STEM CELL AND PLATELET-RICH PLASMA FOR JOINT MANAGEMENT

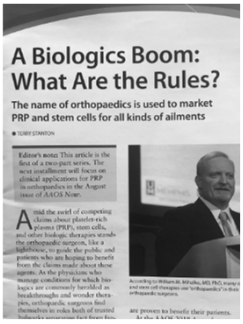
DAVID SCHALL MD.

1

"BIOLOGICS"

- Injectable therapies that may suppress inflammation and promote regenerative pathways
- Natural products that are harvested and are used to supplement a medical process and/or the biology of healing

2


A Biologics Boom: What Are the Rules?

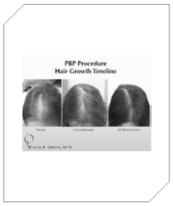
The name of orthopaedics is used to market PRP and stem cells for all kinds of ailments


AAOS Now

JULY 2018

3


PRP (Platelet-Rich Plasma)
PRP Facials & PRP Hair Treatments


PRP Procedure
Hair Growth Timeline

4

2018 AAOS ANNUAL MEETING

- "Explosion of mom-and-pop shops with little or no regulation"
- Retailing of biologics "is a cash business- and is very expensive"
- Google "stem cell centers"- 18 million hits

5

2018 AAOS ANNUAL MEETING

- Study that contacted 271 of 317 centers that market directly to consumers
- Mean cost of treatment for stem cells and/or PRP was $5,156 (range $1,500-$12,000)

6

"BIOLOGICS": 3 MAIN CATEGORIES

1. Endogenous growth factors- PRP
2. Cells-mesenchymal stem cells derived from bone marrow and adipose tissue and embryonic cells from embryonic tissue
3. Amniotic or placental-derived tissues

7

PLATELET-RICH PLASMA (PRP)

8

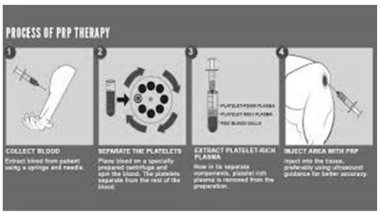
HOT TOPIC IN ORTHOPEDICS

9

6 FACTORS DRIVING POPULARITY OF PRP

10

- CONSISTS OF AUTOLOGOUS BLOOD WITH A PLATELET CONCENTRATION ABOVE NORMAL BASELINE LEVEL



11

- DELIVERY OF GROWTH FACTORS, INFLAMMATION MODULATORS, AND CELL ADHESION MOLECULES FROM A POOL OF DEGRANULATING PLATELETS

12

BIOACTIVE PROTEINS

- PDGF
- INSULIN –LIKE GF I/II
- FGF

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PLATELET GROWTH FACTORS AND CYTOKINES

- Stimulate extracellular matrix synthesis
- Stimulate chondrocyte proliferation
- Promote boney remodeling
- Promote wound healing
- Inhibit catabolic pathways

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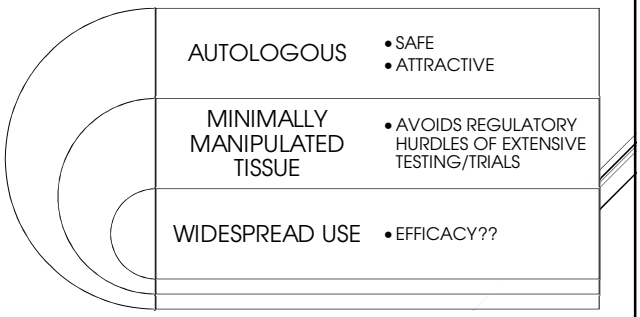
THOUGHT TO FACILITATE AND ENHANCE THE HEALING OF INJURED TISSUE

AUGMENT THE NATURAL HEALING PROCESS BY INCREASING THE CONENTRATION OF THESE CYTOKINES AT THE SITE OF INJURY

15



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FDA REGULATES STEM THERAPIES: MINIMAL OVERSITE

- CRITERIA TO DETERMINE LOW-RISK
- LOW RISK DO NOT REQUIRE TRADITIONAL PRECLINICAL ANIMAL TRIALS OR PHASED CLINICAL TRIALS PRIOR TO HUMAN TREATMENT
- STRONG REGULATORY OVERSITE NOT NEEDED

