The Truth About Regenerative Medicine

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MichiganSportsAndSpine.com
REGENERATIVE MEDICINE

WHOLE FOODS MARKET

100% ORGANIC ZONE
REGENERATIVE MEDICINE (BIOLOGICS)

- Platelet Rich Plasma (PRP)
- Stem Cells (bone marrow vs. adipose)
- Combo (PRP and stem cell)
- Future . . .
ATHLETES WHO HAVE HAD PRP & STEM CELL THERAPY

Peyton Manning
Kobe Bryant
Tiger Woods
History of PRP

20+ year history of use

- Orthopedics
- Sports medicine
- Dentistry
- ENT
- Neurosurgery
- Ophthalmology
- Urology
- Wound healing
- Cosmetic
- Cardiothoracic Surgery
- Maxillofacial Surgery
Platelet Rich Plasma (PRP)

- A concentration of platelets above the patient’s normal baseline
- 2X – 12X
- Manufactured with FDA approved tabletop device within 10 – 14min
Blood Components

- 93% RBCs
- 6% Platelets
- 1% WBCs
- Goal of PRP:
  - Decrease RBC to 5%
  - Increase platelets to 94%

Centrifugal Blood Separation

Plasma (PPP) → Platelets/White Blood Cells (PRP) → Red Blood Cells
THE PROTEINS THAT CONTROL THE FIRST THREE STAGES OF THE HEALING CASCADE ARE FOUND IN SPECIFIC BLOOD COMPONENTS:

- PLASMA
- WHITE BLOOD CELLS
- PLATELETS
**CONCLUSIONS**

- Platelet Concentrate and VEGF stimulate chemotactic migration of MSC’s in a dose-dependent manner.
- Platelet Concentrate stimulates proliferation of MSC’s in a dose-dependent manner.


Haynesworth, SE; Kadiyala, S; Liang, L; Bruder, SP; DePuy AcroMed, DePuy Orthopedics, and Case Western Reserve University.
PRP Contraindications

- Platelet Dysfunction Syndrome
- Sensitivity to bovine thrombin
  - If using gel
- Thrombocytopenia
- Hyperfibrinogenemia
- Hemodynamic instability
- Septicemia
What About Stem Cells?

• Stem cells need growth factors to be told what to do, otherwise they don’t heal anything.

• Is a higher PRP concentration advantageous to grow a mesenchymal stem cell (MSC) in culture?
PRP vs Stem Cell

- PRP is *NOT* stem cells.
- PRP is platelet rich plasma. This biological medicine elicits a healing response.
- PRP stimulates native cells and native stem cells to repair when administered.
Recent Research - Musculoskeletal

• Good recent review article of PRP from American Osteopathic Association

• The studies showed **statistical improvement** with PRP therapy

• “The lack of standardization of PRP preparation”
  
  – Various matrices used to localize the injections at site of injury

• Study shows mostly positive effect of PRP, as well as critiques of studies
STEM CELL THERAPY
Clinical Outcome of Bone Marrow Concentrate in Knee Osteoarthritis

Kristin S. Oliver, MD, Matthew Bayes, MD, David Crane, MD, Chakrapani Pathikonda

ABSTRACT

Background: Knee osteoarthritis is an increasing health concern in the adult population. Non-surgical treatment options for pain reduction and function improvement are limited in number and provide only short-term relief. The potential of regenerative therapies to go beyond temporary symptom reduction and delay or negate the need for total knee joint replacement is exciting to both patients and providers.

Purpose: This study evaluated the clinical efficacy of autologous intra-articular bone marrow concentrate with autologous lipoprecipitate as a treatment option for osteoarthritis of the knee. Additionally, bone marrow concentrate samples from a patient population subset not necessarily enrolled in this study, but IRB approved, were sent for outside laboratory analysis.

Study design: This study is a prospective case series.

Methods: Treatment registry data for 70 patients diagnosed with Kellgren-Lawrence Stage 2-4 knee osteoarthritis were analyzed. Data regarding adverse events and Knee Injury and Osteoarthritis Outcome Score metrics were obtained at baseline, 90 days, and 180 days. Samples of bone marrow concentrate from 11 patients were sent to an outside source for laboratory analysis.

Results: Adverse events were limited to transient pain and swelling of the treated joint. The mean reported KLOs changes from pre-procedure to 180 days post-procedure were as follows: Pain +1.81, Activities of Daily Living +1.56, Symptoms +1.73, Quality of Life +3.03, and Sports/Recreation +1.81. Laboratory analysis of the samples demonstrated statistically significant increases in concentration of platelets, Interleukin-1 receptor antagonist, and IL-1B. Thromboelastography ratio was additionally statistically significant at 193.54 when processed with a 2% Hct setting, and 720.62 when processed with a 15% Hct.

