PainWeek

Regenerative Therapy for Chronic Pain: Fact or Fiction?

Nebojsa Nick Knezevic, MD, PhD

Chicago, April 2nd 2022.

1

Title & Affiliation

Nebojsa Nick Knezevic, MD, PhD
Vice Chairman for Research and Education
Department of Anesthesiology and Pain Management
Advocate Illinois Masonic Medical Center
Clinical Professor of Anesthesiology and Surgery
University of Illinois College of Medicine
Chicago, IL

PainWeek

2

Disclosure

- The author declares NO conflict of interest.

UIC THE UNIVERSITY OF ILLINOIS AT CHICAGO

Advocate Illinois Masonic Medical Center

PainWeek

3

Learning Objectives

- Summarize the underlying mechanism of action and potential for different biologic regenerative therapies
- List the potential adverse effects of regenerative therapies
- Cite current strategies to improve outcomes when utilizing biologic regenerative therapies
- Describe background information on PRP and BM-MSC and their role in the treatment of different chronic pain conditions (LBP, musculoskeletal degenerative disease, OA, etc)

PainWeek

4

Regenerative Medicine: Background

- Essential ability of the body to heal itself
- Regenerative medicine: foster innate repair mechanisms and supplement w/ homologous or autologous biologic agents

- Biomedical approaches:
  - Cell therapy - injection of MSCs (mesenchymal stromal/ stem cells; medicinal signaling cells) or progenitor cells
  - Immunomodulation therapy - induction of regeneration by biologically active molecules administered alone or as a complex of infused cells
  - Tissue engineering - transplantation of in vitro grown organs and tissues

PainWeek

5

Goals of Regenerative Therapy

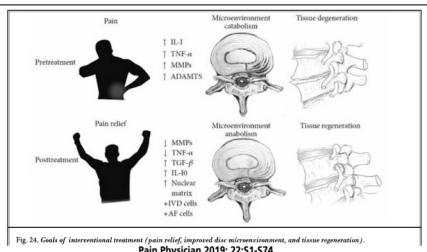


Fig. 24. *Goals of interventional treatment (pain relief, improved disc microenvironment, and tissue regeneration).*
Pain Physician 2019; 22:S1-S74

PainWeek

6

Currently Available Biologics (PRP)

- Platelet-rich plasma (PRP) – immunomodulation therapy
- Centrifuged whole blood, extraction of PRP (growth-factor rich)

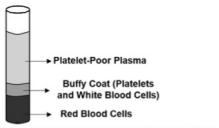


Fig. 1. Example of platelet-rich plasma (PRP) preparation. The buffy coat is the PRP, PRP-related growth factors.

Med Clin N Am 100 (2016) 199-217

PAINWEEK

7

Currently Available Biologics (PRP)

- Inflammatory environment – platelets secrete growth factors from alpha granules & stimulate anabolic healing processes

Table 1
Growth factors identified within platelet-rich plasma and their biological functions

Name	Abbreviation	Function
Platelet-derived growth factor	PDGF	Stimulation of fibroblast production, chemotaxis, TGF-β1, collagen production; upregulation of proteoglycan synthesis of fibroblasts, smooth muscle cells, chondrocytes, osteoblasts and mesenchymal stem cells
Insulin-like growth factor-1	IGF-1	Promotion of cell growth, differentiation, recruitment in bone, blood vessel, skin, other tissues; upregulation of collagen synthesis with PDGF of fibroblasts
Transforming growth factor-beta 1	TGF-β1	Promotion of fibroblast proliferation, extracellular matrix formation, cell viability, production of collagen from fibroblasts; suppressed interleukin 1-mediated effects on proteoglycan synthesis in cartilage
Vascular endothelial growth factor	VEGF	Promotion of cell growth, migration, new blood vessel growth and antiapoptosis (anti-cell death) of blood vessel cells
Basic fibroblastic growth factor	bFGF	Stimulation of collagen production, angiogenesis and myoblast proliferation
Epidermal growth factor	EGF	Promotion of cell recruitment, proliferation, differentiation, angiogenesis, cytokine secretion by mesenchymal and epithelial cells
Connective tissue growth factor	CTGF	Promotion of angiogenesis, cartilage regeneration, fibrosis, platelet adhesion

From Wang SZ, Rui YF, Tan Q, et al. Enhancing intervertebral disc repair and regeneration through biology: platelet-rich plasma as an alternative strategy. Arthritis Res Ther 2013;15(5):220; with permission.

