Orthobiologics and Regenerative Medicine in Rehabilitation

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Objectives

• Understand uses and type of orthobiologic interventions
• Discuss physiology and mechanism of healing
• Comprehend rehabilitation principles, guidelines, and precautions with biologics on board
• Appreciate outcomes with different biologics and address expectations for recovery

What is Biotechnology

• Biotechnology is used to treat articular cartilage, tendon, ligament, muscle, and bone pathologies that currently have less than satisfactory solutions.
• Treatments can potentially restore quality of life for many people around the world.” -Malar Muniandy (Nurse Manager- KLSMC Stem Cells)

What are Orthobiologics????

• Orthobiologics are substances that are found naturally in your body that help you heal more efficiently.
• “Orthobiologics are used to improve the healing of fractures, injured muscles, tendons and ligaments. When they are used in higher concentration, they may help to hasten the healing process.” (Singh, 2015)
• These include:
  – Matrix materials: Bone grafts, autologous blood, artificial matrix materials
  – Growth Factors: Platelet rich plasma, Bone morphogenic proteins
  – Stem Cells: Mesenchymal, progenitor
What are Orthobiologics

• Can be cardioregenerative and neuroprotective (Uccelli et al., 2011).
• Not an ethical dilemma as adult stem cells are used in orthopaedics.
  – No embryonic harm or harvesting
• Promising new treatment for cartilage pathology (Hardingham et al., 2010, Richardson et al., 2010, Saw et al., 2013)

Stem Cells

• Definition:
  – Capable of self renewal
  – Potential to differentiate into specialized tissue
  – “an unspecialized cell that gives rise to differentiated cells (hematopoietic stem cells in bone marrow).”-Merriam-Webster

• Types
  – Embryonic
  – Adult

Platelet Rich Plasma (PRP)

• Not harming fetuses
  – We do not... I repeat... DO NOT harm embryos, fetuses, or babies!!!
  – These are AUTOLOGOUS Stem cells
• A cure all
• Guaranteed

Goal of Regenerative Medicine

• The goals of regenerative medicine are to implement the intrinsic regenerative ability of damaged tissues as well as to identify novel cell-based therapies for tissues that lack a repair process (e.g., cartilage), fail to repair (such as bone tissue that lacks a fracture-healing ability) or need a more functionally efficient reparative process (such as heart muscle after a myocardial infarction)

What Orthobiologics are NOT

• Harming fetuses
  – We do not... I repeat... DO NOT harm embryos, fetuses, or babies!!!
  – These are AUTOLOGOUS Stem cells
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Problems with current methods

• Inconsistent
  – Surgical procedure
  – Rehabilitation protocols and treatment
• Donor site tissue
  – Healthy vs pathological vs patient health
• Expensive
  – Often not reimbursed by insurance
• Patient compliance
Pathology Sources

Biological

• Leads to release of signaling molecules
  – Cytokines, nitric oxide, prostaglandins, and neuropeptides (pro-inflammatory)
  – Joint inflammation
  – Swelling
  – Pain
  – Loss of joint homeostasis
  • ARTHRITIS

Pathologies

Mechanical

• Cartilage Injury -> joint wear (DJD)
• Ligament Tears -> joint degeneration
• Meniscus tears -> meniscus tears & joint degeneration

Current Uses: S.C. & PRP

• Musculoskeletal System
  – Muscles
  – Tendons
    • Patellar, rotator cuff, medial/lateral epicondylitis
  – Ligaments
    • Partial UCL, PCL, MCL tears
    • Following surgical procedures
  – Bones
  – Joints (cartilage)
    • Cartilage defects
  – Connective tissue

Why Are We Using Orthobiologics?

• To prevent further more invasive surgery
  – TKA, THA etc.
• Improve healing time
• Improve healing process of damaged tissues or poorly vascularized tissues
  – Cartilage, tendon, ligament
• Decrease pain associated with poorly healed pathology
• Decrease swelling
Platelet Rich Plasma

- Also known as Platelet Rich Serum, Platelet Rich Concentrate, Autologous Platelet Gel.
- Platelet-rich plasma is an autologous suspension of platelets prepared from whole blood via double centrifugation techniques.
- The normal platelet count in whole blood in a healthy individual is between 150000-45000 per microliter. To be labeled as platelet rich plasma the platelets should be of 4-5 times of the baseline.
- This rich concentrate is rich in growth factors including platelet derived growth factor, transforming growth factor, platelet factor 4, interleukin-1, platelet-derived angiogenic factor, epidermal growth factor, platelet derived endothelial growth factor, epithelial cell growth factor insulin-like growth and vascular endothelial growth factor.

