MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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# PERIPHERAL BLOOD STEM CELL (PBSC) FOR ARTICULAR CARTILAGE REGENERATION (AN UPDATE)

## SUMMARY OF TECHNOLOGY

Peripheral blood (PB) is a potential source of chondrogenic progenitor cells that can be used for cartilage repair and regeneration. PB-derived stem cells (PBSCs) can be obtained by a minimally invasive procedure with fewer complications than bone marrow (BM) harvesting. Moreover, PBSCs also have the ability to be used in autologous transplantation, which benefits patients in clinical applications and facilitate the development of a one-stage surgical solution and other cell-based therapies. PBSCs considerably warrant further clinical trials due to their superiority and safety in clinical settings and positive effects for articular cartilage repair.

## INNOVATIVENESS

| | |
|---|---|
| Novel, completely new | |
| Incremental improvement of the existing technology | |
| New indication of an existing technology | / |

## DISEASE BURDEN

Articular cartilage (AC) injury is a common disease that usually caused by sport injuries, accidental trauma or joint diseases. It is a very limited self-repair ability and the small injuries would progress to larger lesions over time if left untreated, and eventually lead to osteoarthritis (OA). The injuries will result to in severe knee pain, swelling and joint stiffness, which seriously affect patient's quality of life (QOL).[1,2,3]

The biological repair of injured AC may reduce the medical costs by restoring the healthy native tissue and providing long-term symptom control.[4]

## CURRENT OPTIONS FOR PATIENTS

There are various surgical methods currently used in the effort to regenerate hyaline cartilage such as microfracture, osteoarticular autograft transfer system, mosaicplasty and autologous chondrocyte implantation (ACI).[5]

Since a decade, a synthetic and biologic adjuncts including the use of hyaluronic acid (HA), platelet rich plasma (PRP), mesenchymal stem cells (MSC) and peripheral blood progenitor cells (PBPC) are the emerging options for articular cartilage injuries.[6]

## POTENTIAL IMPACT OF TECHNOLOGY

An electronic search of databases such as PubMed and general databases such as Google Scholar were conducted by using these keywords either singly or in any combination; peripheral blood stem cells (PBSCs), articular cartilage regeneration and articular cartilage repair. All searches were limited to human study and conducted up to 10$^{th}$ April 2022.

Three clinical trials, two prospective cohort study and one case study were identified.

a) Clinical impact

A Phase IIB clinical trial by Saw K-Y et al. reported the efficacy and safety of intra-articular injections of autologous peripheral blood stem cells (PBSCs) plus hyaluronic acid (HA) after arthroscopic subchondral drilling. A total of 69 patients (intervention group: n=36; control group: n=33) aged 18 to 55 years with International Cartilage Repair Society (ICRS) grade 3 and 4 chondral lesions (size ≥3 cm$^2$) of the knee joint were included in this trial. The intervention group underwent arthroscopic subchondral drilling received intra-articular injections of PBSC (8ml) plus HA (2ml) and control group received intra-articular injections of HA plus physiotherapy. The intervention group was injected intra-articular once per week until fifth week. At six, 12$^{th}$ and 18$^{th}$ month after surgery, the injection repeated once per week for three weeks duration. The primary endpoint evaluated the International Knee Documentation Committee (IKDC) for a knee-specific measure of symptoms, function, and sports activity and Knee Injury and Osteoarthritis Outcome Score (KOOS) up to two years, meanwhile the secondary endpoint included all other KOOS subdomains (other symptoms, activities of daily living, quality of life and sports or recreational), Numeric Rating Scale (NRS) for pain, and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores.[7]

At 24 months, the mean IKDC scores for the control and intervention groups were 48.1 and 65.6, respectively ($p< 0.0001$). The mean for KOOS-pain subdomain scores were 86.0 for intervention group compared to 59.0 for control group ($p<0.0001$). All other