PAINWEEK

Med Clin N Am 100 (2016) 199-217

8

PRP

- Most efficacy seen in treating inflammatory states
- Used more in arthritic conditions (SIJ, facet joint, etc) than for treating disk degeneration
- However, some evidence suggests that PRP may aid in reducing chronic inflammation assoc. w/ degenerative pathologies

Ex: Several studies comparing intra-articular injections of PRP vs. local anesthetic/corticosteroid showed:

- Short-term relief similar; however, more sustained long-term improvement with PRP

PAINWEEK

9

PRP Classification System

- Based on presence of WBC and fibrin architecture present

4 Different Types of PRP:

=Low-density fibrin types = injectable & used most for MSK conditions

- 1.) Pure PRP (**PPRP**) – No WBC, low-density fibrin network
- 2.) Leukocyte-rich PRP (**L-PRP**) increased [WBC], low-density fibrin network

=High-density fibrin types = clot formation with growth factor (used less for MSK)

- 3.) Pure platelet-rich fibrin (P-PRF) – No WBC, high-density fibrin network
- 4.) Leukocyte and platelet-rich fibrin (L-PRF) – increased [WBC], high-density fibrin network

painweek

10

PRP Variables

- PRP therapy – dependent on the function of the host's platelets
- PRP injectate – recommended to be at least 2.5 x greater than the peripheral plasma concentration

- Lesser concentrations – likely sub-therapeutic
- Greater concentrations – reduces osteoclastic activity (needed for remodeling process)

Variables influencing GF-profile of PRP

• 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

Pain Physician 2019; 22:51-574

painweek

11

Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study

Yetsa A Tuakli-Wosornu [1], Alon Terry [2], Kwadwo Boachie-Adjei [3], Julian R Harrison [4], Caitlin K Gribbin [5], Elizabeth E LaSalle [6], Joseph T Nguyen [7], Jennifer L Solomon [8], Gregory E Lutz [9]

- Aim: improvement in pt-reported pain & function w/ single injection of autologous PRP into symptomatic degenerative IV-disks
- 47 pts with chronic (≥6mo) mod-severe discogenic LBP refractory to conservative Tx
- Tx-grp (n=29): Single injection of 3-4mL autologous PRP
- Control grp (n=18): Single injection of 3-4mL contrast agent
- Outcome measures: Improvement in pain (SF-36) & function (FRI) compared to control

	Control Mean or N	Control SD or %	PRP Mean or N	PRP SD or %	P Value
N	18		29		
Age	43.80	8.91	41.40	8.08	.359
Female gender	16	84.2%	15	51.7%	.031

PM&R
Volume 8, Issue 1, January 2016, Pages 1-10

painweek

12

Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study

Yetsa A Tuakli-Wosornu [1], Alon Terry [2], Kwadwo Boachie-Adjei [3], Julian R Harrison [4], Caitlin K Gribbin [5], Elizabeth E LaSalle [6], Joseph T Nguyen [7], Jennifer L Solomon [8], Gregory E Lutz [9]

Results:

- 8wk follow-up: PRP-grp demonstrated improvement in pain (SF-36), **although not significant**
- 8wk follow-up: pts receiving autologous intradiscal PRP showed significant improvement in function (FRI) vs. controls
- 1yr follow-up: PRP grp maintained significant improvement in function (FRI)

Conclusions:

- Study demonstrates significant & long-lasting improvement in pt function w/ PRP for chronic discogenic LBP

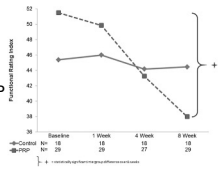


Figure 2. Change in Functional Rating Index over time from baseline to 6 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number of observations analyzed at the given time point.

