



Non-surgical management of chondral defects and OA-Mesenchymal stem cells

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Chondral and OA lesions

- 12% of the population will suffer chondral lesions
- These progress to osteoarthritis
- 15% of the Australian population suffer Osteoarthritis

Management Options

- The basics
 - Activity modification
 - Weight loss

- Oral Pain Relief
 - Paracetamol
 - NSAIDS
 - Glucosamine
 - Fish oil

Management Options

- Injectable pain relief
 - Cortisone
 - Synvisc
 - PRP

Management Options

- Surgical interventions
 - Chondral Defects
 - Microfracture
 - MACI
 - Osteoarthritis
 - Arthroscopic debridement
 - Joint replacement

Management Issues

- **NSAIDS**
 - 1.6-2 times increase in AMI and stroke
- **Cortisone**
 - Avg 3 weeks duration in Knee OA
- **Hyaluronic acid (Synvisc)**
 - May have some chondro-protective effect though evidence is limited
 - Pain relief peak at 3 months
 - Lasts about 6+ months

Management Strategies

- **Mircofracture**

- Aim to recruit bone marrow progenitor cells, and convert into them chondrogenic cells (Vasiliadis, et al, 2010)
- Deterioration after 18 mths to 2 years in 3 studies(Harris, et al, 2010)

- **MACI** (Harris, et al, 2010)

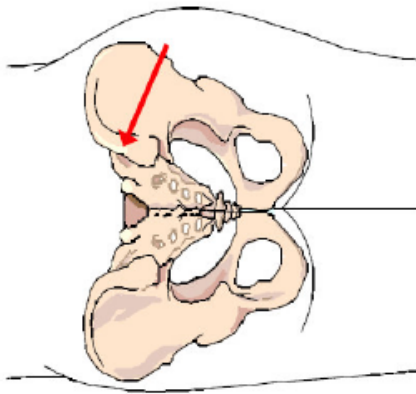
- Harvest, culture and implantation of chondrocyte plug
- 3 studies have shown it is better than microfracture at 1-3 yrs
- 3 studies have shown no difference one out to 5 years
- 1 study microfracture better than MACI at 2 yrs

Management Strategies

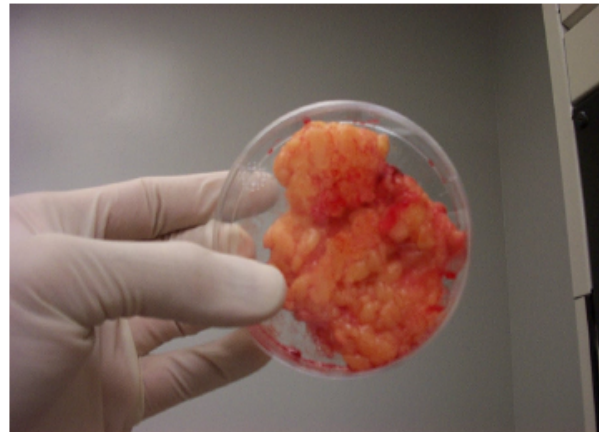
- **Arthroscopic debridement**
 - “the clean up”
 - No evidence of benefit (Laupattarakasem et al, 2008)

- **Joint replacement**
 - Effective
 - High financial burden on the healthcare system (March & Bagga, 2004)

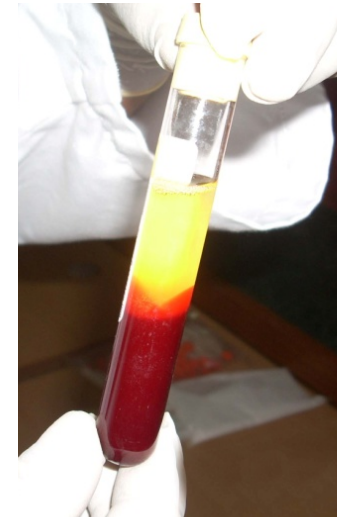
Mesenchymal stem cells (MSC) Source



Bone marrow



Adipose



Blood

MSC- Harvest

Bone Marrow Biopsy

- Two step process
 - Cell expansion – increase numbers of MCS
 - Mixed with PRP

- Single process
 - Bone marrow biopsy
 - Centrifuge and remove buffy coat
 - Mixed with PRP

