THE JOINT REPLACEMENT CLINIC

Real world evidence of improved clinical outcomes of pain and function in 45 knee osteoarthritis patients with Bone Marrow Oedema Lesions administered Pentosan Polysulphate Sodium (PPS)

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DISCLOSURE

Member of the Medical advisory board Paradigm

Osteoarthritis and Bone Marrow Lesions (BMLs)

- BMLs are associated with:
  - numerous pathologies
  - is becoming recognized as a considerable pain generator
  - an entity linked to the worsening of patient prognosis
    - *- Starr et al Acta Radiologica 2008*

Osteoarthritis and Bone Marrow Lesions (BMLs)

- BMLs with knee OA predict progression of disease and joint replacement - *Tanamas et al Rheumatology 2010*
- Enlarging BMLs are strongly associated with more cartilage loss -*Hunter et al Arthritis & Rheumatology 2006*

Osteoarthritis and Bone Marrow Lesions (BMLs

- BMLs demonstrated areas of high metabolic activity expressing pain sensitisation, neuronal, extracellular matrix and proinflammatory signalling genes that may explain their strong association with pain – *Kuttapitiya A, et al. Ann Rheum Dis 2017*

- Currently there are no drugs registered to treat OA with BML

Pentosan Polysulphate Sodium (PPS)

- PPS is a highly sulphated xylan in continuous human use since 1947
- Originally developed in Germany as a post-surgery thromboprophylactic agent
- PPS has approximately 1/20 of the anti-coagulant activity of heparin
- PPS has fibrinolytic action mediated through release of tissue-type plasminogen activator (tPA) from the endothelium

Pentosan Polysulphate Sodium (PPS)

- Injectable PPS is currently approved by the European Medicines Agency for thromboprophylaxis

- The oral form of drug is approved by the US FDA for treatment of interstitial cystitis (painful bladder syndrome).

- PPS has a strong safety profile

Rational for PPS use in OA patients with BMLs

- ***Previous human use of Pentosan Polysulfate Sodium (PPS) in subjects with OA***
  - *Kumagai et al 2010*: Open label 20 patient; 2 mg/kg-s.c. weekly for 6 weeks
  - *Ghosh et al 2005:* RDBPC 114 patients (1:1); 3 mg/kg i.m. weekly for 4 weeks
- ***Pre-clinical evidence that PPS has anti-inflammatory effects in vitro and in vivo***
  - *Sunaga et al:* inhibits NF-kappaB translocation
  - *Smith et al:* reduction in clinical symptoms in 104 dogs administered sc PPS

Rational for PPS use in OA patients with BMLs

- ***PPS has multiple pharmaceutical effects to treat bone lesions***
  - Chondroprotection (inhibition of MMP's and ADAMTS)- *Troberg et al 2012*
  - Anti-inflammatory (Anti TNF and Anti IL-1)-*Bawalya et al 2017*
  - Improved sub-chondral vascularity- *Ghosh and Cheras 2001*

Case report: Effects of PPS treatment in a 70 yo patient with BML and joint effusion

- *A 70-year-old female*
  - *Previous knee arthroscopy*
  - *Presented with pain of the left knee.*
  - *Initial MRI reported a post meniscectomy re-tear.*

Case report:

- *Medial femoral condyle oedema measured 11 x 7 x 12mm (CC x transverse x AP)*
- *Medial tibial plateau oedema measured 8 x 8 x 8mm (CC x transverse x AP).*
- *Lysholm Knee score:*
  - *Baseline = 37 with problems in stair climbing and limping*

Case report: After evaluation PPS administered:

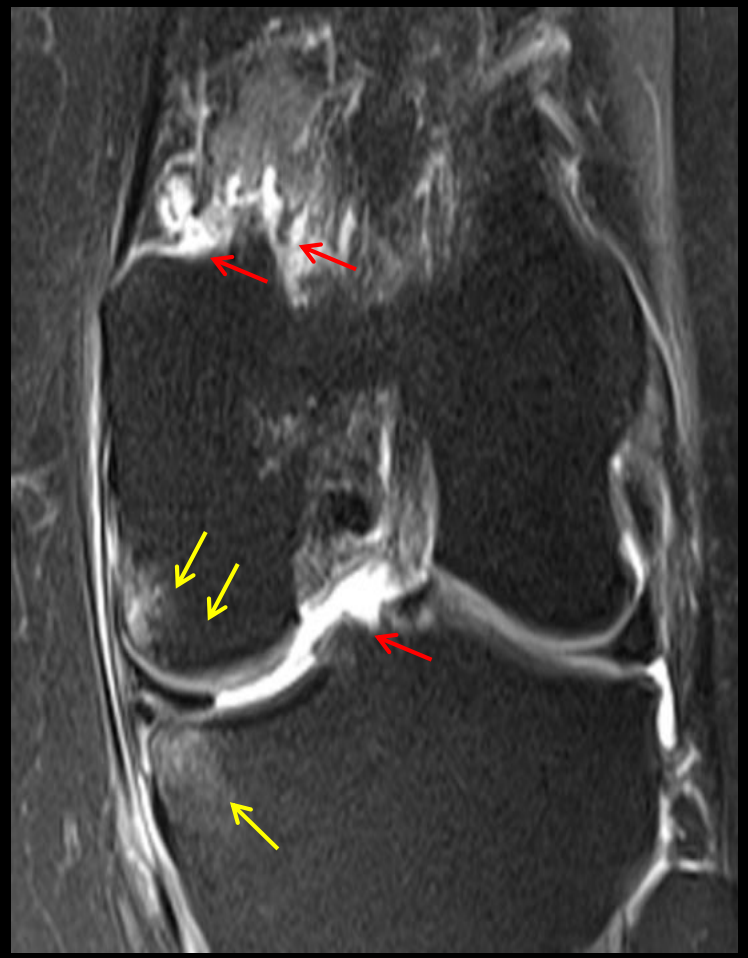
i.m. at a dose of 2mg/kg twice/week 4 weeks

- **Post treatment MRI scans:** Complete resolution of bone oedema medial femoral condyle and medial tibial plateau.

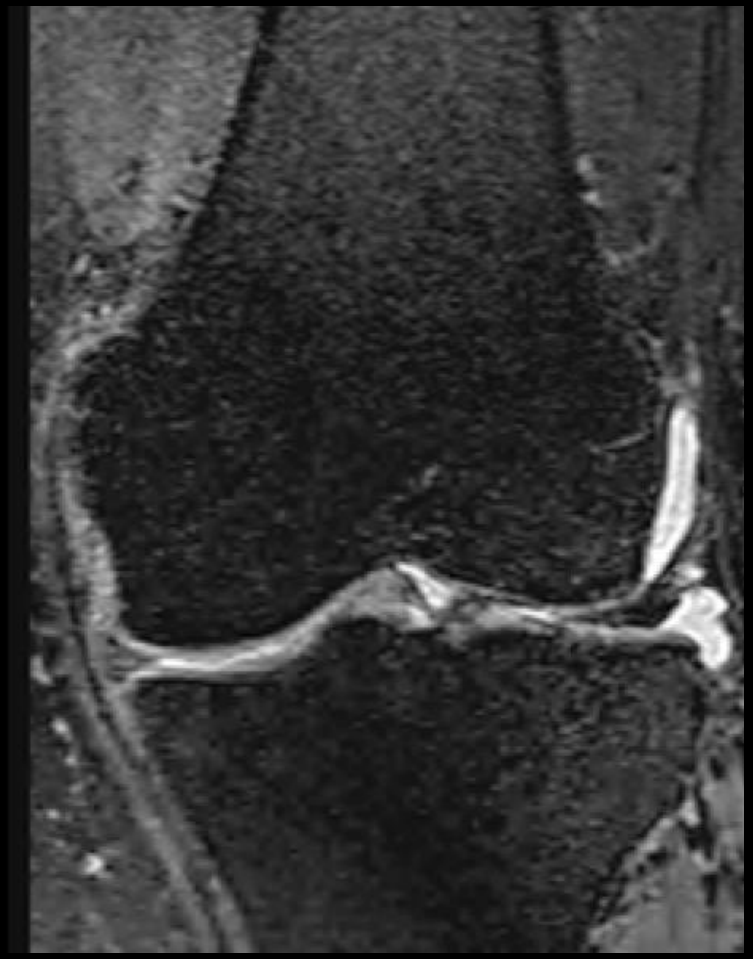
Lysholm Knee score 2 to 4 weeks post last injection reported a score of **65.**

No patient reported **pain** was presented.