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FDA: LACK OF REGULATORY HURDLES BECAUSE:

- Little manufacturing manipulation
- Autologous with no systematic effect
- Cannot combine with other products
- Utilized in homologous way-original function
- Bone marrow aspirates
  PRP

18

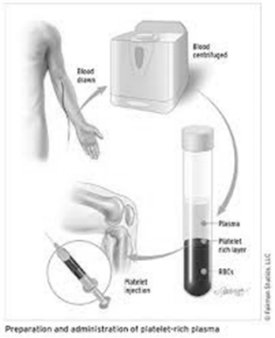
PREPARATION OF AUTOLOGOUS BLOOD

TWO STAGED CENTRIFUSION

19

"SOFT SPIN"	• SEPARATES PLATELET-CONTAINING PLASMA FROM RBC/WBC • 1,200-1,500 RPMs
"HARD SPIN"	• SEPARATES PLASMA INTO PLATELET-RICH AND PLATELET-POOR PORTIONS • 4,000-7,000 RPMs
HETEROGENOUS PLASMA CONFIGURATIONS	• 40 + COMMERCIALLY AVAILABLE SYSTEMS • DIFFER IN CENTRIFUGATION TIME, INITIAL BLOOD VOLUME, ACTIVATING AGENTS/TECHNIQUES

20



Preparation and administration of platelet-rich plasma

21

TWO MAIN CATEGORIES BASED ON CELLULAR COMPOSITION

LEUKOCYTE RICH PRP: LEUKOCYTE CONCENTRATION ABOVE PHYSIOLOGIC BASELINE

LEUKOCYTE POOR PRP: LEUKOCYTE CONCENTRATION BELOW PHYSIOLOGIC BASELINE

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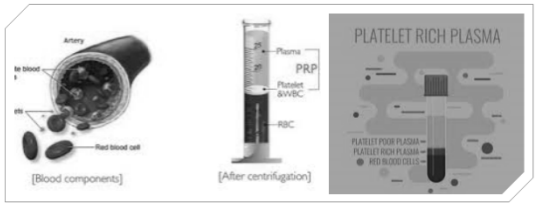

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PRP SYSTEM

24

STUDY DESIGN IN LITERATURE

ALL USES OF PRP

25

LITERATURE

- Wide heterogeneity of preparation methods
- Injection methods and frequency vary
- Difficult to compare studies

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JB JS THE Journal OF Bone & Joint Surgery

1769

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A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting

A Systematic Review of the Clinical Orthopaedic Literature

Jorge Chahla, MD, PhD, Mark E. Cinque, MS, Nicolas S. Piuzzi, MD, Sandeep Mannava, MD, PhD, Andrew G. Geeslin, MD, Iain R. Murray, MD, PhD, Grant J. Dorman, MSc, George F. Muschler, MD, and Robert F. LaPrade, MD, PhD

Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, and The Cleveland Clinic Foundation, Cleveland, Ohio

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A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting

A Systematic Review of the Clinical Orthopaedic Literature

- Systematic review of literature looking at PRP preparation protocols and PRP composition utilized in clinical trials
- 105 trials between 2006 and 2016

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TABLE I PRP Processing System Used in the Studies That Reported That Information (N = 54)*