MSC- Harvest

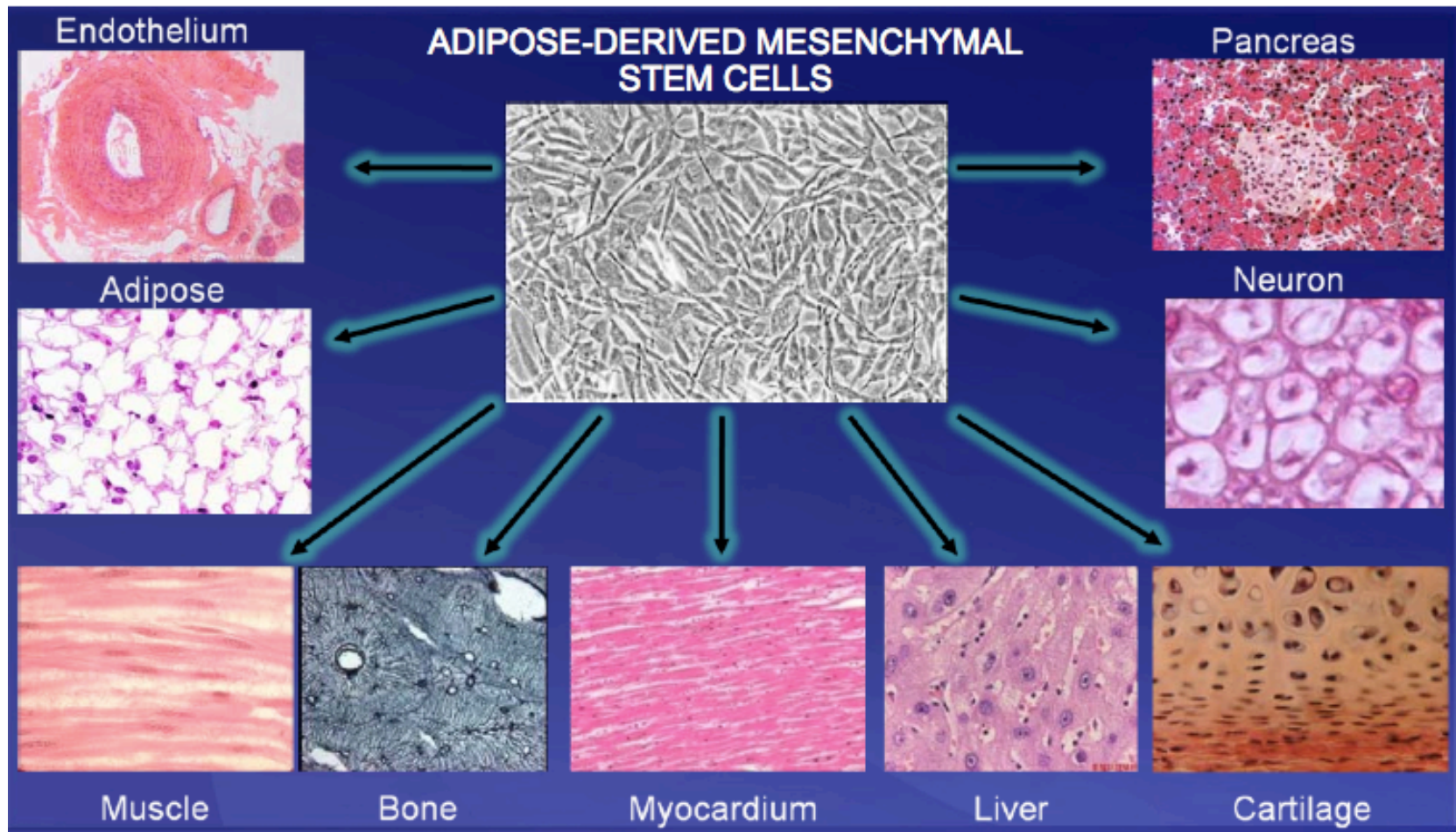
- **Blood – using apheresis**
 - Done following injection of GM-CSF
 - Low yield of cells
 - Requires culture to get enough MSC
 - 4 hour harvest procedure