PM&R
Volume 8, Issue 1, January 2016, Pages 1-10

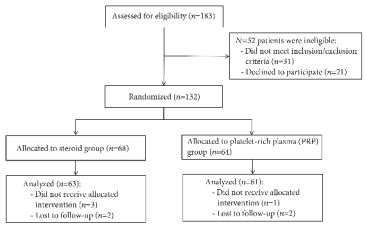
13

Ultrasound-Guided Transforaminal Injections of Platelet-Rich Plasma Compared with Steroid in Lumbar Disc Herniation: A Prospective, Randomized, Controlled Study

Zhen Xu, Shaoling Wu, Xiao Li, Cuicui Liu, Shengnuo Fan, and Chao Ma

Neural Plasticity
Volume 2021, Article ID 5558138

- RCT, 12-month follow-up
- 124 patients who suffer from radicular pain due to lumbar disc herniation received ultrasound-guided transforaminal injections of either PRP or steroid



14

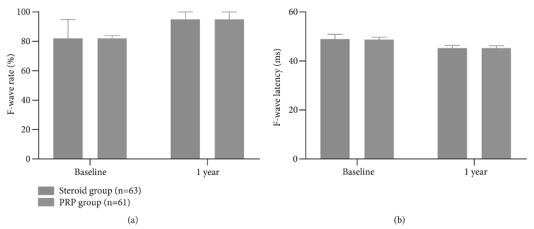


Figure 4: Comparison of F-wave rate and latency between the PRP ($n = 61$) and steroid ($n = 63$) groups. No significant difference was found in terms of F-wave (a) rate and (b) latency between the PRP group and the steroid group both before and after operation. The error bars represent the 3rd quartile.

Neural Plasticity
Volume 2021, Article ID 5558138

15

A Prospective Study Comparing Platelet-Rich Plasma and Local Anesthetic (LA)/ Corticosteroid in Intra-Articular Injection for the Treatment of Lumbar Facet Joint Syndrome

Jinping Wu, MSc*; Jingjing Zhou, MSc*; Chibing Liu, MSc*; Jun Zhang, MSc*; Wei Xiong, MSc*; Yang Lv, MSc*; Rui Liu, MSc*; Baiqiang Wang, MSc*; Zhenwu Du, MD, PhD*†; Guizhen Zhang, MD, PhD*†; Qinyi Liu, MD, PhD*
*Department of Orthopaedics, The Second Hospital, Jilin University, Changchun, Jilin; †Department of Imaging and Nuclear Medicine, The Second Hospital, Jilin University, Changchun, Jilin, China

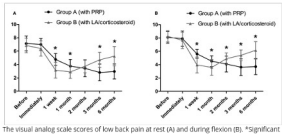
- **Aim:** to determine efficacy btw autologous PRP & LA/Corticosteroid intra-articular injection in pts w/ Lumbar Facet Joint Syndrome
- 46 total subjects with chronic facet joint pain & failure of 1mo conservative treatment
- PRP gr. (23): Intra-articular injections (1/sx'ic level) of 0.5ml autologous PRP
- Steroid gr. (23): Intra-articular injections (1/sx'ic level) of 0.5% lidocaine w/ 5mg/mL betamethasone
- **Outcome measures:** Pain (**VAS**) at rest & during flexion, & lumbar function w/Roland-Morris Disability Questionnaire (**RMQ**) & Oswestry Disability Index (**ODI**)

painweek

Pain Practice, Volume 17, Issue 7, 2017 914–924

16

A Prospective Study Comparing Platelet-Rich Plasma and Local Anesthetic (LA)/ Corticosteroid in Intra-Articular Injection for the Treatment of Lumbar Facet Joint Syndrome



The visual analog scale scores of low back pain at rest (A) and during flexion (B). *Significant difference between groups (P < 0.01). PRP , platelet-rich plasma; LA , local anesthetic.