Make and Model	Method	No.
GPS (Biomet)	Centrifugation	25
Magellan Autologous Platelet Separator System (Medtronic Perfusion Systems [now Arteriocyte])	Centrifugation	9
Arthrex ACP Double Syringe System (Arthrex)	Centrifugation	7
Centrifugation (not specified)	Centrifugation	7
PRGF technique (BTI Systems)	Centrifugation	5
SmartPReP 2 system (Harvest Autologous Hemobiologics)	Centrifugation	4
Platelet-pheresis system with a leukoreduction set, COBE Spectra LRS Turbo (Rontis Medical)	Platelet-pheresis	3
Cascade autologous platelet system (Musculoskeletal Transplant Foundation)	Centrifugation	2
Haemonetics MCS1 9000 cell separator with a specific kit for platelet apheresis, 995-E (Haemonetics)	Platelet-pheresis	2
Huons HC-1000 system (Huons)	Centrifugation	1
Harvest system (Harvest)	Centrifugation	1
PRP fast biotech kit PPT-Platelet Preparation Tube (MyCells)	Centrifugation	1
Centra CL2 (IEC)	Centrifugation	1
Kubota refrigerated centrifuge 9800 (Kubota)	Centrifugation	1
Jouan 8/4i centrifuge (Jouan)	Centrifugation	1
RegenKit (Regen Laboratory)	Centrifugation	1
Tabletop centrifuge 2420 (Kubota)	Centrifugation	1
Centrifuge (Beckman)	Centrifugation	1
Accelerate Sport platelet concentration system (Exactech)	Centrifugation	1
Prosys PRP platelet concentration system (Tozai Holdings)	Centrifugation	1
Clinispin Horizon 755VES centrifuge (Woodley Laboratory Diagnostics)	Centrifugation	1
LC6 Centrifuge (Sarstedt)	Centrifugation	1
Labofuge 400R (Herseus)	Centrifugation	1
Standard centrifuge, J-6B (Beckman)	Centrifugation	1
PRF (Vivostat)	Centrifugation	1
Total		80

*PRGF = plasma rich in growth factors.

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Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, and The Cleveland Clinic Foundation, Cleveland, Ohio

- Only 11 studies(10%) provided comprehensive reporting that included a clear description of preparation protocol that could be used by subsequent investigators to repeat the method

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A Call for Standardization in Platelet-Rich Plasma Preparation Protocols and Composition Reporting

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Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, and The Cleveland Clinic Foundation, Cleveland, Ohio

- Only 17 studies(16%) provided quantitative metrics on the composition of the final PRP product
- Current reporting does not enable comparison of PRP products being delivered to patients

32

PRP subtypes ?? Yes indeed.

- WBC rich PRP
- WBC poor PRP
- Activated PRP
- Non activated PRP
- RBC rich PRP
- RBC poor PRP
- PRP- Prolo
  - PRP-ozone
  - PRP-BMAC

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Table 2

Variables That May Influence the Growth Factor Profile of Platelet-rich Plasma

Variable	Description
Donor	Age Gender Comorbidities Concurrent medications (including anti-inflammatories) Nutritional status
Processing	Blood collection and storage conditions Spin protocol (speed, time) Activation protocol (agent, concentration, timing) Storage
Delivery	Form of delivery (gel, solution) Timing of delivery in relation to isolation Timing of delivery in relation to activation Host factors (similar to donor factors) Injury chronicity

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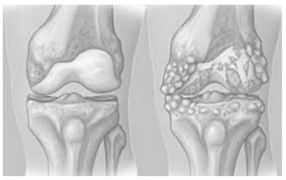
OVERVIEW OF TRIALS/STUDIES

35

PRP INJECTIONS IN KNEE META-ANALYSIS



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LITERATURE: STEM CELLS/PRP FOR KNEE ARTHRITIS

- Meta-analysis scanned 420 reports in literature-PRP
- Six had level III evidence or stronger
- PRP recent meta-analysis-19 higher quality investigations-7 studies good response to treatment, 4 studies reported bad response

37

EFFICACY OF PRP INJECTIONS IN KNEE OA : SYSTEMATIC REVIEW AND META-ANALYSIS

- Laudy et al. BJSM. 2014
- Meta-analysis: 317 studies/trials-10 meet criteria
- 6 randomized control studies, 4 observational studies

38

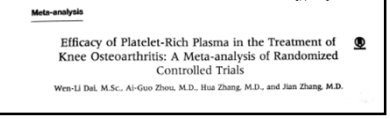
EFFICACY OF PRP INJECTIONS IN KNEE OA : SYSTEMATIC REVIEW AND META-ANALYSIS

- Laudy et al. ***BJSM***, 2014
- PRP more effective for pain reduction compared with placebo at 6 months post injection
- PRP vs hyaluronic acid-significant difference in favor of PRP on pain reduction/improved function at 6 months post-injection
- Almost all trials had high risk of bias

39

EFFICACY OF PRP INJECTIONS IN KNEE OA : SYSTEMATIC REVIEW AND META-ANALYSIS

- Dia et al. Arthroscopy. 2017
- Meta-analysis of randomized control trials
- Systemic review and quantitative analysis of 10 level I randomized control studies(1069 patients)


Meta-analysis

Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials

Wen-Li Dai, M.Sc., Ai-Guo Zhou, M.D., Hua Zhang, M.D., and Jian Zhang, M.D.