- **Adipose**
 - Abundant source of MSC
 - Likely originate from the bone marrow and form a reservoir of Stem cells (Han et al, 2010)
 - High numbers – 1-3 million/ml
 - Painless procedure

MSC – Bone Vs Adipose

- CD markers on MSC (Zuk, et al, 2002)
 - Differences related to homing and mobilisation of haematopoietic cells
 - Adipose CD49d pos and CD106 neg
 - Bone Marrow CD49d neg and CD 106 pos
- Both capable of multiple lines of differentiation (Zuk, et al, 2002)
- ADSC have immunomodulator effects equivalent to BMSC (Yoo et al, 2002)
- Both capable of being converted to Cartilage

Adipose derived stem cells - Pluripotent



Adipose derived stem cells – Paracrine cells

- Been shown to release 127 different soluble factors
- Have a quick onset of action (Song, et al, 2010)
 - Hours - days
 - Not likely solely differentiating into the target tissue
- Effect can be reproduced by application of cell free culture medium (Song et al, 2010)
- Growth factors secreted by ADSC well known to stimulate into chondrocyte growth

Animal Chondral Studies

- Dogs
 - RCT Significant decreased lameness and stiffness in elbow (Black et al, 2008)
 - RCT - significant decrease in pain, lameness and improved ROM in Hips (Black et al, 2007)

- Rabbits
 - Chondral defect healing in Rabbits (Olivera et al 2010)

- Horses
 - Vet stem – Claim 3000 horses treated with 0.2% complication rate of local swelling (www.vetstem.com)
 - Claim treatment of joint, tendon and ligament injury commercially since 2003

Animal ADSC Studies

Table 1. Representative preclinical animal studies using adipose-derived stromal/stem cells and stromal vascular fraction cells

| Tissue type | Defect | Species | References |
|------------------------|---|-------------------------|--------------------|
| Adipose/soft tissue | Fat pad generation | Murine, rat, ovine | [51-60] |
| | Lipodystrophy | Murine | [48,61] |
| | Burn/radiation trauma | Murine | [62-64] |
| Bone | Critical sized defect | | |
| | Craniofacial | Murine, rat | [65,66] |
| | Long bone | Murine | [67] |
| | Spinal fusion | Rat | [68,69] |
| Cardiac | Myocardial infarction | Murine, rat | [42,43,70,71] |
| Central nervous system | Vascular injury/stroke | Murine, rat | [44,46,72] |
| | Spinal cord trauma | Rat | [47] |
| | Multiple sclerosis | Murine | [33] |
| Gastrointestinal tract | Crohn's disease/inflammatory bowel syndrome | Murine | [73] |
| Hematopoiesis | Bone marrow transplantation | Murine | [74,75] |
| Joint | Osteoarthritis | Canine, caprine, equine | [76-79] |
| Liver | Acute toxicity/regeneration | Murine | [80-88] |
| Pancreas | Type 1 diabetes mellitus | Murine, rat | [48,89,90] |
| Renal | Acute ischemia | Rat | (JMG, unpublished) |
| Skin | Wounds, burns | Murine, porcine | [62,64,91] |
| Tendon | Tendonitis | Equine | [92] |
| Urinary bladder | Incontinence | Rat | [93] |
| Vascular | Hind limb ischemia | Murine, rat | [36,41,45] |