Conclusions: This study of intra-articular injection of autologous bone marrow concentrate in patients diagnosed with knee osteoarthritis demonstrates encouraging results for positive outcomes without complication. Further study with randomized controlled trials is warranted to prove the potential of this intervention. With laboratory analysis of samples of bone marrow concentrate we were able to identify the presence of statistically significant increase in the concentration of platelets and IL-1B.

What is known about the subject: Bone marrow concentrate is known to contain a host of growth factors and stem cells and has been shown in animal studies to promote the regeneration of cartilage. There are two clinical studies published showing the efficacy of bone marrow concentrate in patients with knee osteoarthritis.

What this study adds to the existing knowledge: This study supports the findings of the two published clinical studies of bone marrow concentrate in patients with knee osteoarthritis. This alternative treatment option provides positive patient outcomes with low risk.

Keywords: Bone marrow concentrate, platelet rich plasma, interleukin-1 receptor antagonist, knee osteoarthritis.

Introduction

Osteoarthritis is the most common cause of musculoskeletal pain and disability in the knee joint. Symptomatic knee OA occurs in 10% of men and 11% of women aged 60 or older. In the third National Health and Nutrition Examination Survey, approximately 37% of participants aged 60 or older had radiographic evidence of knee osteoarthritis. By 2030, the demand for primary total knee arthroplasties is projected to grow by 673% to 3.48 million procedures. The economic impact of knee OA is becoming an increasing concern. Estimated costs due to hospital expenditures of total knee joint replacements were $28.5 billion in 2009 and are expected to continue to rapidly rise with our aging “baby-boomer” population.

Current nonsurgical treatment options for knee OA focus on short-term relief of symptoms. These interventions include physical therapy, activity modification, bracing, oral medications, and intra-articular use of steroids.
Musculoskeletal

- American Journal of Sports Medicine
- Mayo Clinic study
- Prospective, single-blind, placebo-controlled trial
- 25 patients with b/l knee OA
- One knee injected with BMAC + PPP, other injected with saline
- Both knees experienced dramatic and statistically significant improvements (p<0.19)
What is a stem cell?

- Stem cells are multipotent: they can grow new tissue. This is how the body heals injuries.
- We can use our own stem cells which are stored in our bone marrow as undifferentiated mesenchymal cells, and adipose tissue.
- Easy to obtain. Simple outpatient procedure to obtain the cells, concentrate them in a centrifuge, and inject them into the joint.
Stem Cells

• Have ability to **self-renew**
• Can continue to divide for a length of time
• Can be induced to differentiate into specialized cells with distinct functional characteristics (phenotypes)
  – Bone, cartilage, nerve, fat, connective tissue, cardiac and liver cells
Stem Cells: Why do they work?

- We treat all of the sources of pain in and near the joint: nerve, soft tissue/capsule, tendon

Known to:

Decrease

- inflammation
- nerve pain

Increase

- anti-inflammatory effect
- HGH and testosterone within the joint: helps to improve healing
- grow new cartilage
Stem Cells: Pain Scores over 1 year

Pre-surgical: 4.9
2 weeks: 2.9
6 weeks: 2.8
3 months: 3.0
6 months: 2.7
1 year: 3.3

(-1.6) (p<0.001)
Stem Cells: Too good to be true?

No

- We have used autologous stem cells for 10 years
- Case series supports what we thought: pain relief can begin in 2 weeks and continue for many months
- More than one treatment may be needed
- **Overall success rate ~90%**
- Risk: Age > 85, poorly controlled diabetes/heart failure, smoking, severity of OA
So, WHO IS A CANDIDATE?
*Note: Not all stem cell procedures are created equally.
Michigan Sports & Spine Center

- Follow FDA guidelines
  - Minimal manipulation
    - No culture expansion
    - No collagenase use
  - Point of care
  - No IV use of cells
- Most commonly treated diseases
  - Knee Osteoarthritis
  - Hip Osteoarthritis
  - Shoulder pain
  - Elbow pain
  - Spine pain
Stem Cells OA: INITIAL VISIT

• Physical Exam
• Weight bearing 4 view x-rays
• MSK Ultrasound: Defines soft tissue
• Review of all treatment options, including knee replacement or other surgery
Stem Cells OA:
TREATMENT DAY

- Treatment time average: 90 min
- Walk in, walk out
- Valium given if needed
- All injection sites are anesthetized using lidocaine to minimize pain, and ultrasound guided
- Typical response: It hurts more to inject the knee than to take the bone marrow or fat
Aspiration Technique

• Placement BM needle
  – Seat well on PSIS/Cortex
  – Insert 3 cm from cortex (PSIS)

• Rotate trocar as drawing back
  – 2 cc every 90 degree rotation
  – After 360 withdraw trocar 0.5 cm
  – Repeat until just under cortex
  – If more volume needed
    • Replace stylet
    • Redirect
Stem Cell OA: POST-CARE