40

EFFICACY OF PRP INJECTIONS IN KNEE OA : SYSTEMATIC REVIEW AND META-ANALYSIS

- Dia et al. Arthroscopy. 2017
- Compared platelet-rich plasma injections with both hyaluronic acid and saline injections for knee OA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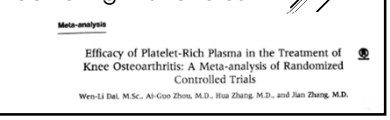
EFFICACY OF PRP INJECTIONS IN KNEE OA : SYSTEMATIC REVIEW AND META-ANALYSIS

- Dia et al. Arthroscopy. 2017
- Similar results of PRP and HA at 6 months
- At 12 months PRP had significantly better pain relief and functional improvement than HA
- 8 of 10 level I studies had "a high risk of bias"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EFFICACY OF PRP INJECTIONS IN KNEE OA
: SYSTEMATIC REVIEW AND META-ANALYSIS

- Kanchanatawan et al. ***ESSKA***. 2015
- 9 of 551 studies met inclusion criteria of randomized control

Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee

Wichan Kanchanatawan[1] · Alisara Arirachakaran[2] · Kornkit Chaijenkij[3] · Niti Prasathaporn[4] · Manusak Boonard[5] · Peerapong Piyapittayanun[2] · Jatupon Kongtharvonskul[6]

43

EFFICACY OF PRP INJECTIONS IN KNEE OA
: SYSTEMATIC REVIEW AND META-ANALYSIS

- Kanchanatawan et al. ***ESSKA***. 2015
- PRP vs HA or placebo
- In short term outcomes, PRP injection has improved functional outcomes and improving symptoms vs HA or placebo in mild/mod knee OA

Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee

Wichan Kanchanatawan[1] · Alisara Arirachakaran[2] · Kornkit Chaijenkij[3] · Niti Prasathaporn[4] · Manusak Boonard[5] · Peerapong Piyapittayanun[2] · Jatupon Kongtharvonskul[6]

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PRP – LEUKOCYTE POOR VS LEUKOCYTE RICH

45

LEUKOCYTE POOR VS RICH PRP AND OA OF KNEE

- Riboh et al. ***Am J Sports Med***. 2016
  - Meta-analysis
  - Superior Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC) scores in pts with leukocyte poor PRP vs Hyaluronic acid

46

LEUKOCYTE POOR VS RICH PRP AND OA OF KNEE

- Riboh et al. ***Am J Sports Med***. 2016
  - No difference in those treated with Leukocyte-rich PRP and hyaluronic acid

47

LEUKOCYTE POOR PRP AND OA OF KNEE

- Patel et al. ***Am J Sports Med***. 2013
  - Prospective, randomized, double blind trial
  - Leukocyte-poor PRP compared with saline placebo injection for early bilateral knee OA

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LEUKOCYTE POOR PRP AND OA OF KNEE

- Patel et al. ***Am J Sports Med***. 2013
  - 78 patients/156 knees
  - 3 groups:
    1. Single PRP injection
    2. 2 PRP injections 3 weeks apart
    3. Single saline injection
  - Followed 6 months

49

LEUKOCYTE POOR PRP AND OA OF KNEE

- Patel et al. ***Am J Sports Med***. 2013
  - Significant difference($p<0.001$) in favor of PRP compared to saline using VAS, WOMAC and patient satisfaction at 6 months

50

LEUKOCYTE POOR PRP AND OA OF KNEE

- Smith et al. ***Am J Sports Med***. 2016
  - FDA-sanctioned, randomized, double-blind, placebo controlled clinical trial
  - Leukocyte poor PRP vs saline
  - 30 pts/30 knees-series of 3 weekly injections
  - Moderate knee OA (LK grade 2-3)

