AUTOLOGOUS PERIPHERAL BLOOD STEM CELLS FOR ARTICULAR CARTILAGE REPAIR

HEALTH TECHNOLOGY ASSESSMENT SECTION
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DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Introduction

Articular cartilage exhibits little or no ability for self-repair, resulting in progressive tissue loss and dysfunction following isolated cartilage injuries. There are various surgical methods currently used in the effort to regenerate hyaline. However, more often than not the treatments result in the formation of fibrocartilage. Emerging evidence indicates that direct intra-articular injection of stem cells may boost the normally limited repair and limit destructive process.

This information was requested by the Director of Medical Development Division, Ministry of Health Malaysia following Minister of Health instruction to review the proposal by [redacted] to endorse the technology as a standard treatment for patients with articular cartilage defects.

Objective/aim

To assess the efficacy and safety of autologous peripheral blood stem cells for articular cartilage regeneration

Results and conclusions

There were two studies on peripheral blood stem cells identified, a randomised controlled trial (in-press) and a case series. [redacted] also provided unpublished long term non-comparative data on efficacy and safety. Three studies on intra-articular mesenchymal stem cells were included as well.

The usage of the new technique that “is the combination of the microfracture surgery or subchondral drilling, and the administration of hyaluronic acid and peripheral blood stem cells” is an innovation introduced at the [redacted].

Limited good level of evidence showed that intra-articular injection of peripheral blood stem cells in combination with hyaluronic acid (HA) resulted in improvement of the quality of articular cartilage repair when compared to treatment with HA alone as observed from the MRI and histologic findings. The evidence showed that there was no serious adverse event or complications reported when applying this procedure.

Multi centre studies such as prospective double blind RCT need to be conducted to gather more evidence to prove the reliability, efficacy and safety of this technology before it could be recommended as standard treatment options for cartilage repair.

Methods

Literature was searched through electronic databases which included MEDLINE, Cohrane Library via Ovid, EMBASE, PubMed and general databases such as Google Scholar.

The search strategy used these terms either singly or in various combinations: Autologous peripheral blood stem cells, PBSC, cartilage injury, articular cartilage repair and osteoarthritis

The search was limited to human study. The last searched was conducted on 19 January 2013.

AUTOLOGOUS PERIPHERAL BLOOD STEM CELLS FOR ARTICULAR CARTILAGE REPAIR

1. INTRODUCTION

Articular cartilage exhibits little or no ability for self-repair, resulting in progressive tissue loss and dysfunction following isolated cartilage injuries.[1] The goals of successful cartilage repair include reducing pain, improving symptoms, and long term function; preventing early osteoarthritis and subsequent total knee replacements; and rebuilding hyaline cartilage instead of fibrous cartilage.[2]

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). [2] However, more often than not the treatments result in the formation of fibrocartilage. Recent studies has investigated synthetic and biologic adjuncts to current methodology, including the use of hyaluronic acid (HA), platelet rich plasma (PRP), mesenchymal stem cells (MSC) and peripheral blood progenitor cells (PBPC).[3]

Emerging evidence indicates that direct intra-articular injection of stem cells may boost the normally limited repair and limit destructive process.[1]

Saw et al began investigations regarding cell therapy for cartilage regeneration in a goat model utilizing subchondral drilling in three groups: one with no post-operative injections, one with post-operative injections of HA alone and one with post-operative injections of bone marrow aspirate where the Gill score illustrated best outcomes in the group treated with injections of bone marrow aspirations (BMA) and HA.[4] Following that, they initiated a pilot clinical study using peripheral blood stem cells (PBSC) as opposed to cultured MSC or marrow aspirate due to the ease of harvest and the increase potential of this cell line.[5]

This information was requested by the Director of Medical Development Division, Ministry of Health Malaysia following Minister of Health instruction to review the proposal by [redacted] to endorse the technology as a standard treatment for patients with articular cartilage defects.