KOOS subdomain, NRS, and MOCART scores were statistically significant at month 24 ($p<0.0001$) (Figure 1).[7]

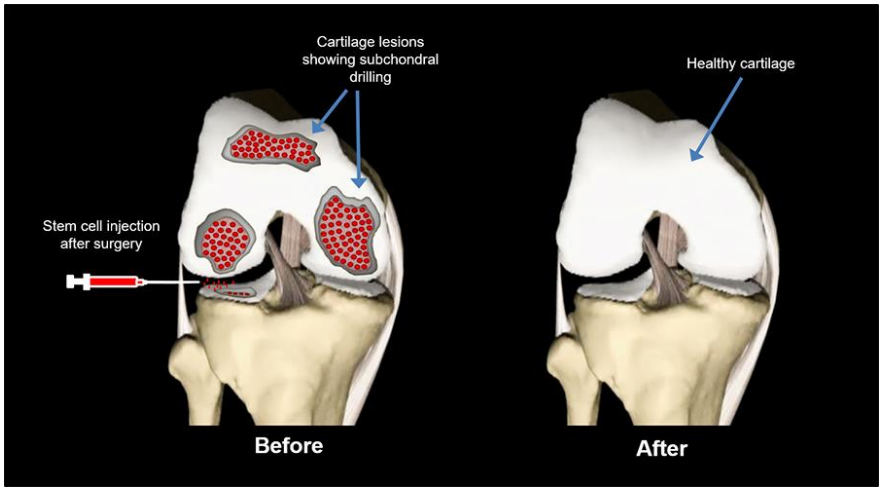
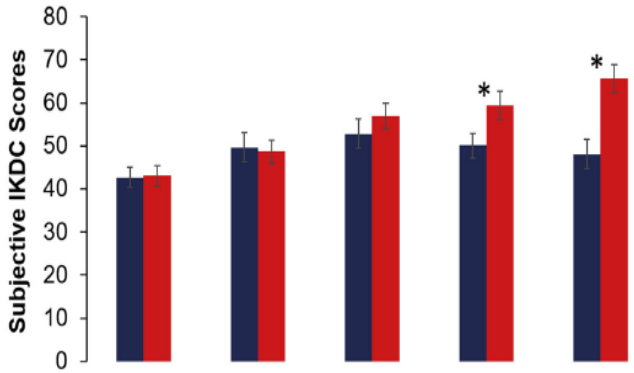
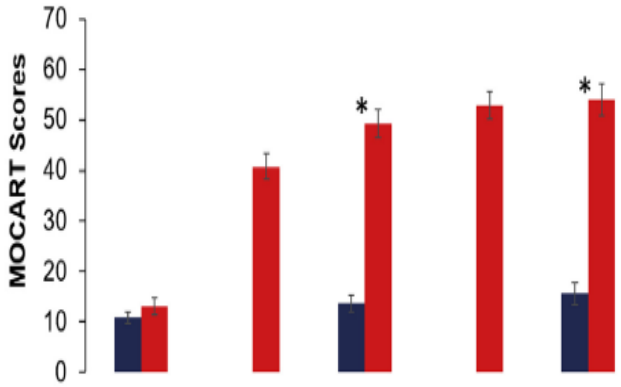


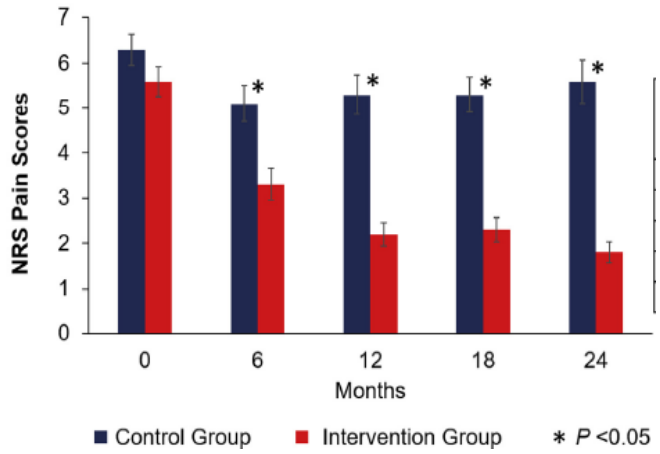

Figure 1: Patients with large cartilage knee defects before and after surgery (post stem cell injection)




| 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 |

Figure 2: 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 ($p< 0.05$) 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

