Outline

- Case
- Natural history of muscle strains
- Evaluation of muscle strains with US and MRI
- The problem: How to accelerate healing?
- Typical Care
- What we did
- Literature

The Case:
MLS Soccer Player History, PE

- 29 October 2011 game
- 30 yo male
- Sudden onset Rt ant thigh pain while sprinting
- Immediately subbed out
- Weak hip flexion & knee extension
- No palpable mm. defect
- Clinical dx grade 2-3 quad strain
- RICE, no NSAIDs initiated
The Case: MLS Soccer Player

- 1 day post injury
- MRI: Undersurface tear of the rectus femoris, lateral to the central tendon slip, 10cm distal to the hip joint, approx 80% depth.
  - Hemorrhage in and around the MT junction
  - High Grade 2
- US: extensive edema and muscle fiber disruption just lateral to the central slip of the proximal rectus femoris tendon and extending much of the depth of the muscle belly (Grade 2C).

Clinical Grading

- Grade 1: Not so bad
- Grade 2: In between
- Grade 3: Bad

MRI Grading

- Grade 1: IM feathery hyperintensity w/o mm fiber disruption
- Grade 2: IM hyperintensity w/ extension along fascial planes; irregular mm fibers; hematoma (pathonomic)
- Grade 3: Extensive hematoma, edema; complete mm fiber discontinuity
**US Grading #1**

- Grade 1: Hypoechoic area < 1 cm diameter
- Grade 2: Hypoechoic area 1 to 3 cm diameter
- Grade 3: Hypoechoic area > 3 cm diameter & retraction


**US Grading #2**

- Grade 1: < 5% of muscle volume or X-sectional diameter
- Grade 2: 5-50%
- Grade 3: Complete tear w/complete retraction

US Grading #3???

- Grade 0: WNL
- Grade 1: Muscle edema only
- Grade 2a: Partial mm. tear, < 33%
- Grade 2b: Partial mm. tear, 33-66%
- Grade 2c: Partial mm. tear, 66-99%
- Grade 3: Complete tear
Grade 3, Lat Gastrocnemius

Mature hematoma separating the muscle ends
So, what are the key elements to predict recovery?

- Without bundle tears?
  - 1-2 week recovery

- With bundle tears & im hematomas?
  - ≥ 4 weeks recovery

Dx US Timing

- < 2 hrs post injury: hematoma is still forming
- 2 to 48 hrs: ideal
- > 48 hrs: hematoma can spread outside of mm.
- Hamstring: ASAP after 2 hrs
- Quad, gastroc up to 2-3 days

US vs. MRI

- US
  - Inexpensive, available in the office, dynamic imaging, Power Doppler for hyperemia, can use for needle guidance

- MRI
  - More sensitive to detect ongoing muscle healing
  - Better able to detect edema

References:

The Problem

- Injury sustained at time 0
- We saw him 1 d later
- Next games are
  - 3d post injection (5d post injury)
  - 6d post injection (8d post injury)
  - 20d post injection (22d post injury)
- It's playoffs
- How to RTP yesterday?

Natural History of Muscle Strains

- How long does it typically take to RTP?
- Dearth of literature
- Central quad APONEUROSIS tears in 35 high-level Spanish soccer teams
  - Ultrasound study; NOT in professional athletes
  - Proximal: 45.1 d w/ 4cm tear (length)
  - Distal: 32.9 d w/ 3.9cm tear


Natural History of Muscle Strains

- MLS trainer(s) very aggressive guesstimates
- Grade 1: 10 to 14 days
- Grade 2: 2 to 4 weeks
- Grade 3: 4 to 8 weeks
Typical Muscle Strain Care

- **RICE**

- Timing matters: NSAIDs interfere with the late proliferation stage of a repaired rotator cuff tendon healing in rats.

- Possibly a short period of immobilization (2 to 6 days)

Typical Muscle Strain Care


- No clear consensus on how to accelerate recovery.

Pathophysiology

- The phases of the healing processes after direct or indirect muscle injury are complex but clearly defined and include well-coordinated steps: degeneration, inflammation, regeneration, and fibrosis.

- The problem: How to accelerate tissue healing, improve muscular regeneration, increase neovascularization and reduce fibrosis, allowing rapid recovery after muscle lesions?
How to achieve the fastest recovery possible?