2. OBJECTIVE/AIM

To assess the efficacy and safety of autologous PBSC for articular cartilage regeneration

3. TECHNICAL FEATURES

3.1 Autologous PBSC

The method used which includes microfracture surgery or subchondral drilling in combination with the institution of HA and peripheral blood stem cells (PBSC) for the neochondrogenesis was patented on November 2012 (US Patent). The patent covers the collection, processing and cryopreservation of the PBSC packaged together with the surgical technique.

Patients were put in standard arthroscopic technique in the supine position without a tourniquet. Saline solution irrigation bags were chilled in an ice-water bath before use to minimize bleeding during the arthroscopic procedure. The method used is arthroscopic subchondral drilling modified from principles established by Steadman JR et al for microfracture and Pridie KH for drilling.

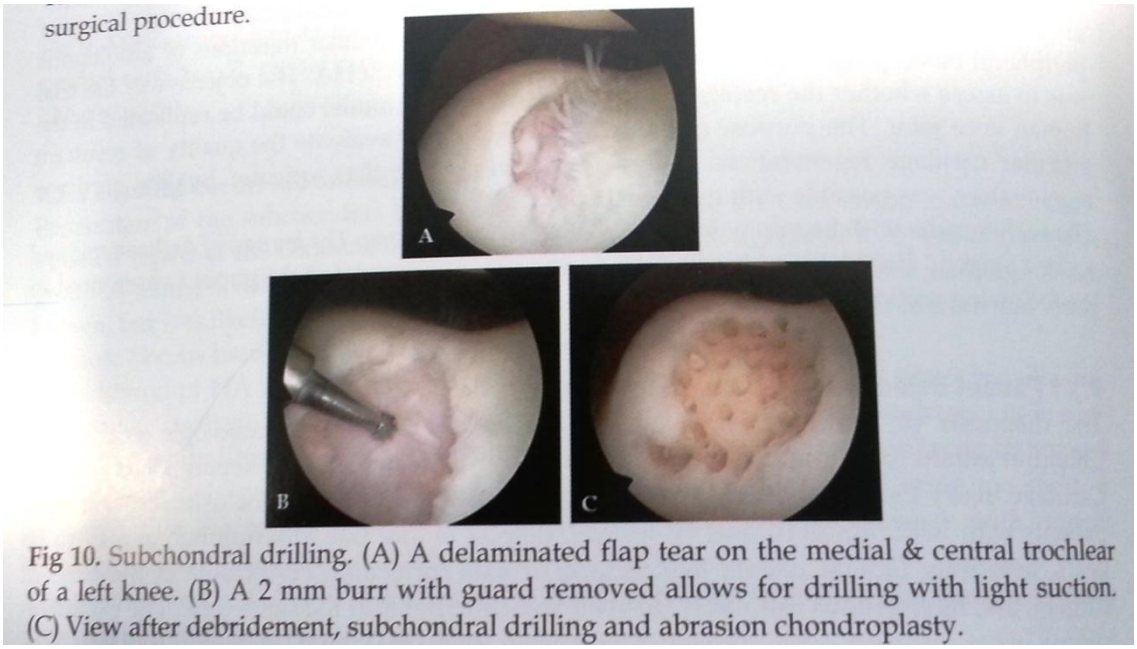

Figure 1. Subchondral drilling and abrasion chondroplasty

First, the extent of the cartilage injury was defined with a probe. A 3.5 mm full-radius shaver is used to debride loose cartilage to a stable margin; often a straight or curved arthroscopic biter is required as well. A 2-mm burr, with its guard removed, “drills” from the surface of the defect to the bone marrow, creating a conduit. The remaining area within the margin is also drilled to a depth of 5 to 10 mm. Initially the drill holes were spaced 3 to 4 mm apart, currently the goal of 1 to 2 mm between drill holes is preferred. Abrasion chondroplasty up to a depth of 1 mm is performed with burring of the bony area between drill holes which resulted in an extended area of bleeding bone, hence a larger surface area for the initiation of articular cartilage repair with PBPCs and HA. The arthroscopic portals are closed with no 3- nylon suture. A mixture of 20 mL of 0.5%

bupivacaine hydrochloride and epinephrine, 3 mL of 1 mg/mL morphine and 2 mL of HA is injected into the operated knee at the end of the surgical procedure.[5]