About 70.8% of patients had IKDC and KOOS-pain subdomain scores exceeding the minimal clinically important difference values (MCID). The MCID values of IKDC and all KOOS subdomains were shown in Table 1.[7]

| | | % 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

Table 1: MCID Values of IKDC and All KOOS Subdomains for the Intervention Group

Turajane et al. reported a clinical evaluation for early osteoarthritis (OA) patients that failed conservative intervention for more than six months. Sixty patients below 60 years old (males; n=19, females; n=41) with chondral lesions were graded according to the

International Cartilage Repair Society (ICRS) grade III and IV lesions. The osteoarthritis knee was classified as Kellgren-Lawrence (KL) stages I to III. The primary endpoint and secondary endpoint for this trial were to evaluate the need for total knee arthroplasty (TKA) at 12 months and measuring WOMAC scores at one, six, and 12-month follow-up. In regenerating articular cartilage, the patients were divided into three groups. The Group 1 (males; n=10, females; n=10) received the combination of intra-articular autologous activated peripheral blood stem cells (AAPBSCs) with growth factor addition (GFA) consisted of platelet-rich plasma (PRP) and human granulocyte colony-stimulating factor (hG-CSF) along with HA in conjunction with arthroscopic micro-drilling mesenchymal cell stimulation (MCS). Meanwhile, Group 2 (males; n=3, females; n=17) received the same combination with the exception of hG-CSF. Patients in Group 3 (males; n=6, females; n=14) only received intra-articular HA without any arthroscopic surgery (control group). Each group received one weekly injection for three consecutive weeks and was evaluated at one, six, and 12 months.[8]

The primary endpoint for total knee arthroplasty (TKA) was necessary for patient in Group 3 (n=3) compared to none from Group 1 and Group 2. The WOMAC scores showed significant differences between the three groups. The total WOMAC scores were divided into pain subscale, stiffness subscale and functional subscale. The scores were assessed at six and 12 month after the treatment. (Table 2)

| **Time/groups** | **6 months** | | | | **12 months** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **WOMAC score** | **Total** | **Pain** | **Stiffness** | **Function** | **Total** | **Pain** | **Stiffness** | **Function** | **Total knee arthroplasty (TKA)** |
| Group 1 versus group 2 | S | S | NS | S | NS | NS | S | NS | |
| Group 1 versus group 3 | S | S | S | S | S | S | S | S | |
| Group 2 versus group 3 | S | S | BS | NS | S | S | BS | S | |
| Groups 1 + 2 versus group 3 | | | | | S | | | | S |

*S= significant; NS= nonsignificant; BS= borderline significance.

*Group 1=patients received autologous activated PBSCs with growth factor addition (GFA) consisted of platelet-rich plasma (PRP) and human granulocyte colony-stimulating factor (hG-CSF) along with HA

*Group 2= patients received autologous activated PBSCs with growth factor addition (GFA) consisted of platelet-rich plasma (PRP) along with HA

*Group 3= patients only received intra-articular HA without any arthroscopic surgery (control group).