Human ADSC Studies

Table 2. Published clinical case reports and clinical trials

| Indication | Study type | Number of patients | Follow-up period | References |
|----------------------|--------------|--------------------|------------------|--|
| Soft tissue | | | | |
| Breast augmentation | Case reports | 403 | Up to 6 years | [9-11] (K Yoshimura, personal communication, University of Tokyo) |
| Craniofacial | Case reports | 58 | 9 to 13 months | [10,21] (K Yoshimura, personal communication, University of Tokyo) |
| Irradiation fibrosis | Case reports | 20 | 31 months | [18] |
| Orthopedic | | | | |
| Craniofacial | Case reports | 2 | >12 months | [25,26] |
| Immune | | | | |
| Crohn's disease | Phase I | 5 to 9 | 12 to 30 months | [27-31] |
| Multiple sclerosis | Case reports | 3 | 7 months | [33] |

Human Case Studies – Bone Marrow

- Intra-articular knee injection of BMSC (Centeno et al, 2008)
 - Treatment of diffuse OA
 - 19% increase in cartilage volume at 3 months
 - 28% increase in Meniscus volume at 3 months
 - VAS decreased from 4 to 0.5 at 3 months
- Intra-articular knee injection of BMSC and PRP (Centeno et al, 2008 b)
 - Treatment of femoral chondral lesion
 - 29% decrease in defect size at 6 months

Human Case Studies – Bone Marrow

- Intra-articular hip injection of BMSC (Centeno et al, 2006)
 - Treatment of diffuse OA of the hip
 - Improve cartilage coverage and joint space on MRI
 - No significant improvement of symptoms

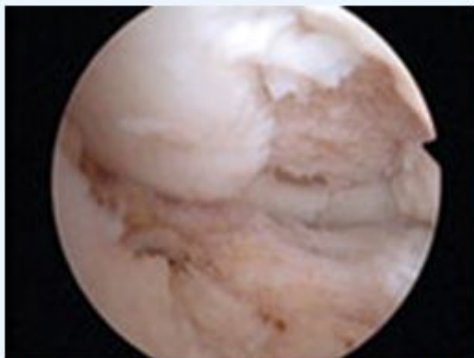
Human Case Studies – Bone Marrow

Injection of expanded BMSC (Centeno et al, 2010)

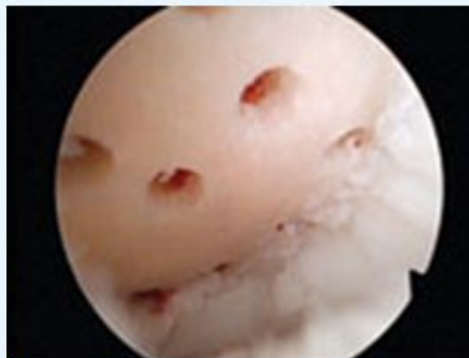
- Safety data
 - IV disc – 13 patients
 - Peripheral joint- 213 patients
- 45 patients followed for 2 years with MRI
 - No Malignant change
- 9 patients – joint effusion
- 2 Infection – Bone marrow biopsy site
- 1 Worsening of back pain – no MRI changes
- 1 Disc prolapse at site of injection
- 1 Schwannoma – identified 8 months post injection not a site of injection
- 1 PE 2 weeks post Bone marrow (no stem cell therapy)

Human Case Study - Blood

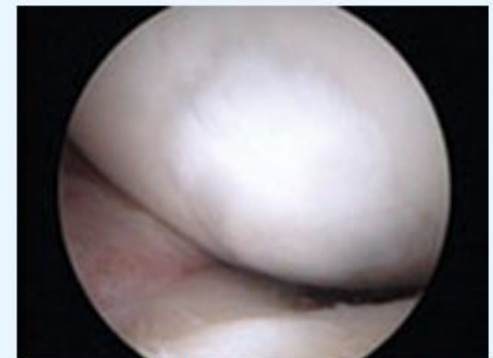
- Blood derived mesenchymal stem cells
 - Pilot study of 10 cases
 - Microfracture + Blood derived stem cells and Hyaluronic acid



This arthroscopic image shows a lateral femoral condyle chondral lesion of a patient's right knee.



The view of the same knee after subchondral drilling.



A second-look arthroscopic image shows healing at 1-year follow-up.

