weight loading over the subsequent 6 to 12 weeks. This is to avoid overloading the PFJ. Restrictions from partial to full weightbearing on stairs for the first 3 to 6 months after surgery are advised depending on the size of the PFJ chondral defects. As forces are exerted across the patellar and trochlear surfaces during knee motion, there is an associated shearing component that needs to be minimized in the early stages of chondrogenesis. If not, this shearing component from the drill holes is akin to a "cheese grater" and may "grate" off the normal component of the cartilage surfaces when the drilled patella glides over the trochlear or vice versa. As chondrogenesis progresses in 6 to 12 weeks and the feeling of clinical PFJ crepitation decreases, we then tailor progressive static and dynamic loading in terms of increasing the load when patients are standing with flexion of their knees. Stationary bike cycling commences at 6 weeks with variable cycling angles depending on the desired areas of contacts over the previously drilled PFJ, initially cycling without applying any resistance. As the PFJ crepitus decreases with progressive chondrogenesis, resistance is then gradually increased during cycling. Drilling involving both the FTJ and PFJ takes into consideration the 2 variables of postoperative physiotherapy regime and is tailored accordingly.

The main differences comparing the KART procedure to the widely performed microfracture surgery are shown in Table 5. The crucial significant difference is the ability of the KART procedure to repair and regenerate cartilage approaching 95% of normal articular cartilage histologically and hence potentially provide better endurance to the repair cartilage.[23] Microfracture surgery, on the other hand, heals by fibrocartilage, and therefore the repair tissue is likely to break down more readily.

This study adds to a body of literature evaluating PBSCs for cartilage repair. At other independent sites, similar encouraging results have been seen, including 2 case series and 1 comparative study comparing open implantation of PBSCs to open implantation of bone marrow concentrate.[26,37,38]

In 2016, the US Food and Drug Administration approved the next generation of autologous chondrocyte implantation (ACI), known as matrix-assisted autologous chondrocyte implantation (MACI). Efficacy data were based on a 2-year, prospective multicenter RCT, comparing MACI to microfracture, in which MACI outperformed microfracture alone with KOOS subdomains. Histologic evaluation based on International Cartilage Repair Society II score of biopsy specimens for 116 patients and MRI evaluation of the morphology of cartilage repair tissue showed no statistical significance between the groups.[39] A prospective clinical study evaluating Osteochondral Autograft or Allograft Transfer Systems and ACI illustrated predominately fibrocartilage-type healing response on histology.[40]

Regardless of the results seen in all current cartilage repair technologies, studies[41,42] have determined that 10 years after treatment with current procedures, a significant number of patients fail the treatment, which is defined by the patient requiring a reoperation because of symptoms resulting from a lack of healing of the treated defect. Of those who survive, 50% of them have OA.[3]

Our method of chondrogenesis with stem cells in massive chondral defects may not stop future wear-and-tear processes such as degenerative OA, but it does address cartilage defects by regenerating resilient repair cartilage approaching 95% of normal articular cartilage histologically.[23] The technology aims to restore knee cartilage back to its preinjury status, reestablishing the smooth gliding surfaces of the knee joint and thus enabling patients to experience normal or near-normal knee function and continue with relatively pain-free activities of daily living and ultimately slowing or regressing the pathogenesis of OA. The results are best illustrated in Figures 3 and 4. Figures 5 and 6 show an example of multiple large chondral defects with "bone-on-bone" cartilage loss over the patellofemoral and tibiofemoral aspects of the knee joint. The extent of cartilage loss in this example remains a challenge for existing cartilage repair technologies to address.

Selecting an appropriate control group for this "unmet medical need" study was challenging. Our previous RCT (published in year 2013)[22] comparing arthroscopic subchondral drilling into grade 3 and 4 chondral lesions concluded that postoperative intra-articular injections of autologous PBSCs plus HA resulted in an improvement of the quality of articular cartilage repair over the same treatment without PBSCs, as shown by histologic and MRI evaluation. However, in this previous RCT,[22] the subjective IKDC clinical scores at 2 years showed no statistical significance comparing the 2 groups. This can be explained by the fact that the 2013 RCT was not designed to address massive chondral defects as opposed to this current "unmet medical need" RCT specifically tailored for massive chondral defects. Those smaller lesions were traditionally treatable by marrow stimulation procedures alone, with 2-year results in the control group (subchondral drilling plus HA injections) likely similar to published microfracture series.[43] The overall conclusion from that publication is that without stem cells, repair tissue is inferior-quality fibrocartilage. We believe that histology showing high-quality repair cartilage is one of the key factors to the success of the cartilage restoration procedure. As this is a developing technology, incremental improvement can only be made with recently found evidence-based medicine. Our publication in 2015[23] combining high tibial