Table 2: WOMAC score and subscale analysis

There was statistical significance pooled result for Group 1 and Group 2 (p=0.033) (Table 3).

| 12 month follow up | Group 1 (n=20) | Group 2 (n=20) | Group 3 (n=20) | p value |
|---|---|---|---|---|
| Total knee arthroplasty (TKA) | 0 | 0 | 3 | Pooled groups 1 and 2 at 12 months: p<0.033 |

Saw K-Y et al. reported the evaluation of articular cartilage regeneration in patients with chondral lesions (International Cartilage Repair Society (ICRS) grade 3 and 4) were treated by intra-articular injections of hyaluronic acid (HA) with and without peripheral blood stem cells (PBSC) after arthroscopic subchondral drilling. Two group comprised of 25 patients were treated with PBSC and hyaluronic acid (HA) and 25 patients in control group. After a week of surgery, all the patients received five weekly injections up to six months. At six months of treatment, three additional intra-articular injections were administered at weekly intervals. There was a significant difference of the average age for two groups. The control group was 42 years and the average age of the intervention group (PBSC and HA) was 38 years (p= 0.031). The morphologic grading of the magnetic resonance imaging (MRI) was obtained at 18 months showed significant difference between intervention group (point scale; 9.9) and control group (point scale; 8.5)(p=0.013). The intervention group scored 14% higher with flush morphologic features, 23% higher on good repaired cartilage fill and 20% higher with no gap integration.[9] (Table 4)

| Finding | No (%) | |
|---|---|---|
| | Intervention group (PBSC + HA) | Control group (HA only) |
| Repaired lesion morphologic features | | |
| Flush | 38 (68%) | 32 (54%) |
| Proud | 8 (14%) | 8 (14%) |
| Depressed | 10 (18%) | 19 (32%) |
| Repaired cartilage fill | | |
| Good (67%-100%) | 46 (82%) | 35 (59%) |
| Moderate (34%-66%) | 6 (11%) | 10 (17%) |
| Poor (0%-33%) | 4 (7%) | 14 (24%) |
| Peripheral repaired cartilage integration | | |
| No gap | 44 (79%) | 35 (59%) |
| Small (gap of ≤2 mm) | 9 (16%) | 15 (25%) |
| Large (gap of >2 mm) | 3 (5%) | 9 (15%) |

Table 1: Comparison of control to intervention group with MRI morphologic scoring

According to the International Cartilage Repair Society Visual Assessment Scale II (ICRS II) score, the histologic scores for intervention group averaged 1066 compared to control group with average 957 (p=0.022). The histologic features of the intervention

group were more consistent with normal articular cartilage compared with control group.[9]

A prospective cohort study by Richter M et al. reported a comparison of Matrix-Associated Stem Cell Transplantation (MAST) with Autologous Matrix Induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC + PBC) in chondral lesions of the ankle. A total of 129 patients with 136 chondral lesions were included in the study for both MAST and AMIC + PBC groups. Three lesions were located at medial talar shoulder lateral talar shoulder, medial and lateral talar shoulder and tibia. The average lesion size was 1.6/1.8 $cm^2$. The average of follow-up for both groups were 24.4 months for MAST group and 23.8 months for AMIC plus PBC group (ranged months: MAST; 22 to 26, AMIC + PBC; 22 to 25). The visual analogue scale foot and ankle (VAS FA) was improved to 82.3/79.8 (MAST/AMIC + PBC). The follow-up parameters showed no significant difference between groups including follow-up rate, time and VAS FA score, and MRI stage of the chondral lesions.[10] (Table 5)

| Stage and stage description | MAST | | AMIC-PBC | |
|---|---|---|---|---|
| | Preop n (%) | FU n (%) | Preop n (%) | FU n (%) |
| 1 cartilage lesion only | 52 (38) | 34 (31) | 54 (40) | 40 (36) |
| 2a subchondral fracture with surrounding bone edema | 46 (34) | 12 (11) | 43 (32) | 19 (17) |
| 2b subchondral fracture with no surrounding bone edema | 8 (6) | 2 (2) | 9 (7) | 1 (1) |
| 3 detached but undisplaced fragment | 5 (4) | 3 (3) | 7 (5) | 3 (3) |
| 4 displaced fragment | 6 (4) | 2 (2) | 7 (5) | 1 (1) |
| 5 subchondral cyst | 18 (13) | 5 (5) | 16 (12) | 6 (5) |
| MRI-stage for chondral or osteo-chondral lesion negative (no lesion visible) | 1 (1) | 52 (47) | 0 (0) | 42 (38) |