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis

An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

Patrick A. Smith,*† MD
*Investigation performed at the Columbia Orthopaedic Group, Columbia, Missouri, USA

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LEUKOCYTE POOR PRP AND OA OF KNEE

- Smith et al. ***Am J Sports Med***. 2016
  - Significantly greater improvement ($p<0.001$) of WOMAC scores in PRP cohort throughout the study vs saline
  - 12 months after treatment PRP group improved 78% from baseline WOMAC score vs 7% placebo

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PRP INJECTIONS IN KNEE VS HYLAURNIC ACID(HA)

53

PRP VERSES HYALURONIC ACID AND OA OF KNEE

- Feller et al. ***JBJS.*** 2016
  - Randomized, blinded controlled with 12 month f/u
  - 96 pts 3 weekly injections PRP vs 96 patients 3 weekly injections HA

54

PRP VERSES HYALURONIC ACID AND OA OF KNEE

- Feller et al. ***JBJS***: 2016
  - Modest clinical improvement in both groups
  - No difference between PRP and HA
  - Leukocyte Rich PRP

55

PRP VERSES HYALURONIC ACID AND OA OF KNEE

- Filardo et al. ***AM J Sports Med***: 2015
  - Randomized control
  - 3 weekly injections of PRP vs Hyaluronic acid
  - 192 pts with knee OA

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PRP VERSES HYALURONIC ACID AND OA OF KNEE

- Filardo et al. ***AM J Sports Med***: 2015
  - Both groups reported significant improvements in function and symptoms in all subjective scores used($p<0.0005$)
  - Comparative analysis demonstrated no difference between groups at any follow-up time point

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PRP VERSES HYALURONIC ACID AND OA OF KNEE

- Several Randomized control studies performed comparing efficacy of PRP with that of hyaluronic acid
- Superior results with Leukocyte poor PRP vs Leukocyte rich
- Majority of studies show improved outcome compared with hyaluronic acid at short-term f/u

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OVERVIEW OF RESULTS OF PRP STUDIES

- Mixed data/high bias
- Variety of preparations tested
- Variety of injection frequencies tested
- Support for Leukocyte poor PRP in Early/mod OA knee

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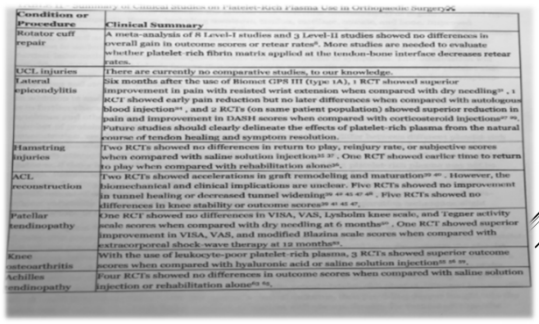

Condition or Procedure	Clinical Summary
Rotator cuff repair	A meta-analysis of 8 Level-I studies and 3 Level-II studies showed no differences in overall gain in outcome scores or retear rates[9]. More studies are needed to evaluate whether platelet-rich fibrin matrix applied at the tendon-bone interface decreases retear rates.
UCL injuries	There are currently no comparative studies, to our knowledge.
Lateral epicondylitis	Six months after the use of Biomet GPS III (type 1A), 1 RCT showed superior improvement in pain with resisted wrist extension when compared with dry needling[39], 1 RCT showed early pain reduction but no later differences when compared with autologous blood injection[40], and 2 RCTs (on same patient population) showed superior reduction in pain and improvement in DASH scores when compared with corticosteroid injections[37,38]. Future studies should clearly delineate the effects of platelet-rich plasma from the natural course of tendon healing and symptom resolution.
Hamstring injuries	Two RCTs showed no differences in return to play, reinjury rate, or subjective scores when compared with saline solution injection[42,43]. One RCT showed earlier time to return to play when compared with rehabilitation alone[28].
ACL reconstruction	Two RCTs showed accelerations in graft remodeling and maturation[29,40]. However, the biomechanical and clinical implications are unclear. Five RCTs showed no improvement in tunnel healing or decreased tunnel widening[29,40-42,45,46]. Five RCTs showed no differences in knee stability or outcome scores[29,40-42,46].
Patellar tendinopathy	One RCT showed no differences in VISA, VAS, Lysholm knee scale, and Tegner activity scale scores when compared with dry needling at 6 months[30]. One RCT showed superior improvement in VISA, VAS, and modified Blazina scale scores when compared with extracorporeal shock-wave therapy at 12 months[28].
Knee osteoarthritis	With the use of leukocyte-poor platelet-rich plasma, 3 RCTs showed superior outcome scores when compared with hyaluronic acid or saline solution injection[35-37].
Achilles tendinopathy	Four RCTs showed no differences in outcome scores when compared with saline solution injection or rehabilitation alone[33-36].