Cold therapy is initiated immediately in the postanaesthesia period and continued throughout the first month after surgery including 1 hour 2 to 3 times per day. On the first post-operative day, continuous passive motion is used on the operated knee for duration of 2 hours. This is continued daily for a period of four weeks. The range of motion is initially set at 0° to 30° and progresses as the clinical situation improves. Patients with subchondral drilling to the weight bearing femorotibial joint are instructed on crutch-assisted partial weight bearing (15 to 20 kg) for the first 4 weeks. This progresses to full weight bearing in 6 to 8 weeks.[5]

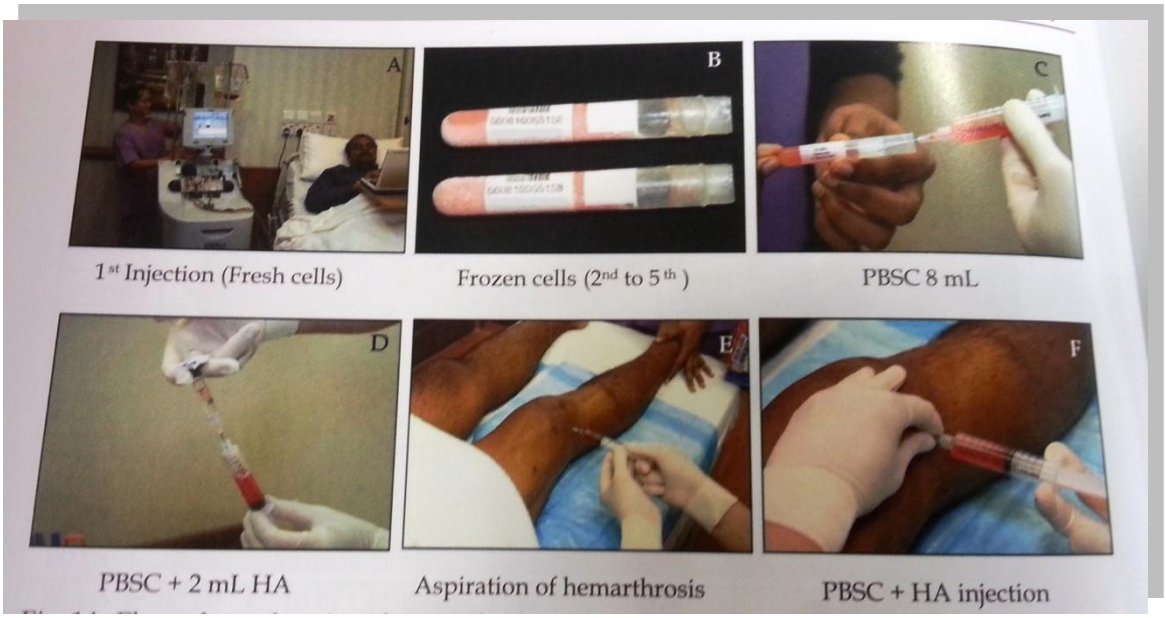

Figure 2. Flowchart showing the protocol for articular cartilage regeneration with PBSC and HA

On post-operative days 4, 5 and 6, patients were given a morning dose of 300 µg of Neupogen subcutaneously. On post-operative day 7, autologous PBPCs were collected by an automated cell separator (apheresis) by central venous. Venous access was achieved through a femoral double-lumen catheter placed into contralateral leg, under ultrasound guidance, performed by a consultant radiologist. Apheresis was performed. A fresh aliquot of 8 mL of PBPCs was separated for fresh –intra-articular injection into the operated knee. The remaining PBPCs were cryopreserved in 10% dimethyl sulfoxide and divided into 4 mL cryvials for storage in liquid nitrogen at -196°C. Flow cytometry with CD34+ (haematopoietic stem cells) and CD105+ (markers for MSC) was quantified. On post-operative day 7, 8 mL of the fresh PBPCs is mixed with 2 mL of HA and injected into the operated knee joint under aseptic conditions in the outpatient

clinic. At four subsequently week interval, 8 mL (from two 4-mL cryovials) of the frozen PBPCs were obtained from the laboratory, allowed to thaw to room temperature, mixed with 2 ml of HA and injected into the operated knee joint.[5]

3.2 Competing Technologies

Microfracture surgery is an articular cartilage repair surgical technique that works by creating tiny fractures in the underlying bone. This causes new cartilage to develop from a so-called super-clot.