Variables	Group A (n = 23)	Group B (n = 23)	P
Male	10 (43.48%)	9 (39.13%)	0.77
Female	13 (56.52%)	14 (60.87%)	
Ages (years)	52.91 ± 7.60	52.78 ± 7.23	0.95
BMI	22.56 ± 1.39	22.38 ± 1.45	0.66
VAS at rest	7.09 ± 1.06	6.74 ± 1.10	0.26
VAS during flexion	8.04 ± 0.88	8.13 ± 0.87	0.69
Duration of pain (months)	19.43 ± 12.30	16.73 ± 12.03	0.35
With referred pain	9 (39.13%)	11 (47.83%)	0.552
Sides of pain			
Left	5 (21.74%)	7 (30.43%)	0.707
Right	7 (30.43%)	6 (26.09%)	
Bilateral	11 (47.83%)	10 (43.48%)	
Levels treated			
Single level	5 (21.74%)	7 (30.43%)	0.502
Multiple levels	18 (78.26%)	16 (69.57%)	

Results:

- Intergroup pain assessments (VAS) @ rest & with flexion
- 1mo FU: significant pain improvement in both groups
- 3 & 6mo FUs: significant improvement maintained only in PRP gr.

painweek

Pain Practice, Volume 17, Issue 7, 2017 914–924

17

A Prospective Study Comparing Platelet-Rich Plasma and Local Anesthetic (LA)/ Corticosteroid in Intra-Articular Injection for the Treatment of Lumbar Facet Joint Syndrome

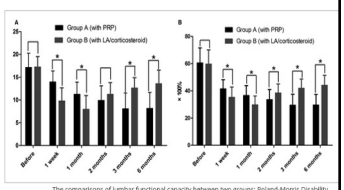
Jinping Wu, MSc*; Jingjing Zhou, MSc*; Chibing Liu, MSc*; Jun Zhang, MSc*; Wei Xiong, MSc*; Yang Lv, MSc*; Rui Liu, MSc*; Baiqiang Wang, MSc*; Zhenwu Du, MD, PhD*†; Guizhen Zhang, MD, PhD*†; Qinyi Liu, MD, PhD*
*Department of Orthopaedics, The Second Hospital, Jilin University, Changchun, Jilin; †Department of Imaging and Nuclear Medicine, The Second Hospital, Jilin University, Changchun, Jilin, China

Intergroup comparison of lumbar functional capacity w/ RMQ (panel A) & ODI (panel B)

- 1mo FU: significant functional status improvement in both groups
- 3 & 6mo FUs: significant improvement maintained only in PRP grp

Conclusions:

- PRP produces significant improvements in pain & functionality with longer duration efficacy than LA/CS



The comparisons of Lumbar functional capacity between two groups: Roland-Morris Disability Questionnaire (A) and Oswestry Disability Index (B). *Significant difference between groups (P < 0.05). PRP , platelet-rich plasma; LA , local anesthetic.

painweek

Pain Practice, Volume 17, Issue 7, 2017 914–924

18

A Randomized Double-Blind Controlled Pilot Study Comparing Leucocyte-Rich Platelet-Rich Plasma and Corticosteroid in Caudal Epidural Injection for Complex Chronic Degenerative Spinal Pain

Ricardo Ruiz-Lopez [1], Yu-Chuan Tsai [2 3] Pain Pract. 2020 Jul;20(6):639-646.

- Aim: determine safety & efficacy btw Leucocyte-Rich PRP (LR-PRP) & Corticosteroid w/ caudal epidural injections for pts with complex chronic lumbar spinal pain
- 50 total pts. – complex chronic degenerative spinal pain
- randomly assigned 1:1 to caudal epidural inject. w/ corticosteroid (CS) or LR-PRP
- CS-gr.: 20mL CS-mixture – triamcinolone acetonide 60mg, 3.5mL contrast
- LR-PRP-grp: 20mL autologous LR-PRP mixture – 16.5mL of LR-PRP, 3.5mL contrast
- **Outcome measures:** Pain levels (VAS), Functioning/Quality of life (SF-36), & any adverse Tx-related effects; evaluations @ 1, 3, & 6mo post-Tx

Table 1. Patient Demographic Data

Characteristics	Corticosteroid Group (n = 25)	LR-PRP Group (n = 25)	P Value
Age (mean ± SD)	61 ± 12.60	68 ± 13.06	NS
Sex (M:F)	10:15	11:14	NS