Preop, preoperatively. FU, follow-up. Lesion based analysis, MAST pre-op, n=136; MAST FU, n=110; AMIC + PBC preop, n=136; AMIC + PBC FU, n=112. Distribution pre-op versus FU; $Chi^2$, $p < 0.01$ (MAST and AMIC+ PBC). Distribution pre-op MAST versus AMIC + PBC, Chi2, $p = 0.86$. Distribution FU MAST versus AMIC + PBC, $Chi^2$, $p = 0.52$.

Table 5: MRI based classification of 129 patients with 136 chondral lesions

In another prospective cohort study by Monckeberg et al. reported 20 patients (male, n=13; female, n=7) with grade 3b knee osteochondral lesions who underwent arthroscopic microdrilling surgery. Following the procedure, the PBSC (10ml) was suspended in autologous PRP and injected into the lesions as a clot adherent. After the surgery, the joint was immobilised for 24 hours and intra-articular injection of the cryopreserved PBSC (5ml) plus PRP were administered into the compromised joint once a week for three weeks. The clinical and radiological evaluation included International Knee Documentation Committee (IKDC) score and a visual analog scale (VAS) score at the following time points: before surgery, six months after surgery, one year after surgery, and then yearly until the last follow-up five years after surgery. The magnetic resonance imaging (MRI) was assessed at six months preoperatively, one year after surgery, and then yearly until the five year follow-up by quantifying the newly formed tissue repair using ICRS morphologic score system (MSS). The results showed the mean age at the time of surgery was 32.7 years (range 21 to 47 years). The mean

time between diagnosis and surgery was 4.3 months, and the minimum follow-up period was 4.5 years (range 4.5 to 5.8 years). The locations of the lesions, sizes and ICRS classification are summarized in Table 6.[11]

| Location | n | ICRS grade | Larger diameter (mm) |
|---|---|---|---|
| Trochlea | 9 | 3.5 ± 0 | 21.7 ± 7.4 |
| Femoral condyle | 5 | 3.5 ± 0 | 16.5 ± 2.1 |
| Patella | 6 | 3.3 ± 0.8 | 12.6 ± 5.1 |

Data are expressed as mean±standard deviation. ICRS, International Cartilage Repair Society.

Table 6: Characteristics of the osteochondral knee injuries (n=20).

The mean preoperative IKDC score was 50.5 (42 to 61). At the six-month follow-up, the mean values were 60.79 and 90.97 (p=0.32). At the six-month follow-up, the mean values were 70.8 (p=0.043). At the end of the total follow-up period (five years), the mean IKDC score was 82.2, that significantly higher than the preoperative score (p=0.024).[11] (Figure 3)

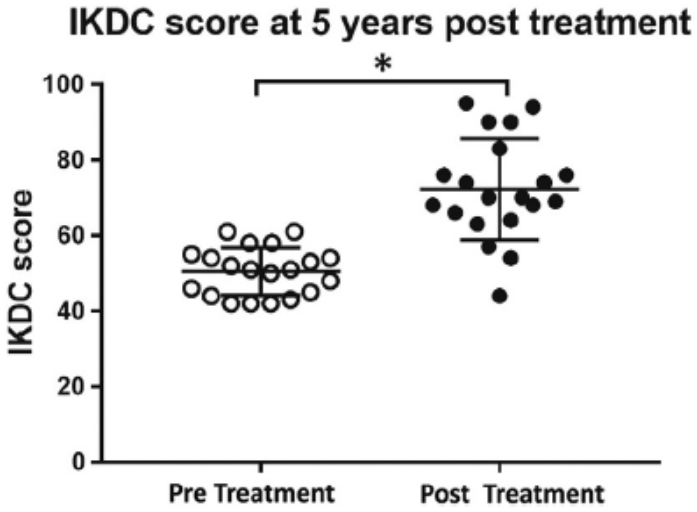



Figure X: Change in International Cartilage Repair Society (ICRS) score between pre-treatment and 5 years post-treatment.