Mosaicplasty (osteochondral cylinder transplantation) - uses small cylindrical autografts (also known as “plug”) harvested from less weight bearing areas of the femoral condyle articular surface (e.g. intercondylar notch) and placed in the cartilage defect. When multiple plugs are moved into a damaged area the result is a mosaic appearance--the multiple small plugs of cartilage look like mosaic tiles.

Osteoarticular autograft transfer system (OATS) - In the OATS procedure the plugs are usually larger, and therefore only one or two plugs are needed to fill the area of cartilage damage. Because of this it does not take on the mosaic appearance, but the principle is the same as mosaicplasty.

Autologous chondrocyte implantation (ACI)
ACI was introduced in Sweden in 1987. ACI of the knee is a two-stage procedure. The initial stage involves arthroscopy, where the knee is examined; the lesion is evaluated and small pieces of healthy cartilage are harvested from a less weight bearing area (usually the femoral notch or the medial or lateral rim of trochlea). Individual chondrocytes are isolated in vitro by collagenase digestion, cultured in media containing patient’s serum, and, following a period of cellular division, chondrocytes are retrieved for reimplantation. Reimplantation is the second stage of the process. A parapatellar arthrotomy is undertaken and the defect is debrided to the subchondral bone. Through a second incision, a periosteal patch is harvested from the proximal medial tibia and sutured to the defect rim. Fibrin glue or sealant is applied to the peripheral border of the patch to create a watertight seal. Then, the harvested chondrocytes are injected beneath the periosteal patch.

Viscosupplementation
Viscosupplementation is an intra-articular therapeutic modality for the treatment of knee osteoarthritis (OA) based on the physiologic importance of hyaluronan in synovial joints. Its therapeutic goal is to restore the viscoelasticity of synovial hyaluronan, decrease pain, improve mobility and restore the natural protective functions of hyaluronan in the joint. The short-term mode of action of viscosupplementation is believed to be based on the pain-relieving effect of the elastoviscous fluid in the affected joint. In the long term, the restoration of joint mobility due to relief of pain is thought to trigger a sequence of events which

restores the trans-synovial flow and subsequently the metabolic and rheological homeostases of the joint.[6]

4. METHODS

4.1. Searching

These scientific databases were searched such as;

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- Embase 1988 to 2013 Week 02
- EBM Reviews - Cochrane Central Register of Controlled Trials- December 2012
- EBM Reviews – Database of Abstracts of Review of Effects (4rd Quarter 2012)
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to December 2012
- EBM Reviews - Health Technology Assessment - 4th Quarter 2012
- NHS Economic Evaluation Database - 4th Quarter 2012
- PubMed

Other database or websites as below were also searched

- EuroScan
- INAHTA
- US FDA

General databases such as Google and Google Scholar were also searched. Information was also obtained from [redacted]. Animal studies were excluded.

The last search was conducted on 19 January 2013.

Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Articular cartilage defects/osteoarthritis/injury
Interventions	Autologous peripheral stem cells
Comparators	microfracture, osteoarticular autograft transfer system, mosaicplasty, autologous chondrocyte implantation (ACI), hyaluronic acid (HA), platelet rich plasma (PRP), mesenchymal stem cells (MSC)
Outcomes	Articular cartilage regeneration Quality of life Improvement in joint function Reduce pain
Study design	All primary and secondary studies of acceptable quality
	English full text article

Exclusion criteria

Study design	Animal studies

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) an

Data were extracted and summarised in evidence table (see Appendix 3). The data were not pooled and only qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

There were two studies on PBSC identified, a randomised controlled trial (in-press) and a case series. All the studies were related and written by the same author. [redacted] also provided unpublished long term non-comparative data on efficacy and safety. There were three studies on intra-articular MSC included as well.