Images: Saw K-Y

Human Case Study - Adipose

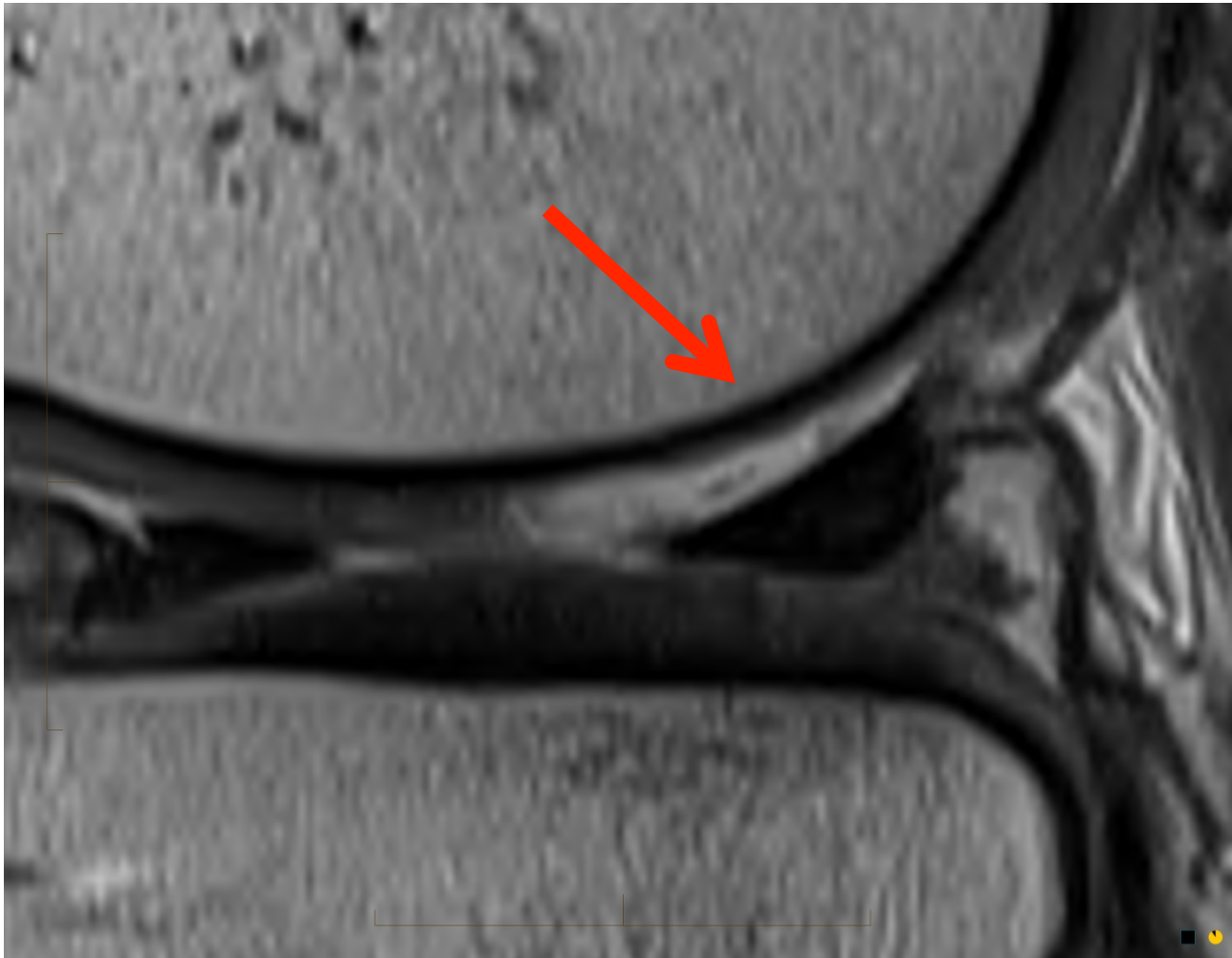
43 year old male

- Pain for 10 years
- “Ex” – Soccer Player
- Large lateral femoral condyle chondral lesion
- Treated with
 - Cortisone
 - Synvisc
 - PRP
 - Refused surgery
- Ongoing pain with exercise VAS 7/10

MRI – Pre Treatment 23.08.2010



MRI – Pre Treatment 23.08.2010



Stem Cells Harvest

AdiStem Ltd.