There was a significant difference in VAS scores between the mean pre-operative score (5.3). At the end of the five-year follow-up period, the mean VAS score was 1.1, which was significantly less than the preoperative score (p= 0.0018). In the evaluation of cartilage repair on MRI, the main MSS was 3.2 preoperatively and 9.7±1.6 (range five to 12) at five-year follow-up. The difference was statistically significant (p=0.0021). (Figure 4) From this study, 85% of the patients showed favorable clinical and radiological improvement of osteochondral knee lesions. The patients achieved clinical stabilisation and well-repaired tissue without tissue involution or tissue deterioration at five years of follow up.[11]


Figure 4: The patients' magnetic resonance imaging (MRI) scores at 5 years post-treatment)

Another study by Saw K-Y et al. reported on a case study of eight patients with varus deformity of the knee joint underwent arthroscopic subchondral drilling (ICRS grade 4 bone-on-bone lesions of the medial compartment with concomitant high tibial osteotomy (HTO)). The procedure for HTO was indicated for patients with significant of varus deformity by defining a weight bearing longitudinal axis equal to or greater than 50% (Figure 5). This study histologically evaluate the quality of articular cartilage regeneration from medial compartment after arthroscopic subchondral drilling.[12]

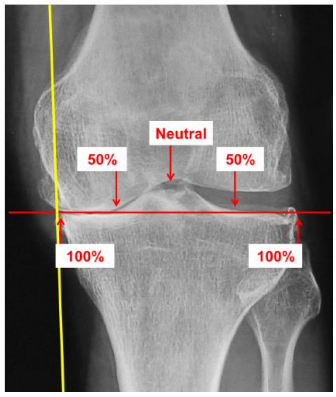



Figure 5: Radiograph showing significant varus deformity defined as the weight-bearing longitudinal axis in the coronal plane being equal to or greater than the 50% mark. The horizontal red line represents the point at which the longitudinal axis, crosses the tibial plateau. The yellow line represents the axis alignment.

The intra-articular injection using autologous PBSC (8ml) plus HA (2ml) was conducted a week after surgery and repeated once a week for five weeks. After six months up to 18 month after surgery, three additional weekly intra-articular injections comprised 4ml of PBSCs and 2ml of HA were given to the patients. The serial radiographs showed completely bone healing at the osteotomy site by three to six months of the treatment.

Arthroscopically, the regenerated articular cartilage appeared smooth and fully integrated with the surrounding old cartilage without any delamination.
There was a statistically significant difference between the regenerated cartilage and normal cartilage biopsy specimens (biopsy from the medial femoral condyle (MFC) and medial tibial plateau (MTP)) with p=0.0065.[12] (Figure 6)