5.1. Safety

As stated by FDA "a challenge posed by stem cell therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumours, severe immune reactions, or growth of unwanted tissues."[7]

In the RCT, one patient in the control group developed a below knee deep vein thrombosis (DVT) diagnosed by duplex ultrasound one day after surgery. The patient was treated without any long term sequelae. Other adverse events reported include swelling in knee, warmth in knee, difficulty moving knee, and pain at injection site. There was no statistically significant difference on

occurrence of the adverse events between the two groups. No post-operative infection and persistent bleeding reported.[8] Level 1

The long term unpublished data on safety was available for 108 patients. None of the patients developed infection. In addition patients were also observed for development of soft tissue tumour, bone tumour, and unforeseen abnormalities, where none of the patients developed these complications.[9]

There were no reports of clinically significant complications such as infections, knee swelling/effusion, allergy or other known adverse events related to the harvesting or arthroscopic procedure in the three studies on intra-articular stem cells.[10-12] Level II-1, Level III

The search was expanded further to look at the long term effect of MSC usage for articular cartilage and not other sources of stem cells or other indications. Wakitani et al first reported the use of expanded MSCs for repair of cartilage defects in 2002 in Japan. Cells from bone marrow aspirate of 12 patients with osteoarthritic knees were culture expanded, embedded in collagen gel, transplanted into the articular cartilage defect, and covered with autologous periosteum at the time of tibial osteotomy. Clinical improvement was not found to be different between the experimental group and a group of 12 control patients who underwent high tibial osteotomy alone.[13] In 2011, Wakitani et al reported a follow up study of 31 of the 41 patients (three patients had died and five had undergone total knee arthroplasty) who had received MSCs for articular cartilage repair in their clinics between 1998 and 2008. At a mean of 75 months (range 5 to 137) since the index procedure, no tumours or infections were identified. Function was not reported. In the absence of controlled studies, the benefit of this procedure in comparison with established alternatives is unclear.[14]

5.2 Efficacy

The initial case series included five patients. The second-look arthroscopy in these patients showed articular cartilage regeneration and histologic sections showed features of hyaline cartilage. The authors concluded that articular hyaline cartilage is possible with arthroscopic subchondral drilling followed by post-operative intra-articular injections of autologous PBPCs in combination with HA.[5] Level III

The randomised controlled trial included 50 patients with chondral injury aged between 18 to 50 years old. All the patients have International Cartilage Repair Society (ICRS) grade 3 and 4 lesions of the knee joint. Patients with history of more than one surgery on the knee in question or previous lower extremity or significant peripheral vascular disease, a body mass index (BMI) of 35 or greater, a varus or valgus deformity of more than 10 degrees, a deformity requiring osteotomy or complex surgery were excluded. The patients were not blinded, but the assessors were blinded. [8] Level I

The patients were randomised to two groups. All patients received eight post-operative intra-articular injections. The control group received 2 mL of HA upon each injection. The intervention group received 8 mL of PBSC in combination with 2 mL of HA. Prior to the intra-articular injections, the operated knee was aspirated for haemarthrosis.[8] Level I

The average age of the control was 42 and the average age of the intervention group was 38 years (p=0.031). At 24-month time point, the average subjective International Knee Documentation Committee (IKDC) score improved in both groups but there was not statistically significant difference between the two groups. The morphologic grading of the MRI data obtained at 18 months showed statistical significant difference between the two groups where the control group averaged 8.5 and the intervention group averaged 9.9, p=0.013. There was no significant difference in International Cartilage Research Society Visual Assessment Scale (ICRS) mapping between the intervention and control group at the initial surgery and during the second–look arthroscopy and biopsy at 18 months. However, there was significant difference in the histology and grading utilizing ICRS II. The average score for the control group was 957 and the intervention group was 1066, p= 0.022.[8] Level I

According to the unpublished long term data provided by [redacted], about 400 patients received the treatment. However, the long term data on efficacy was available only for 101 patients. Data for more than three years was available for 15 patients and the mean IKDC score at 36 months was 65.9. Only three patients were followed-up up to 66 months. The mean IKDC score raised from 50 at baseline to more than 70 scores at 18 months and sustained at above 60 score until 66 months.[9]