After extraction, before application, platelets are activated with calcium chloride and the resultant platelet clot may be applied to the site of injury. Platelets begin secreting these proteins within 10 minutes of clotting (Singh, 2015)

Stem Cells

- Present in bone marrow, fat, synovial membrane, periosteum.
- Stem cells are special cells in the body which can differentiate into any other type of cell.
  - Differentiate into 2nd generation cells where they specify tissue based on matrix needs, location, damaged tissue, growth factors present, and structural demands.
- Stem cells are summoned during healing process to the area of repair based on inflammatory factors, growth factors.
  - Matrix provides framework for stem cells
  - Growth factors act on stem cells to cause the repair of the injured tissue.

S.C.: Bone Marrow Aspirate

Uses of Biologics

- After apheresis stem cell viability after cryopreservation on average at time of last injection is 83.61% (with pharmacological mobilization)- Dr. K.Y. Saw, 2016
- Neupogen given on post op day 4, 5, or 6 and apheresis harvesting performed on day 7
Stem Cell Storage

- PBSC collected and first injection given as FRESH cells on day 7.
- One injection per week for the next 5 weeks
- ***All Injections given with HA (Hyalgan-sodium hyaluronate/Hyaluronic acid derivative)

Chondrogenesis- Is it Possible

Currently
- Microfracture to stimulate bleeding
- Bone marrow aspirate (BMA) autologous stem cells- (7,000-10K per harvest)
- Injection series with rehabilitation
- Produces fibrocartilage

Hypothesized
- Bone drilling procedure to stimulate bleeding
- Utilize pharmacological stem cell mobilization and apheresis to collect stem cells and cryopreserve.
  - Harvest 100-120 million autologous stem cells
  - Regular injection intervals with rehabilitation
  - Produces hyaline cartilage

Outcomes

- ACI- 1st generation ACI leads to patient satisfaction 77% of time, but long term full restoration of knee function can’t be achieved (Niemeyer et al., 2014)

BMAC Outcomes

- Studies show BMAC is used and is effective however studies used different outcomes (Gigante et al., 2012, Gobbi et al., 2015)
- Mod knee OA have better outcomes with BMAC compared to advanced (Centeno et al., 2014, Kim et al., 2014)
- BMAC combined with PRP- did not show any significant difference in outcomes compared to BMAC individually (Centeno et al., 2014).
- Focal cartilage defects >3 cm with microfracture- outcomes were better with younger people, smaller lesions, fewer number of lesions. (Enea et al., 2013)

Chahla et al., 2016
OA at Talus

- Systematic review shows no long term studies supporting BMAC for treatment of chondral defects.
- Studies offer conflicting results on long term outcomes and patient satisfaction.

PRP Outcomes

- Patellar tendinopathy
  - Therapeutic regiment of eccentrics, US guided PRP, and Dry needling accelerated rehab compared to exercise and dry needling alone
  - Effects of PRP dissipates over time (Dragoo et al., 2014)

Regional Interdependence

- Concept of Regional Interdependence is the relationship of adjacent and distant segments have on motion and stability of body parts of seemingly unrelated sections that can contribute to pathology or have an effect on one another. (Wannier et al., 2007)
- New definition:
  - Does not limit to musculoskeletal system
  - “The concept that a patient’s primary musculoskeletal symptom(s) may be directly or indirectly related or influenced by impairments from various body regions and systems regardless of proximity to the primary symptom(s).” (Sueki et al., 2013)
Full and adjacent body segment assessment

Joint by Joint Approach

Car Analogy

• If you have a flat tire, is it because the tire is bad or is it because the alignment was off and/or the shocks bad causing the tired to have abnormal wear.
• Does fixing the tire solve the problem?
• Be sure to fix the alignment and treat the shocks.