Data were analyzed with the unpaired t-test.
LR-PRP, leukocyte rich platelet-rich plasma; NS, nonsignificant; SD, standard deviation.

painweek

19

Results:

Follow-up (1 month)

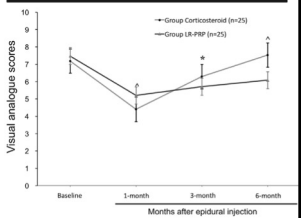
- both groups improved significantly from baseline pain
- CS-gr. had significantly lower pain scores

Follow-up (3 and 6 months)

- PRP-gr. had significantly better pain scores
- CS-gr. lost significance by 6mo
- neither group reported complications or adverse events related to Tx @6mo FU

Table 2. Visual Analog Scale Scores

Time of Measurement	Corticosteroid Group (n = 25)	LR-PRP Group (n = 25)
Baseline VAS score	7.18 ± 0.95	7.48 ± 1.12
VAS score after epidural injection		
1 month	4.40 ± 0.92*	5.20 ± 0.69*
3 months	6.28 ± 0.86*	5.70 ± 0.97*
6 months	7.53 ± 0.60	6.08 ± 0.99*



painweek

Pain Pract. 2020 Jul;20(6):639-646.

20

	Physical Functioning	Role-Physical	Bodily Pain	General Health	Physical Component Summary
Corticosteroid group					
Baseline	34.74 ± 18.42	26.42 ± 33.14	53.42 ± 26.40	53.14 ± 17.12	141.1 ± 70.18
6 months	35.42 ± 21.32	31.14 ± 39.42	60.14 ± 28.14	54.24 ± 23.14	151.74 ± 84.24
P values	0.291	0.711	0.008	0.82	0.39
LR-PRP group					
Baseline	31.30 ± 20.80	27.20 ± 32.14	54.10 ± 28.73	52.24 ± 22.11	140.10 ± 75.12
6 months	59.74 ± 22.57	57.40 ± 40.10	79.42 ± 17.42	56.16 ± 19.23	226.14 ± 61.02
P values	0.001	0.001	0.001	0.0001	0.001
Between-group P values	0.001	0.0001	0.0001	0.0008	0.0001

- SF-36 results on physical functioning & quality of life (QOL) measures

Follow-up (6 months)

- Both groups – significant improvements in bodily pain scores
- LR-PRP – only the PRP-gr. demonstrated significant improvements in functionality & other QOL domains

Conclusions: LR-PRP results in superior long-duration improvements to pain & functionality in pts w/ complex chronic lumbar pain vs. CS

painweek

Pain Pract. 2020 Jul;20(6):639-646.

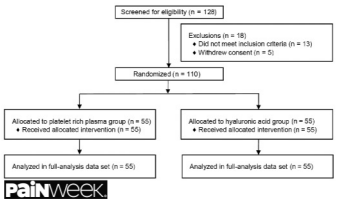
21

Clinical Efficacy of Platelet-Rich Plasma Injection and Its Association With Growth Factors in the Treatment of Mild to Moderate Knee Osteoarthritis

A Randomized Double-Blind Controlled Clinical Trial As Compared With Hyaluronic Acid

The American Journal of Sports Medicine
2021;49(2):487–496

Yong-Beom Park,* MD, PhD, Jun-Ho Kim,† MD, Chul-Won Ha,‡§‖ MD, PhD, and Dong-Hyun Lee,‖ MD



- RCT, Level of evidence: 1
- 110 patients with symptomatic knee osteoarthritis received a single injection of leukocyte-rich PRP or HA
- Follow-ups: 6 weeks, and 3 and 6 months

22

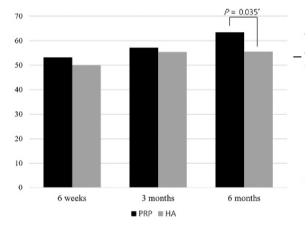


Figure 2. Patient Global Assessment scores for the PRP and HA treatment groups. The scores at 6 months were higher in the PRP group than the HA group. HA, hyaluronic acid; PRP, platelet-rich plasma.