Effects of PPS treatment in a 70 y.o. with BML and joint effusion



Pre- PPS MRI
Showing BME Lesions (yellow arrows) effusions in joint space (red arrows)
Lysholm Score: 37



Post- PPS MRI
Showing complete resolution of BME lesions and effusions
Lysholm Score: 65

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BMC Musculoskeletal Disorders

CASE REPORT Open Access

Improved clinical outcome measures of knee pain and function with concurrent resolution of subchondral Bone Marrow Edema Lesion and joint effusion in an osteoarthritic patient following Pentosan Polysulphate Sodium treatment: a case report

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Abstract

Background: At present, there are no registered products for the treatment of subchondral Bone Marrow Edema Lesion (BML) and associated knee pain. Patients who do not respond to current anti-inflammatory therapies are left with limited treatment options, and may resort to operative management with Total Knee Arthroplasty (TKA). We report the use of Pentosan Polysulphate Sodium (PPS) for the treatment of BMLs of the knee.

Case presentation: We report the case of a 70-year-old female with knee osteoarthritis presenting with a high level of knee pain, scoring 8 on the Numerical Rating Scale (NRS), and functional limitation demonstrating a poor Lysholm Knee Score of 37. MRI scans of the knee revealed subchondral BML in the medial femoral condyle and medial tibial plateau. The patient was administered a course of Pentosan Polysulphate Sodium (PPS) intramuscularly twice weekly, for 3 weeks. MRI scans 2 weeks post-treatment showed complete resolution of the bone marrow edema at the medial femoral condyle and medial tibial plateau with concomitant recovery from pain (NRS pain score of 0), and a 43% improvement of the Lysholm Knee Score. In addition, marked reduction in joint effusion was also demonstrated in the MRI scan post PPS therapy.

Conclusion: The MRI interpretations demonstrate improved clinical outcome measures ensuing therapeutic intervention with PPS, and warranting further investigation into the efficacy of PPS in the treatment of BML associated pain and dysfunction in the osteoarthritic population via randomized controlled trial, or equivalent rigorous methodological technique.

Keywords: Bone marrow edema lesion, MRI, Knee osteoarthritis, Joint effusion; Pentosan polysulphate sodium

TGA Special Access Scheme (SAS)
for the Compassionate use of PPS in OA patients

- The injectable drug Pentosan (or PPS) is not currently registered in Australia (although it is registered in 4 of the 7 major Pharmaceutical markets). Because the drug is registered overseas but not in Australia, treating physicians in Australia can access drugs like Pentosan for compassionate use via the Therapeutic Goods Administration (the TGA) Special Access Scheme (SAS) category B.

TGA Special Access Scheme (SAS) for the Compassionate use of PPS in OA patients

- One of the key conditions for approval for compassionate use of PPS is that the patient has ***failed current standard of care treatments***.

Paradigm is the supplier of the injectable PPS to treating doctors who have obtained TGA-SAS approval and the **current data set of 45 patients** were collated by Paradigm's report to TGA obtained from treating doctors in a number of medical practices in Australia.

TGA Special Access Scheme (SAS)
for the Compassionate use of PPS in OA patients

- All patients signed consent to treatment and to patient confidentiality protected (de-identified) in any reviews or reports which may be published.

OA case series patient profile: Treated under the TGA-SAS

- **45 patients**
  - 25 (55.5%) males and 20 (44.5%) females,
  - median age of 59 years (range 31 to 84 years)
  - had been clinically diagnosed OA with subchondral BMELs through an MRI.

- .

OA case series patient profile: Treated under the TGA-SAS

- At the onset of PPS treatment all patients:
  - were symptomatic with OA pain for at least six months
  - had failed current standard of care which involved treatment with analgesics, NSAIDs (non-steroidal anti-inflammatory drugs), corticosteroids, stem cell and PRP.

OA case series patient profile: Treated under the TGA-SAS

- **70%** of the patients had moderate to severe BMELs with a size ranging from **5mm to >20mm** in diameter.