- PRP
- Stem cells: Autologous Fat Graft, Bone Marrow, Placental, Amniotic
- Platelet Poor Plasma

Growth Factors

- Many in vitro and in vivo studies show that GF’s play a role in muscle regeneration

PRP has Growth Factors

- Platelet-Derived Growth Factor (BDGF)
- Transforming Growth Factor beta (TGF-beta)
- Fibroblast Growth factor (FGF)
- Insulin-Like Growth Factor 1 (IGF-1)
- Connective Tissue Growth Factor (CTGF)
- Epidermal Growth Factor (EGF)
- Hepatocyte Growth Factor (HFG)
PRP in Animal Model

- Rat tibialis anterior, small or large strain
- Contraction-induced injury (single large & multiple small reps)
- PRP injected at days 0, 3, 5, 7
- Symphony II plt conc sys (Depuy)
- Measured
  - GF's increased: PDGF inc 5x, IGF-1 inc 27%
  - Max isometric CTX pre, post


PRP in Animal Model

- Myogenesis occurred (myoD & myogenin increased)
- IGF-1, FGF-2, HGF, and TGF-β1 are thought to be key regulators for myogenesis
- IGF-1 stimulates the proliferation and differentiation of myoblasts (skeletal muscle precursor cells) and improves muscle regeneration.

PRP in Animal Model

- In vivo, FGF-2 enhances the diameter and number of regenerating fibers.

- In vitro, HGF is able to activate quiescent mm. stem cells.
**PRP in Animal Model**


- **Satellite cells**: dormant in uninjured skeletal muscle.

- Can be stimulated by injury to proliferate or differentiate into **mononucleated myoblasts**.

- These myoblasts fuse to form multinucleated **myotubes**.

- These myotubes then form **new skeletal muscle**, replacing damaged or lost tissue.

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**Muscle Inj’s & PRP in Humans, US guided**

- 30 pts, PRP vs. Conservative Rx (Ultrasound), Comparative Study PRP x 1 inj, 5cc (from 40cc blood); Faster pain relief, strength, more normal echotexture on US (Bubnov R, Voskodanov V, Semeniv I. Med Ultrason. 2013 Jun;15(2):101-S. Ultrasound guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study.)

- 53 pts, 50-60cc PRP x 3 inj’s q 7d (from 350cc blood; PRP was frozen), used thrombin & Ca++ to activate: Pain relief, increased strength, normal echotexture on US (Blood Transfus. 2014 Jan;12 Suppl 1:s229-34. Bernuzzi G, Petraglia F, Pedrini MF, De Filippo M, Pogliacomi F, Verdano MA, Costantino C. Use of platelet-rich plasma in the care of sports injuries: our experience with ultrasound-guided injection.)

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**PRP vs. Standard Rx?**

- Case control study

- **HAMSTRING** injuries in NFL players

- 5 PRP, 5 rehab only

- 6cc PRP (Biomet) from 54cc blood

- Injected 24-48 hrs post injury, US guidance

- No significant difference in RTP (20 vs 17 days)

What about Platelet Poor Plasma?

- The rat model didn’t evaluate it
- Fibrin scaffold may help to fill the void

What about Mesenchymal Stem Cells?

High regenerative capacity of these cells in various musculoskeletal tissues including skeletal muscle.

1. Proliferate in vivo for an extended period
2. Strong capacity for self-renewal
3. Resistance to stress
4. Multilineage differentiation toward muscle, bone, neural, endothelial, and hematopoietic cell lineages
5. Induction of neovascularization


Where can I get MSC’s?

- Adipose
- BM
- Placenta
- Amniotic Fluid
Calvin's Transmogrifier: MSC Multilineage Potential

Muscle, Tendon, Cartilage, Bone, Fat, Nerve

What's in the MSC box?

Mechanism of Action for MSC Transmogrification

“Letting the individual site dictate the need through complex signaling and paracrine activities, may be more advantageous than total isolation of elements...”

It is becoming increasingly clear that stem cells tissue repair by direct differentiation and **paracrine effects** leading to neovascularization of injured site and chemoattraction of host cells. The factors invoked in paracrine action are still under investigation.


Biological approaches to improve skeletal muscle healing after injury and disease.