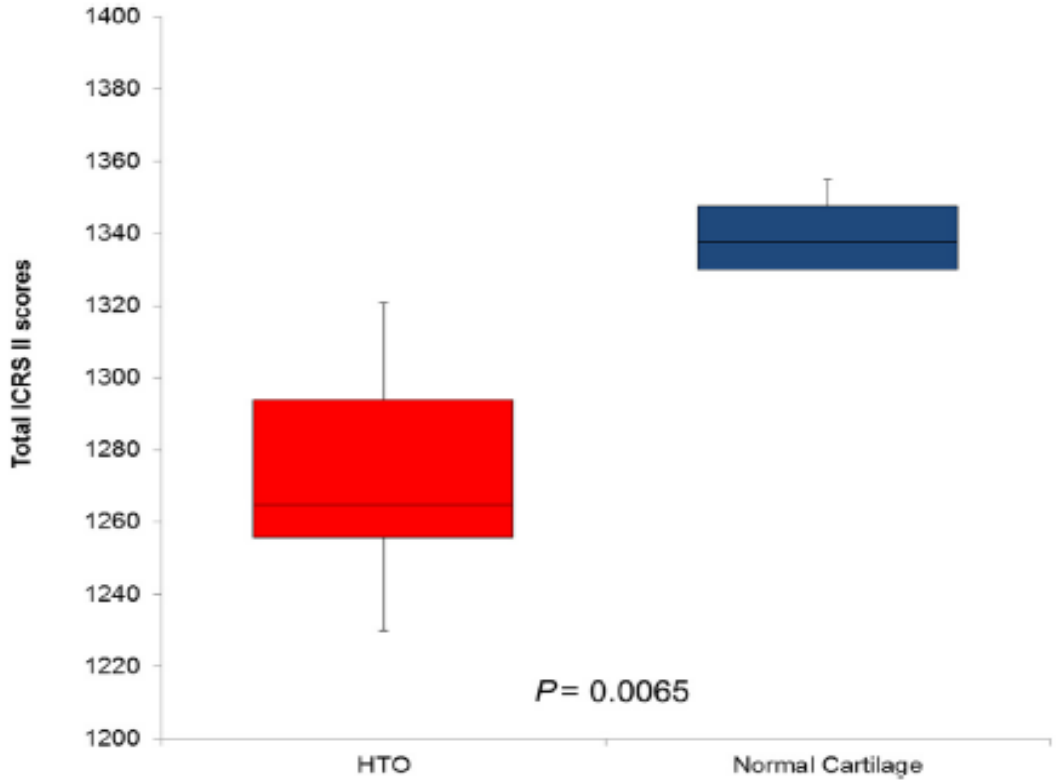



Figure 6: Box plot comparing International Cartilage Repair Society Visual Assessment Scale II (ICRS II) scores of high tibial osteotomy (HTO) cases versus normal articular cartilage

The findings of arthroscopy and histologic assessment of MFC and MTP at 2 years as shown in Figure 7. The mean time from surgery to hardware removal and biopsy was 25.9 months (ranged between 15 to 58 months).[12]