- **30%** had lesions **<5mm** in diameter

PPS Treatment regimen and Clinical outcome measures in patients

PPS treatment administered twice weekly by subcutaneous injections for 3 to 6 weeks

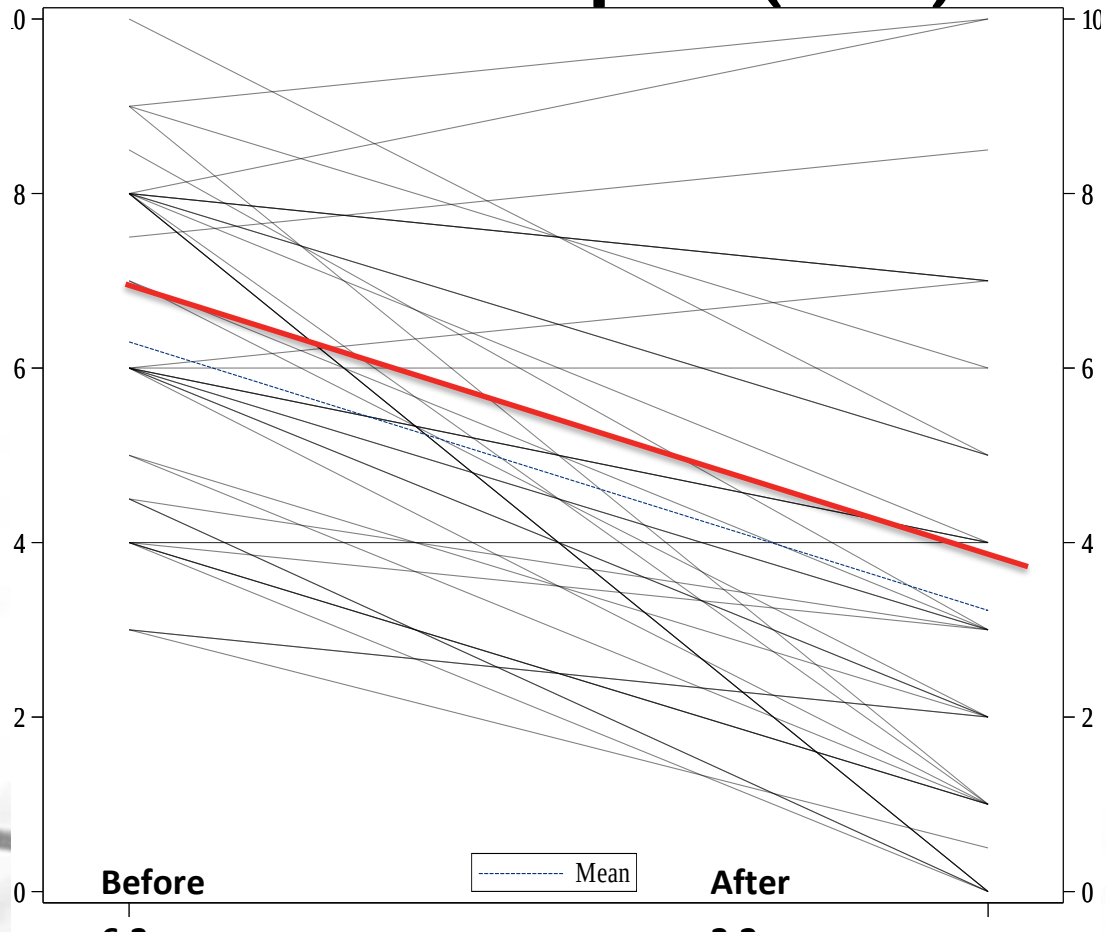
- The **Numeric Rating Scale** (NRS) measures pain intensity on an 10-point scale with a score of '0' indicating a state of 'no pain' while a score of '10' reflects the 'worst pain imaginable'. *(Hjermstad et al J.Pain and Symptom Manag. 2011 ; 41(6): p. 1073-93.)*

PPS Treatment regimen and Clinical outcome measures in patients

- The **Lysholm Knee Score (LKS)** is a condition specific outcome measure that contains 8 functional components: Limp (5 points); Support (5 points), Locking (15 points), Instability (25 points), Pain (25 points), Swelling (10 points), Stair climbing (10 points), and Squatting (5 points). (30,31). An overall score of 0-100 is calculated, with scores assigned to rating categories as follows: 95-100 = excellent; 84-94 = good; 65-83 = fair, and <65 = poor . *(Briggs et al JBJS 2006; 88(4): p. 698-705)*