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TABLE III - Grades of Recommendation for Platelet-Rich Plasma Treatment*

Condition or Procedure	Grade
Rotator cuff repair	C
UCL injuries	I
Lateral epicondylitis	C
Hamstring injuries	C
ACL reconstruction	C
Patellar tendinopathy	C
Knee osteoarthritis	B
Achilles tendinopathy	C
Fractures and delayed unions or nonunions	C

*Grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention. Grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention. Grade C indicates conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention. Grade I indicates that there is insufficient evidence to make a recommendation.

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No benefits seen with PRP injection in patients with acute Achilles tendon ruptures

ORLANDO, Fla. — Results of a double-blind, multicenter, randomized, placebo-controlled trial presented suggest platelet-rich plasma injection offered no patient benefits in the management of acute Achilles tendon ruptures.

"I suggest that the use of [platelet-rich plasma] PRP in soft tissue injuries and possibly chronic injuries is not supported, unless we have more studies similar to this trial with [a] positive effect to justify using PRP in these patients," **Joseph Alsousou, PhD,** said during his presentation.

Alsousou and colleagues randomized 230 patients with Achilles tendon ruptures who started non-surgical management within 12 days of surgery and were treated at 19 trauma units. There were 114 patients assigned to receive PRP injection. Overall, 103 patients received PRP injection and 116 patients received placebo. At 4, 7, 13 and 24 weeks, blinded outcome assess-

NOV, 2018
"I SUGGEST THAT USE OF PRP IN SOFT TISSUE INJURIES AND POSSIBLY CHRONIC INJURIES IS NOT SUPPORTED"

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AAOS GUIDELINES (2016)

Table 1
Consensus Statements on Platelet-rich Plasma

No.	Statement
1	An accepted nomenclature and classification system that encompasses autologous blood/plasma products and categorizes preparations in sufficient detail is required to facilitate comparison across studies. Efforts should be made to involve academics, clinicians, and industry representatives in this process to encourage widespread adoption of the system.
2	The influence of donor variance and processing and delivery factors on the composition of PRP must be established.
3	A validated assay of the efficacy of PRP should be established for each clinical application.
4	The relationship between PRP composition and efficacy should be established.
5	Minimum standards of reporting for all studies (preclinical and clinical) evaluating PRP must be established to facilitate communication and the interpretation and synthesis of scientific investigations. These standards must include measured characteristics of the PRP and factors relating to the donor, processing, and delivery of the PRP.
6	Specific formulations of PRP should be matched with specific pathologic indications.
7	Methods for establishing proof of safety and efficacy of PRP should be determined. This process may require evidence of phenotype stability or viability for each indication.

PRP = platelet-rich plasma

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CONCLUSIONS OF PRP INJECTION FOR KNEE ARTHRITIS

- Mixed data- lack of standardization among studies with regard to PRP preparation and administration
- Difficult to draw definitive conclusions from the currently available data but shows promise
- Support for Leukocyte poor PRP in Early/mod OA knee
- Insufficient Data supporting use other than knee OA

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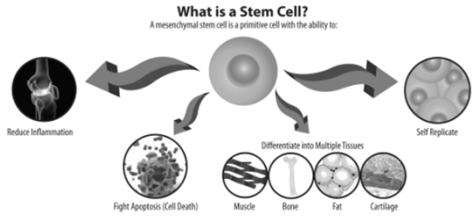
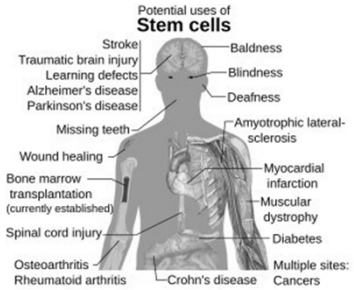