Patients Experiencing Adverse Events at the System Organ Class Level[a]

	PRP	HA
System organ class	6 (10.9)	8 (10.9)
Gastrointestinal disorders	1	0
General disorders and administration site conditions	3	0
Injury, poisoning, and procedural complications	0	2
Musculoskeletal and connective tissue disorders	1	5
Nervous system disorders	0	1
Constipation	1	0
Preferred term[b]		
Injection site pain	2	0
Injection site swelling	1	0
Nasopharyngitis	1	2
Musculoskeletal pain	1	3
Backache	0	2
Headache	0	1

[a]Values are presented as No. (%). HA, hyaluronic acid; PRP, platelet-rich plasma.

The American Journal of Sports Medicine
2021;49(2):487–496

23

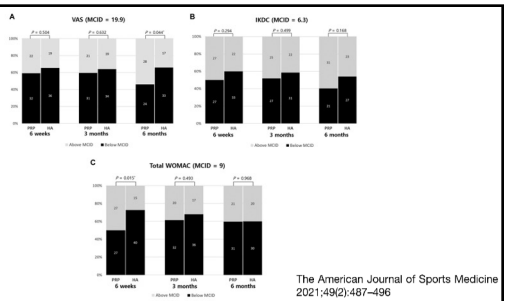


Figure 3. The proportions of patients treated with PRP and HA with scores above and below the MCID for the (A) VAS for pain, (B) IKDC, and (C) WOMAC. The proportion of patients whose scores were above the MCID was higher in the PRP group than the HA group in the majority of the assessments; however, only the VAS scores at the 6-month visit and the total WOMAC scores at the 6-week visit were statistically different. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; MCID, minimal clinically important difference; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

The American Journal of Sports Medicine
2021;49(2):487–496

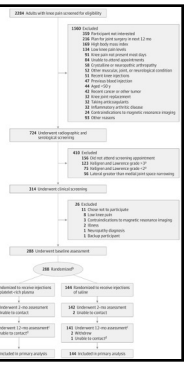
24

Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis

The RESTORE Randomized Clinical Trial *JAMA*. 2021;326(20):2021-2030.

Kim L. Bennell, PhD; Kade L. Paterson, PhD; Ben R. Metcalf, BSc; Vicky Duong, DPT; Jillian Eyles, PhD; Jessica Kasza, PhD; Yuanyuan Wang, PhD; Flavia Cicuttini, PhD; Rachelle Buchbinder, PhD; Andrew Forbes, PhD; Anthony Harris, MSc; Sin Ney P. Yu, MPH; David J Connell, MMed; James Linklater, MBBS; Bing Hu Wang, PhD; Win Min Oo, PhD; David J. Hunter, PhD

- Placebo-controlled, triple-blind RCT
- 288 participants with symptomatic medial knee OA received 3 intra-articular injections at weekly intervals of either leukocyte-poor PRP using a commercially available product or saline placebo
- 12-month follow-up



25

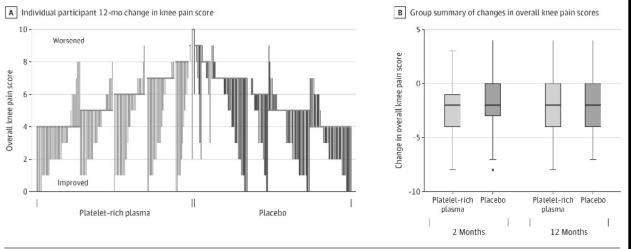
Table 2. Continuous Outcomes at Baseline and 12 Months by Treatment Group[a]