NRS Knee pain scores in 45 OA patients with BML treated with PPS

A Paired t-test was used to compare the before and after scores for knee pain (NRS)



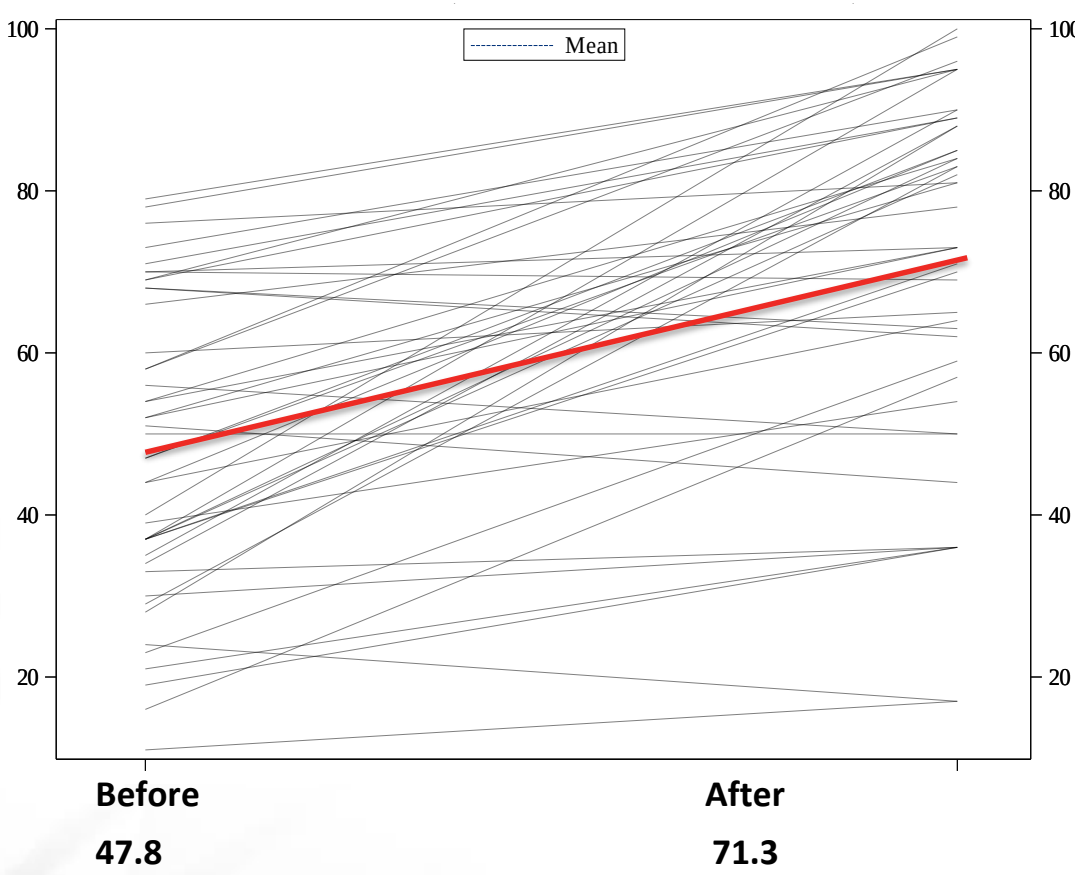
Pain (NRS)

Before-after = 3.1, p<0.0001

50% reduction in knee pain

Lysholm Knee Function Scores in 45 OA patients with BML treated with PPS

A Paired t-test was used to compare the before and after



Function,

Before-after=23.5 p<0.0001

64% improvement

in knee function

Conclusions

Follow-up at 4-6 after the last sc injection of PPS:

- **84.4 %** (38/45) responded with a reduction in knee pain
  - Mean reduction in knee pain scores is **49.8%**

- **84.4 %** (38/45) responded with an improvement in knee function
  - Mean improvement in knee function scores is 64.3%

- Real World Evidence for the successful treatment of painful OA associated with subchondral BMLs who have failed current standard of care

Conclusions

- Long remission periods from pain in excess of 6 months after cessation of treatment

Real world evidence of safety and tolerability in an OA population

Paradigm Biopharma is currently conducting 100 OA patient randomised, double-blinded placebo-controlled multi-centre trial in Australia with a read out of data in Dec 2018.

THANK YOU