Rehabilitation Considerations
1. Diagnosis/pathology/surgical procedure
2. Severity of tissue damage/invasiveness
3. Pain level
4. Duration since injury
5. Tissue healing & quality
6. Patient stage of rehab
7. Current level of function and movement quality
8. Patient Goals
9. Outcomes expectations
10. Psychosocial factors

C.B.R. Principles
• *PRECAUTIONS GUIDE PROGRESSIONS*
• Once tissue is at appropriate healing level for activity...
  - Ability to perform PROGRESSIVE FUNCTIONAL rehab tasks in sequence determines progression.
  - Not given amount of weeks from surgery
• Example): Just because they are 12 weeks out DOES NOT mean they should advance to plyometrics if they can’t perform a basic squat:
  - Full and hip muscle activation
  - Walk without deviations with 2 crutches -> 1 crutch with and without brace.
  - Then can walk without brace and crutches
• Functional tasks are a byproduct of doing basic movement patterns properly, NOT a product of TIME!!!

Grzybowski et al., 2015, Wahoff et al., 2014

Rehabilitation pyramid

Performance

Functional Movement & Strength

Foundational Movement & Strength

C.B.R.

• Return to sport activities
• Advanced plyometrics
• High intensity activities
• Full return to play - usually not performed in PT**

• PROM
• AROM
• Basic strength
• Against gravity strength
• 5/5 MMT
• Function
• Normal gait
• Positional activity
• Reactive demands
• Integration of prior activity demands
• Control environment (plyometrics)
### Rehab Principles
- Continue progressive overloading without over stressing healing tissue
- Move the joint to tell PBSCs that they are in a joint.
- Statically load the joint to communicate to PBSCs they need to turn into cartilage.

### Rehab Post Subchondral Drilling and Stem Cell injection
- CPM 2 hours/day for 1 month
- PWB to full 6-8 weeks
  - Dependent on joint surface (femoral, tibial, patellofemoral)
  - If weight bearing surface start off at 20 kg WB with 10 kg increases per week after week 2.
- Static loading
- Quad setting

### Acute Phase
- Restore normal ROM- passive -> active to patient tolerance
- Improve joint mobility- patellar mobilizations
- Control and manage swelling
- Restore isometric muscular firing patterns and neuromuscular control.
- WB will be procedure dependent

### Sub-Acute Phase
- Progressive static load WB- Procedure dependent
- Continue to progress active ROM
- Allow for healing of weekly injections
- Patient education on home and activity modifications
- Progress isotonic strengthening

### Protective Phase
- Initiate closed chain motion through ROM activities
- Patient should achieve full ROM in this phase
- Continue to progress static loading to full WB
- Restore normal gait kinematics
- Advance open chain exercises
- Progress balance and stability tasks
- Expect crepitus in knee- cheese grater effect

### Intermediate Phase
- Progress closed chain activities to greater depths
- Progress functional strengthening tasks
- Initiate kneeling exercises- procedure dependent
- Advance aquatic therapy with light plyometrics in pool
Dynamic Strengthening phase

- Progress combined body movements in multiple planes without resistance progressing to using resistance
- Light plyometrics initiation
- Initiate deep water running in pool

Advanced phase

- Initiate functional testing
- Provide independent gym program
- Manage patient expectations that cartilage still needs another 6-12 months to fully mature
- Provide guidelines on appropriate activities and progressions
- Advance plyometrics

Dr. K.Y. Saw Results

- It is possible to regrow hyaline cartilage and treat chondral defects in patients with knee OA- Saw et al., 2013, Saw et al., 2011
  - Need proper surgical technique with drilling and close proximity of holes and proper load bearing rehabilitation
- Cartilage surfaces healed at 24 months and were mature and cartilage surfaces were maintained at 34 month mark upon arthroscopic assessment- Saw et al., 2013.
- From 2007-2014- 520 cases:
  - Baseline at 12 months IKDC significantly increased and sustained for 66 months
  - Complications: No adverse effects, no soft tissue or bone tumors or unforeseen abnormalities

Matrix Materials

- Matrix is the framework where cells reside, thrive and make the desired tissue, be it bone, tendon, or ligament. Matrix serves as building blocks that help fill tissue gaps