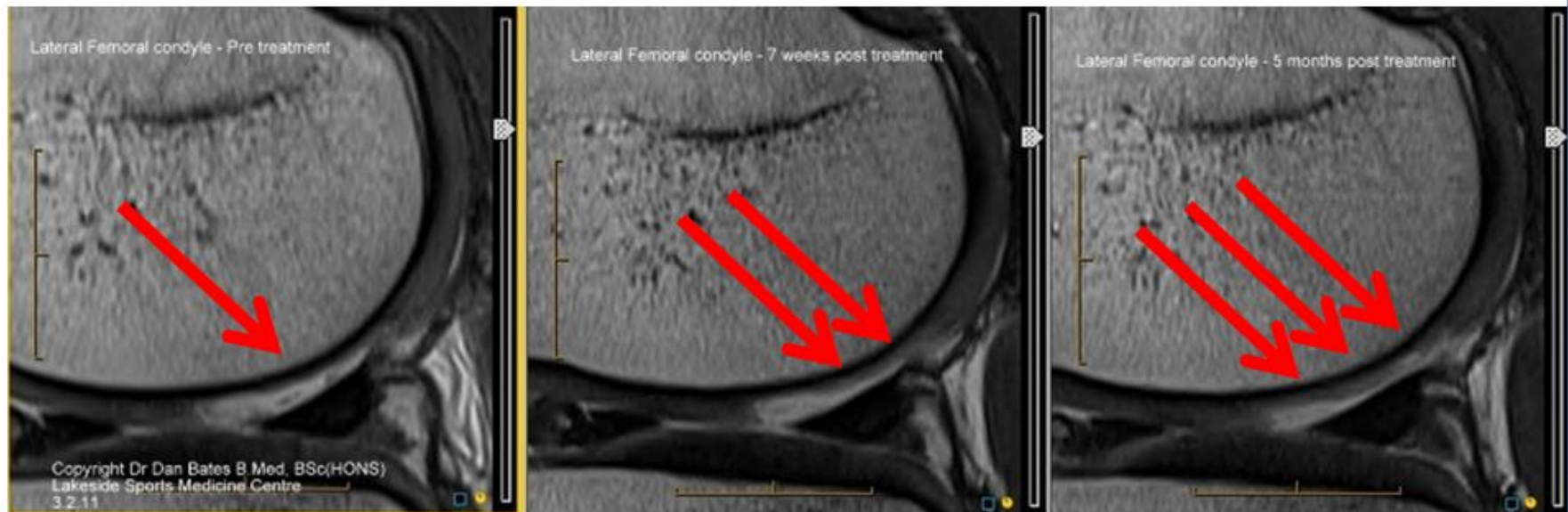
- Mini – liposuction
 - 3mm canula and hand suction with 20ml syringe
 - 7-10g of fat
- Extraction of cells
 - Lecithin
- Activation of cells
 - Platelet rich plasma
 - Low level light irradiation
- US guided injection of cells on the same day

Visual Analogue Scale

- 48 hours of acute synovitis
 - Ice and crutches
 - Too many cells
- VAS scale 7/10 – 0/10 at 2 weeks

MRI – Post Treatment

MRI Findings



Pre-treatment

7 weeks

5 months

Issues

- Only partial healing
 - We will wait to see if further progress with repeat scan in 1 month
 - Move to multiple injections?
- What is the quality of cartilage and how long will it last?
- It is only one! Warrants further study.

Randomised Control Trial

- Treatment of chondral lesions with adipose derived stem cells.
 - Aim to commencement April 2011
 - Age 18-65
 - Pre and post MRI
 - Randomised to Synvisc or PRP + Stem cells
 - Non-treatment group offered the treatment if positive
 - Contacts – Dr Dan Bates 0410 549 082 or danbates@lakesidesmc.com.au

Thankyou