Outcomes	Values, mean (SD)						Difference in change between groups, mean (95% CI)[b]	*P* value
	Platelet-rich plasma (n = 144)			Placebo (n = 144)				
	Baseline	12 mo	Within-group change	Baseline	12 mo	Within-group change		
Primary outcomes								
Overall knee pain score[c,d]	5.7 (1.5)	3.5 (2.6)	−2.1 (2.7)	5.7 (1.5)	3.9 (2.6)	−1.8 (2.5)	−0.4 (−0.9 to 0.2)	.17
Annual change in medial tibial cartilage volume, %[e,f]		−1.4 (7.2)	−1.4 (7.2)		−1.2 (6.8)	−1.2 (6.8)	−0.2 (−1.9 to 1.5)	.81
Secondary outcomes								
Knee pain while walking[c,d]	5.8 (2.1)	3.8 (2.6)	−2.0 (2.6)	5.7 (2.1)	4.1 (2.8)	−1.6 (2.8)	−0.4 (−1.0 to 0.2)	.21
Intermittent and Constant Osteoarthritis Pain score[d,g]								
Constant pain	6.7 (4.1)	3.9 (4.1)	−2.8 (4.8)	6.7 (3.6)	3.9 (4.4)	−2.7 (4.5)	−0.1 (−1.0 to 0.8)	.84
Intermittent pain	10.6 (4.1)	7.4 (4.6)	−3.2 (5.3)	10.4 (3.2)	7.5 (5.2)	−2.9 (4.8)	−0.2 (−1.3 to 0.8)	.68
Knee Injury and Osteoarthritis Outcome Score[d,h]								
Pain	52.9 (15.2)	68.0 (18.2)	15.1 (18.9)	53.5 (13.5)	65.4 (19.9)	11.9 (17.6)	3.1 (−0.8 to 6.9)	.12
Other symptoms	53.9 (15.9)	67.2 (18.9)	13.3 (19.0)	53.3 (16.6)	63.7 (20.1)	10.4 (17.0)	3.3 (−0.5 to 7.1)	.09
Function in daily living	58.7 (16.9)	72.6 (18.4)	13.9 (18.9)	58.8 (16.3)	71.4 (19.7)	12.6 (17.6)	1.3 (−2.5 to 5.2)	.49
Function in sport and recreation	30.1 (19.3)	45.2 (25.3)	15.1 (25.1)	26.0 (18.7)	40.9 (24.9)	14.9 (21.4)	1.9 (−3.0 to 6.9)	.44
Knee-related quality of life	33.8 (15.8)	51.1 (20.1)	17.2 (20.5)	34.2 (16.8)	48.3 (22.0)	14.1 (19.7)	3.0 (−1.3 to 7.3)	.17
Assessment of Quality of Life–8 Dimension score[d,i]	0.72 (0.15)	0.76 (0.16)	0.04 (0.13)	0.72 (0.16)	0.76 (0.17)	0.04 (0.12)	−0.00 (−0.03 to 0.03)	.91

JAMA. 2021;326(20):2021-2030.

26

Figure 2. Overall Knee Pain Individual Participant 12-Month Changes and Group Summary of Changes



A, Each vertical line represents an individual participant, with participants ordered by baseline value (gray dots) and vertical lines extending up (worsened) or down (improved) to the 12-month values. B, Box plots show the summary of changes by group at each time point. Box tops and bottoms indicate the IQRs of the distribution; horizontal lines, medians; and whiskers, furthest points within 1.5× the IQRs. The data point outside of the whiskers is an outlier.

JAMA. 2021;326(20):2021-2030.

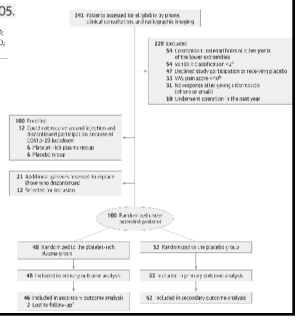
27

Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis

A Randomized Clinical Trial *JAMA*. 2021;326(16):1595-1605.

Liam D. A. Paget, MD; Gustaaf Reurink, PhD; Robert-Jan de Vos, PhD; Adam Weir, PhD; Maarten H. Moen, PhD; Stu M. A. Bierma-Zeinstra, PhD; Sjoerd A. S. Stufkens, PhD; Gino M. M. J. Kerkhoffs, PhD; Johannes L. Tol, PhD; for the PRIMA Study Group