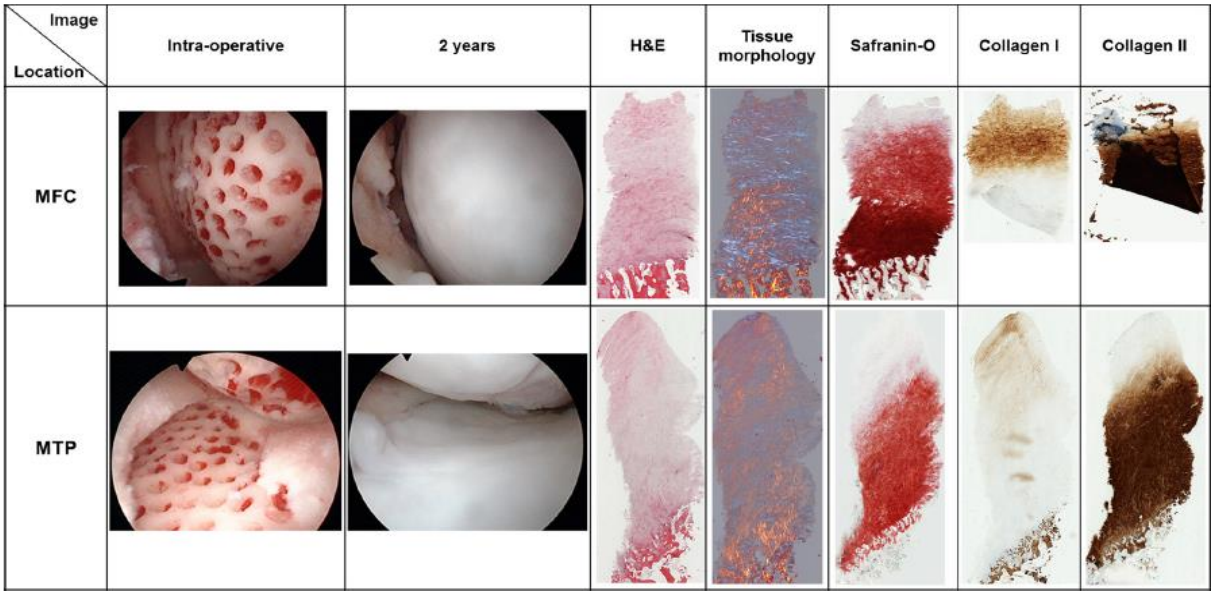



Figure 7: Findings of arthroscopy and histologic assessment of MFC and MTP

On the evaluation of the histologic results, the mean ICRS II score of 1,274 for the regenerated articular cartilage approached 95% of the normal articular cartilage core biopsy scores (mean, 1340).[12] (Table 7)

| Case No. | Time of Biopsy (After Initial Surgery), mo | Location of Biopsy | Mean ICRS II Score by Biopsy Site | Mean ICRS II Score Overall |
|---|---|---|---|---|
| 1 | 30 | MFC | 1,250 | 1,250 |
| 2 | 58 | MFC | 1,230 | 1,230 |
| 3 | 15 | MFC | 1,285 | 1,270 |
| | | MTP | 1,255 | |
| 4 | 25 | MFC | 1,265 | 1,258 |
| | | MTP | 1,250 | |
| 5 | 15 | MFC | 1,300 | 1,318 |
| | | MFC | 1,338 | |
| | | MTP | 1,318 | |
| 6 | 21 | MFC | 1,263 | 1,286 |
| | | MFC | 1,315 | |
| | | MTP | 1,280 | |
| 7 | 22 | MFC | 1,278 | 1,260 |
| | | MFC | 1,243 | |
| 8 | 21 | MFC | 1,320 | 1,321 |
| | | MFC | 1,325 | |
| | | MTP | 1,318 | |

ICRS II, International Cartilage Repair Society Visual Assessment Scale II; MFC, medial femoral condyle; MTP, medial tibial plateau.

Table 7: Data regarding biopsy samples from MFC and MTP

Safety

No serious adverse events, postoperative infections, deep vein thrombosis (DVT) delayed unions or non-unions and vascular injuries were reported in the intervention group (PBSC + HA) at the end of follow up. About 98% of the patients in the intervention group reported none to mild subchondral oedema.[7,8,9,12] No significant difference between acute intra-articular response in the first 24 hours (p=0.513) and delayed intra-articular response after 24 hours (p=0.554).[9]

For patients who treated with MAST and AMIC + PBC, there were no complications of neuropraxia, stiffness, wound healing delay, thrombosis and infection reported until the follow up.[10]

Cost
The price for PBSC for articular cartilage repair is unknown.

Organisational
There is only reported that the MAST and AMIC + PBC procedure are the complex surgical approach for the treatment of chondral lesions of the ankle compared to PBSC procedure after arthroscopic subchondral drilling of bone-on-bone lesions (grade 4) with high tibial osteotomy (HTO) and micro-drilling of knee osteochondral lesions.

Societal/ethical
No societal or ethical issue reported.

## CONCLUSIONS

It concluded that intra-articular PBSCs with PRP or HA regenerated articular cartilage and improved clinical and radiologic outcomes for knee chondral lesions for two up to five years of follow up. In the treatment of osteoarthritis, the avoidance of surgical arthroplasty was achieved at 12 months after PBSC injection compared to HA alone. It showed promise in disease modification with potential inhibition of progression of the disease. A larger clinical trial is warranted to determine the efficacy, safety and cost-effectiveness of the PBSC for articular cartilage repair.

## EVIDENCE

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