- Unloader brace
  - Stage III Lateral OA
  - Stage III and IV Medial OA
  - Meniscal extrusion on MSK US

- No NSAID’s
  - 4-6 weeks post-injection

- Pain Control
  - Opiates for 3–5 days
  - Acetaminophen
  - Ice 15 min, 2-3 hours
Stem Cell OA: POST-CARE

- HEP
  - Start day of injection
    - ROM primarily
  - At 3 days
    - Continue ROM
    - Add isometric quad strengthening
    - Add flexibility
  - At 4 weeks
    - Formal PT
    - Patient dependent
Stem Cell OA: POST-CARE

• Follow-up
  – 2 week nurse phone call
  – 8 week in office visit
    • Subjective and supportive primarily
  – 1 year
    • Ultrasound
    • 3 view wt. bearing x-rays

• 8-10 weeks post injection
  – If less than 75% subjective improvement
    • Advise PRP
  – If 75% or greater improvement
    • Recheck at 1 year
Stem Cell: POST-CARE

- Post-injection pain
  - 3-7 days of increased pain
- Home Exercises
  - Primarily range of motion
- Physical Therapy
  - Begin at 2 weeks
- Resumption of activity
  - Once pain is back to normal
Other Joints Treated?

- Yes
- Common Joints:
  - knee > hip > shoulder > small joints
- Soft tissue: chronic tendon pain (rotator cuff, achilles tendon, patellar tendon, etc), ligament sprains, some nerve pain
- Chronic back pain: yes
Tendinosis with chronic pain, cartilage or bony problem/unresponsive to conventional Tx

Yes

Systemic Disease, poor healing

No

Difficult to Tx injury, AVN, pars fx, tendon necrosis, Non-detached OCD, Grade IV OA

No

Large defect (>1 cm)

No

Yes

Consider checking labs: CBC, CMP, TFT'S, IGF1, Est, Progest, Test, DHEA, cortisol, vitamin D

Yes

BMAC?

No

Yes

PRP with Fat
MUSCULOSKELETAL TREATMENT ALGORITHM

Large defect (>1 cm)

- PRP

No

- PRP

Re evaluate in 4-6 weeks

<80% improved or not met goal activity level

- Yes
  - Repeat PRP consider PRP/Fat

>80% improved or met goal activity level

- Yes
  - Done

Yes

PRP/Fat

BMAC??
Rehabilitation Goals

• Good eccentric and concentric multi-plane strength and dynamic neuromuscular control to allow for return to work/sports

Precautions

• Post-activity soreness should resolve within 24 hours
Physical Therapy & Rehabilitation

After PRP

• Helps facilitate a successful outcome
• **Focus** is on *protection* for healing and *gentle* range of motion
• After the early phases, *strengthening and neuromuscular control exercises* are emphasized throughout the affected extremity
Physical Therapy & Rehabilitation After PRP

- Final stages of rehabilitation - focus is on progressive dynamic extremity control and stability during sport specific movements, such as change of direction and rotational movements.

- General time frames are given for reference to the average, but individual patients will progress at different rates depending on age, associated injuries, pre-injury health status, rehabilitation compliance and injury severity.

- These guidelines are presented in reference to tendon-related procedures, but general guidelines and concepts apply with treatment of ligamentous, joint, and muscle pathologies.
Suggested Therapeutic Exercises

• Continued strengthening of the affected area with increases in resistance, repetition, and/or frequency
• For the upper extremity: progressive training in provocative positions and work/sport specific positions—including eccentric, endurance, and velocity specific exercises
• For the lower extremity: impact control exercises with progression from single plane to multi-planar landing and agility drills with progressive increase in velocity and amplitude
• Sport/work specific balance and proprioceptive drills
• Continued core strengthening
• Return to sport programs (throwing, running, etc.) with symptom / criteria based progressions
Recent Research - Neurologic

- Stroke
- Reviews multiple multicenter studies conducted finding significant improvements in patients with chronic deficits from CVA
- Delivery mostly of autologous MSC stereotactically
Recent Research - Neurologic

- Journal of Neurosurgery
- Reviews multiple clinical trials of using MSC for spinal cord injury
- Mostly administered intrathecally
- Several studies found improvements in ASIA score
Future Directions

- IV Stem Cell
- Studied for conditions including ALS, Ankylosing spondylitis, OA with some promising early findings
- Data so far finds procedure well-tolerated, safe with few recorded adverse events
Future Directions

• Cell Stem Cell
• Researchers and exploring use of genetic engineering of autologous MSCs to compensate for heterogeneity both genetically and age-related regarding
• Optimize by combining MSCs with growth factors, ECM

Musculoskeletal tissue injuries and degeneration are common and debilitating for a high number of patients (Brooks, 2009). Unfortunately, endogenous musculoskeletal tissue regeneration is limited in many cases and may be affected by inflammation and the degree of damage. For example, most fractures of long bones heal spontaneously, whereas large segmental defects fail to heal. Additionally, although articular cartilage has almost no intrinsic reparative potential, tendons and ligaments may heal, but often with inferior properties. The high prevalence of these injuries has led to significant investment in the development of new therapies to enhance healing and augment current surgical interventions. Often the goals are to replicate and recapitulate the natural healing cascade and developmental process by transplantation of tissue-specific stromal and progenitor cells or by exogenous manipulation to enhance the native repair capacity of cells.