There were three studies that utilized intra-articular bone marrow-derived MSC. Lee et al conducted a non-randomised trial comparing arthroscopic microfracture and intra-articular injections of MSCs and HA, and open mesenchymal stem cells implantation. Both groups showed significant improvements in the SF-36 Health Survey, IKDC subjective knee evaluation form and the Lysholm knee scale with a positive time effect demonstrated, p<0.001. There were also improvement in visual analogue scale (VAS) and SF-36 (PCS) in both groups over time but the difference between the two groups were not statistically significant, p = 0.230 and p=0.057 respectively. MRI (done after 1 year) showed encouraging result where neocartilage with good fill and integration observed.[10] Level II-1

Davatchi et al reported a case series involving four patients, with one year follow up. The results showed that walking time for the pain improved for three patients but remained unchanged for one. The number of stairs they could climb and pain on VAS improved but the improvement was mainly for crepitus. There was minor improvement of the range of motion. The author concluded that results were encouraging but not excellent.[12] Level III

Emaddedin et al reported another case series involving six patients. They found that patients were partly satisfied. The pain, functional status of knee, and walking ability was slightly decreased. The MRI comparison at baseline and six months showed increase in cartilage thickness, extension of the repair tissue over subchondral bone and a considerable decrease in the size of oedematous subchondral patches in three out of six patients. The authors concluded that result was satisfactory.[11] Level III

5.3 Limitations

- Selection of the studies was done by one reviewer
- Although there was no restriction in language during the search but only English full text articles were included in this report

6. CONCLUSION

The usage of the new technique that "is the combination of the microfracture surgery or subchondral drilling, and the administration of HA and PBSC" is an innovation introduced at the KLSMC.

Limited good level of evidence showed that intra-articular injection of PBSC in combination with HA resulted in improvement of the quality of articular cartilage repair when compared to treatment with HA alone as observed from the MRI and histologic findings. The evidence showed that there was no serious adverse event or complications reported when applying this procedure.

Multi centre studies such as prospective double blind RCT need to be conducted to gather more evidence to prove the reliability, efficacy and safety of this technology before it could be recommended as standard treatment options for cartilage repair.

7. REFERENCES

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13. Wakitani S. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis and Cartilage. 2002;10(3):199-206.

14. Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45

joints followed for up to 11 years and 5 months. Journal of Tissue Engineering and Regenerative Medicine. 2011;5(2):146-150.

8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. cartilage, Articular/in [Injuries]
2. cartilage injur$.tw.
3. articular cartilage defect$.tw.
4. regeneration/ and Cartilage, Articular/
5. knee injur$.tw.
6. osteoarthritis.mp. or Osteoarthritis/ or Osteoarthritis, Knee/
7. articular cartilage regeneration$.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. peripheral blood stem cells.mp. or Peripheral Blood Stem Cell Transplantation/
10. Peripheral Blood Stem Cell Transplantation/ and Transplantation, Autologous/
11. autologous peripheral stem cell$ transplantation.tw.
12. 9 or 10 or 11
13. 8 and 12

OTHER DATABASES

EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane Database of Systematic Reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS Economic Evaluation Database	
INAHTA	
FDA	
Horizon Scanning Database	
Others	

8.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomisation.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3 Appendix 3

Abbreviation

ACI	Autologous Chondrocyte Implantation
BMI	Body Mass Index
BMMSC	Bone Marrow-derived Mesenchymal Stem Cell
DVT	Deep Vein Thrombosis
HA	Hyaluronic Acid
ICRS	International Cartilage Research Society Visual Assessment Scale
IKDC	International Knee Documentation Committee
KLSMC	Kuala Lumpur Sports Medicine Centre
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal stem cell
PBPC	Peripheral Blood Progenitor Cell
PBSC	Peripheral Blood Stem Cell
RCT	Randomised Controlled Trial
US FDA	United States of America Food and Drug Administration
VAS	Visual Analogue Scale