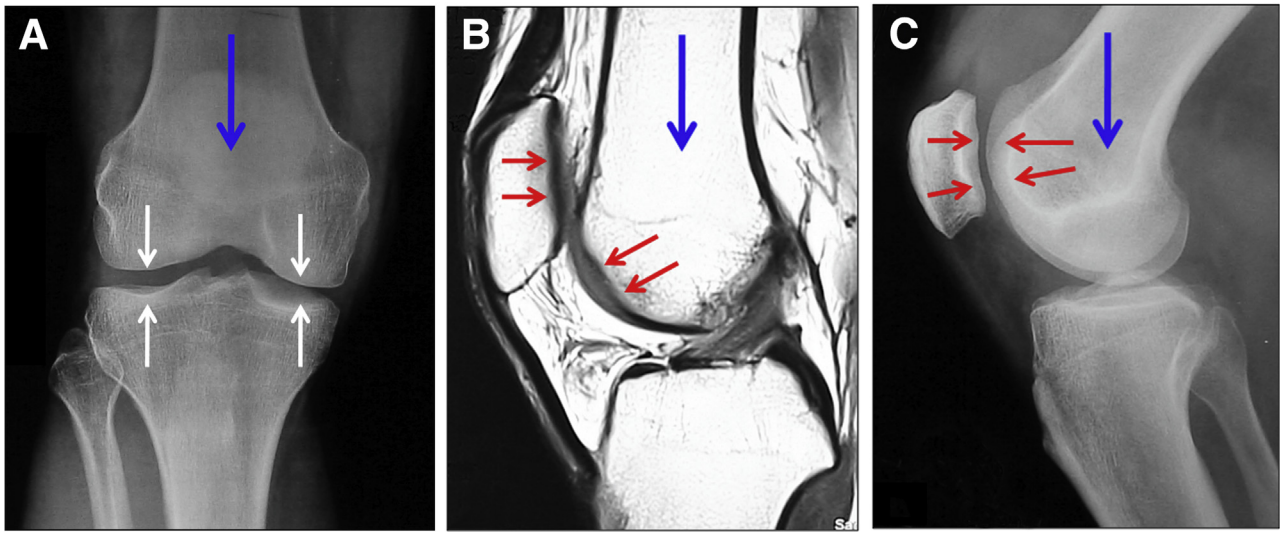


Fig 8. Opposing forces acting across the right femorotibial joint (FTJ, white arrows) and patellofemoral joint (PFJ, red arrows) during load bearing (blue arrow). (A) During normal walking gait, the FTJ naturally provides weightbearing on both the femoral and tibial components. (B) With the knee in full extension, the PFJ does not load the patellar and trochlear components. (C) A variable degree of knee flexion is required to provide sufficient loading across the patellar and trochlear components.

osteotomy with stem cells chondrogenesis showed the ability of the KART procedure to regenerate articular cartilage approaching 95% of normal cartilage histologically. Therefore, it was deemed unethical to have a control group in this current RCT treating massive chondral defects with only subchondral drilling and HA injections, knowing that the repair tissue would be an inferior-quality fibrocartilage. Other current methods of treating chondral lesions were also not appropriate to be selected as a control as those methods have not been shown to be effective to address massive chondral defects,[9,10] similar to the example seen in Figures 5 and 6. These methods include microfracture, subchondral drilling, Osteochondral Autograft or Allograft Transfer Systems, ACI, and MACI. As such, constantly reminding ourselves to do no harm to the control group, we were left with limited options and therefore looked into what other treatments were currently being offered by clinicians facing these challenging cases. We eventually chose HA plus physiotherapy as the control group.

Limitations

As this is an unblinded study, it is susceptible to bias. However, the MOCART score does provide an objective method of charting chondrogenesis when comparing the 2 groups (Fig 3). The control group received no surgery, and therefore symptoms related to mechanical causes, as seen in Table 1, were not addressed. These surgical procedures may provide temporary relief to the control group, affecting the clinical scores at 2 years.[44]

The current data presented for this clinical trial are limited to patients who have completed the 2-year follow-up; data from patients who have not completed the 2-year follow-up were not included in the final analysis. However, the number of patients in this category (control, 5; intervention, 7) is unlikely to influence the overall statistics. At the time of writing, there were also no safety concerns from these 12 additional patients.

Last, the MCID used is derived from a distribution-based method. Future work should combine distribution-based and anchor-based methods to increase the sensitivity of MCID value for this treatment. In addition, patient acceptable symptom state and/or substantial clinical benefit should also be included to assist clinicians to gauge clinical effectiveness of PBSC treatment and truly reflect clinical significance for the study.

Conclusions

Arthroscopic marrow stimulation with subchondral drilling into massive chondral defects of the knee joint

Table 5. Comparison Between KART and Microfracture

KART	Microfracture
Drill holes closer and deeper	Microfractures too far apart and too shallow
No limitation on size of defects	Better results in defects <2 cm^2
PBSCs plus HA intra-articular injections	No cells or HA injections
Early progressive weightbearing	Nonweightbearing for the first 6 weeks
Tailored weightbearing physiotherapy	Nontailored physiotherapy

HA, hyaluronic acid; KART, KLSMC (Kuala Lumpur Sports Medicine Centre) Articular Regeneration Technology; PBSC, peripheral blood stem cell.

followed by postoperative intra-articular injections of autologous PBSCs plus HA is safe and showed a significant improvement in clinical and radiologic scores as compared with HA plus physiotherapy.

Acknowledgment

This study is sponsored by KLSMC Stem Cells Inc and supported by grants from City of Gulf Breeze, Florida, and the State of Florida. The authors thank Dr Surinder Kaur, Ms Malar Muniandy, Ms Amal Mohd Dawam, Ms Alisha Ramlan, Ms Jocelyn Dowse, Ms Casandra Tan, and Mr Wai Choong Koh from Kuala Lumpur Medicine Centre, Malaysia; Dr Candace Anz, Dr Josh Hackel, Mr Johnny Torres, and Ms Mikala McMillion at the Andrews Research and Education Foundation, U.S.A.; and Dr Thong Chwee Ling, Dr Raja Kumar Rajendram, and Dr Gregory Hickman from both study centers.

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