There has been a continuing increase in the number and types of stem and stromal cells being pursued in human clinical trials for treatment of musculoskeletal injuries (Steinert et al., 2013). Most approaches in this area are based on an ex vivo-expanded mesenchymal stromal cells (MSCs) derived from bone marrow (BM). Originally identified and characterized by their multilineage differentiation potential, mesenchymal progenitor cells of BMs in vivo have not been clearly demonstrated to date, particularly because of the lack of methods to identify and define differentiated populations (Romero-Arizmendi et al., 2015). Central bone regeneration progress in the field has been the understanding that stem and progenitor functions of MSCs may not be the key attribute that mediates tissue repair. In addition, there is outstanding controversy over the terminology of exogenously supplied MSCs as stromal cells, and various terms, including mesenchymal stem cells, have been proposed to more accurately reflect their therapeutic functions in vivo (Hagman, 2011). Nevertheless, the therapeutic benefit of these cells has been largely explored. Significant advances have been made in developing strategies that deliver, protect, and recruit stem cells, and the bioengineering field is evolving to improve current surgical techniques.

This review first describes current treatments and reports the recent progress in clinical investigations of stem and stromal cell-based therapies for musculoskeletal repair with a particular focus on bone and fibrocartilaginous tissues. The current understanding of appropriate cell sources and delivery strategies is then illustrated toward endogenous repair of musculoskeletal tissues. Last, emerging therapeutic concepts are highlighted in the context of biomaterials as a particularly attractive tool to control stem and stromal cell behavior both in vivo and in vitro, to recruit endogenous stem cells, and to control the local healing environment. Such approaches have great potential for future therapies in musculoskeletal repair.

Current Surgical Interventions and Associated Limitations

Damage from trauma is a major cause for surgical repair of musculoskeletal structures and comes with the increasing prevalence of post-traumatic and degenerative pathologies. Detailed descriptions of the indications, clinical applications, and outcomes of current surgical procedures have been presented in latest excellent reviews (Baum et al., 2010; Greyson et al., 2015; Sakai and Anderson, 2013). A better understanding of these surgical principles is important because many cell-based interventions have been developed that aim to improve, not substitute, surgical repair (Table 1).

Bone Repair

The inherent repair of bone defects mirrors many events of embryonic development and makes fracture healing one of the rare pathological processes that are regenerative and can ultimately restore damaged tissue to its pre-injury structure, composition, and biomechanical function (Figure 1). In spite of the unique capacity of bone to heal, a number of clinical indications remain where therapeutic intervention is required. In the case of complex trauma with multiple fractures, infections, and tumor-associated and endometriosis disease (e.g., diabetes, osteoporosis, the body’s natural healing response is impaired, and non-union can occur in up to 15% of cases (Grayson et al., 2015). Another debilitating disorder is non-union. Avascular necrosis osteonecrosis, which can lead to collapse of the femoral head and as causes for 15,000-30,000 total hip replacement surgeries in the United States per year (Figure 1). Multi-Angel et al. (2015)
“Which celebrities should I follow to get the best medical advice?”
Jeff S. Pierce, D.O.

• Board Certified in PMR and Pain Medicine
• Team doctor for professional, collegiate and elite sports teams
• Entertainer medical care provider, “Roc Doc”, since 2002 for Palace Sports & Entertainment, Olympia Entertainment and 313 Presents
• As heard on Inside Sports Medicine, Sunday mornings at 8am on 97.1 The Ticket
• Founder of Athletes Unlimited, a non-profit organization for the support and development of athletes with physical challenges
• Treated numerous professional athletes including consulting for the Detroit Red Wings
• Long term author of Hockey Weekly’s “Ask the Doctor” column
• Sports Medicine Team Sponsor for the Susan G. Komen 3 Day for the Cure since 2005
• ADN (Athletes With Disabilities Network) Board Member
• Mentor and supervisor to numerous residents and medical students
• Served 3 terms on the Governor’s Council for Physical Fitness, Health and Exercise
• Director of Interventional Spine/Sports Medicine Fellowship-Preceptorship since 2004
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