STEM CELLS

65



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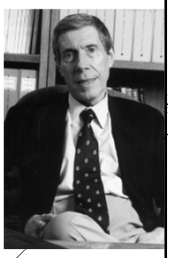
The New York Times

Harvard Calls for Retraction of Dozens of Studies by Noted Cardiac Researcher

Some 31 studies by Dr. Piero Anversa contain fabricated or falsified data, officials concluded. Dr. Anversa popularized the idea of stem cell treatment for damaged hearts.

OCT 15, 2018



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AAOS Now

NOVEMBER 2018

North Dakota Community Challenges Chiropractor Selling Nonautologous Stem Cell Injections

The North Dakota Attorney General's Office and Consumer Protection Division conclude investigations

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Grand Forks Herald

Winter Weather Advisory

January 23, 2019 | 9:00 a.m. - 3:00 p.m. | Memorial Union: Ballroom | Public Welcome

THREE MINUTE THESIS Competition

Stem cell treatment for rotator cuff injuries gets safety approval from FDA: Researchers in North Dakota, South Dakota lead project

By Kevin Wallevand / Forum News Service on Jan 5, 2019 at 1:00 p.m.

Eighteen patients from Fargo and Sioux Falls took part in the study, in partnership with InGeneron, a Houston-based private biotechnology firm that focuses on regenerative medicine.

One of the patients enrolled in the study said the stem cell injections led to the regrowth of a damaged tendon. Other patients reported the stem cell treatment meant more range of motion and less pain.

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STEM CELLS

- 1998 first human embryonic stem cell created
- Stem cells are undifferentiated cells capable of proliferation, self-renewal, and differentiation into specialized cells

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STEM CELLS

- Embryonic and adult stem cells
- Adult stems cells (usually from bone marrow or adipose) differentiate into:
  - Hematopoietic stem cells (HSCs)
  - Mesenchymal stem cells (MSCs)

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MESENCHYMAL STEM CELLS

SOURCES:

- Bone marrow
- Adipose
- Umbilical cord matrix
- Potential to differentiate into cartilage, bone, tendon, and ligaments

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APPLICATION OF MSCS

- Aspiration bone marrow/adipose
- Centrifuged to concentrate cells
- Placed in culture media increasing number/purity of cells
- Injection/placement of cells

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FDA

- Only stem cell products actually approved by FDA are cord blood or placental remnants- typically indicated for pediatric cancer therapy
- None approved for any type of orthopedic use

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FDA

- Public Health Service Act, Section 361
  - "If you are using the HCT/P (human cells, tissues, and tissue based products) that are minimally manipulated and homologous only, you can proceed without FDA approval"

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AAOS 2016

Table 3

Consensus Statements on Stem Cell Therapy

No.	Statement
1	The progenitors contributing to tissue development, regeneration, and healing in each specific tissue must be identified. The mechanisms regulating this contribution must be characterized.
2	The optimum preparation of stem cells for each indication must be established in a systematic fashion. Considerations should include cell number, concomitant use of growth factors, predifferentization, and vehicle.
3	Mesenchymal stem cells isolated from different tissues must be compared to identify the most appropriate cell source for each specific indication.
4	The mechanism responsible for therapeutic effects observed in applications to date must be comprehensively characterized.
5	A standardized assay of stem cell efficacy is needed.
6	Methods for establishing proof of safety of stem cell therapy should be determined in collaboration with industry and regulatory agencies. This process may require evidence of phenotype stability or viability.
7	The most appropriate control for clinical studies evaluating stem cell therapy in each indication must be identified.

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RESEARCH

- Very few level I or II studies-quality of data for efficacy is poor
- No data to support its use but groundwork and guidelines being set
- Relatively safe
- AAOS- "We certainly do not have the evidence to tell our patients they can expect good outcomes"

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THANK YOU!

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