**Terminal differentiation capacity of implanted stem cells is not the major determinant of the cells regenerative potential and that the paracrine effect imparted by the transplanted cells plays a greater role in the regeneration process.**


**We have found that when muscle-derived stem cells (MDSCs) are implanted into a variety of tissues only a small fraction of the donor cells can be found within the regenerated tissues and the vast majority of cells are host derived.**

Mechanism of Action for MSC Transmogrification

- Neo angiogenesis (but not for non-vascularized tissue, such as cartilage)
- Chemo attraction

**Tissue Regeneration: Autologous Regenerative Matrix (ARM)**

The Therapeutic Triad

Cell Proliferation Requires the Interaction of Three Biological Elements:

1. Recruitment of cells to the scaffold
2. Cell division within the scaffold

Signal Proteins and Adhesion Molecules control:

- Undifferentiated Cells - Stem Cells (PRP signaled, Fat or Concentrate of BM Aspirate)
- Scaffold (Native Tissue or Fat)
- Signal Proteins & Adhesion Molecules (PRF)

Compressed Adipose

Compressed lipoaspirate: Adipocytes, ADSCs, SVF, ECM, stromal (perivascular) elements
Return to the Case

- 29 October 2011: Initial injury
- 1d post injury:
  - Evaluation, MRI, US
  - AFG, PRP injection

AFG, PRP Procedure

- Harvest SmartPrep, 60cc whole blood
- 10cc PRP
- High WBC (but high lympho’s, low neutrophils), High RBC
- Injected into and around the defect
  - 5cc concentrated AFG mixed w/3cc PRP
  - Remaining 7cc PRP

Post Injection Protocol

- No NSAIDs
- OK to ice for 10-15 minutes
- Passive stretching, core stabilization and eccentric exercises in a pool twice daily
- Day 5: pool workouts increased to four times daily and gradually added progressive field exercises
- Day 6: minimal pain, good ROM, and able to sprint in practice
Post Injection Outcome

- Decided that he would attempt to play in the next playoff game scheduled that night.
- Day 6 post injection (8 post injury): played 83 minutes
- No thigh pain during or after the game
- During the off-season, continued home rehab program

Repeat MRI, US

- F/U MRI 3/21/12 (6 mos): slight residual quad edema. o/w WNL
- F/U US WNL

Return to Play?

- Proximal rectus femorus central aponeurosis: 45.1 days w/ 4cm tear (length)
- ATC: 2 to 4 weeks for a grade 2 quad mm tear and 4 to 8 weeks for a grade 3 tear
- 8 days after injury: played 83 minutes in playoff game. No further problems with that muscle injury.
Optimal Injection Timing?

- Mouse tibialis ant mm
- Muscle-derived stem cells (MDSCs) are likely derived from blood vessel cells and have a multilineage differentiation potential.
- 4 days after injury significantly promoted angiogenesis, which was induced by high levels of VEGF.

A decrease in fibrosis formation was observed at week 4, when compared with the other groups, after the transplantation of MDSCs at 4 and 7 days after injury.

Losartan + PRP to Decrease Fibrosis & Accelerate Healing (UPMC)

- Mouse tibialis ant model
- Losartan = antifibrotic agent
- Follistatin, a positive regulator of muscle growth, was expressed at a higher level in the PRP + losartan group compared with the other groups.
- Blocking the expression of TGF-β1 with losartan improves the effect of PRP therapy on muscle healing.
- Stimulate muscle regeneration and angiogenesis and prevent fibrosis in contusion-injured skeletal muscle.

Use of an antifibrotic agent improves the effect of platelet-rich plasma on muscle healing after injury.
Losartan + PRP to Decrease Fibrosis & Accelerate Healing (UPMC)

- Losartan accelerated the healing of injured muscle when administered immediately following injury
- Minimum dose of Los used to obtain these results was 300 mg·kg⁻¹·day⁻¹ (30x the equivalent human dose for HTN)
- Timing of administration is critical for optimal results
- Clinically relevant safe human dose of Los (10 mg·kg⁻¹·day⁻¹ initiated 3 days postinjury).
- For a 150 lb man (68kg), 10 mg/kg/d is 680 mg. Typical losartan dosing for HTN is 25-100 mg divided qd to bid.
- Can this dose be tolerated in an athlete?


How to keep the injectate in place?

- Magnetic field applied externally to keep plts in desired position (rat model)

Current Rx Protocol

- Multiple mm. fenestrations (peppering, PNT)
- AFG, PRP into the edges of the torn mm sites
- Remaining PPP, PRP further into the periphery
- Thicker product
  - PPP, centrifuged to get fibrin clot
  - Mix with AFG, PRP, thrombin
- Local vs. Regional anesthesia
- Cytotoxic effects of 'caines (esp. bupivacaine)
- Decreased tenocyte proliferation & cell viability
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