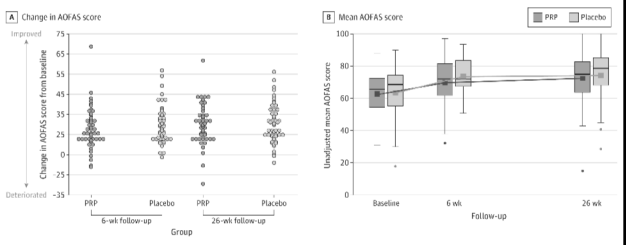
- Multicenter, block-randomized, double-blinded, placebo-controlled trial
- 100 patients were randomly assigned (1:1) to receive 2 ultrasonography-guided intra-articular injections of either PRP or saline placebo
- 26-week follow-up



PainWeek

28

Figure 2. Changes in the American Orthopaedic Foot and Ankle Society (AOFAS) Score in a Study of the Effect of Platelet-Rich Plasma (PRP) Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis

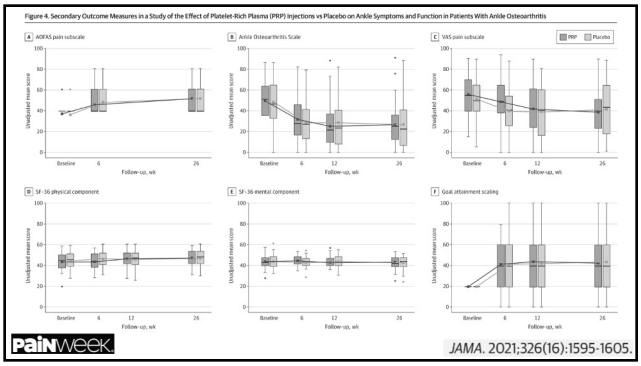


PainWeek

JAMA. 2021;326(16):1595-1605.

29

Figure 4. Secondary Outcome Measures in a Study of the Effect of Platelet-Rich Plasma (PRP) Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis



PainWeek

JAMA. 2021;326(16):1595-1605.

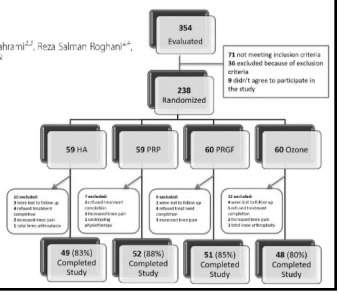
30

The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial

Seyed Ahmad Raeissadat[1,4], Parsa Chazi Hosseini[1,2], Mohammad Hasan Bahrami[1,2], Reza Salman Roghani[4,4], Mohammad Fathi[3,9], Azadeh Goharzaee Arangar[1,2] and Mahtab Darvish[1,2]

BMC Musculoskeletal Disorders (2021) 22:134

- RCT; 12-month follow-up
- 238 patients with mild to moderate knee OA randomized into 4 groups of intra articular injections: HA (3 doses weekly), **PRP** (2 doses with 3 weeks interval), plasma rich in growth factors (**PRGF**; 2 doses with 3weeks interval), or Ozone (3 doses weekly)



painweek

31

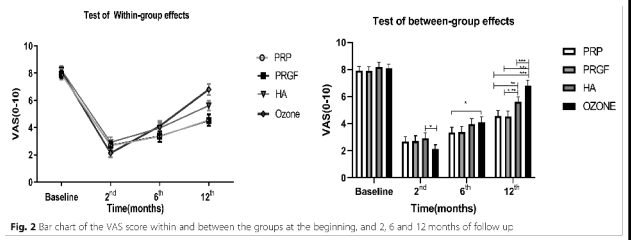


Fig. 2 Bar chart of the VAS score within and between the groups at the beginning, and 2, 6 and 12 months of follow up

painweek

BMC Musculoskeletal Disorders (2021) 22:134

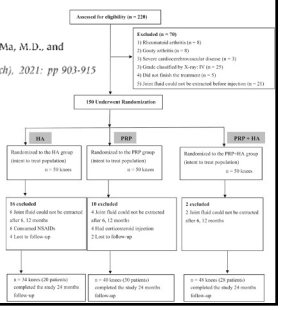
32

Intra-Articular Platelet-Rich Plasma Combined With Hyaluronic Acid Injection for Knee Osteoarthritis Is Superior to Platelet-Rich Plasma or Hyaluronic Acid Alone in Inhibiting Inflammation and Improving Pain and Function

Zhe Xu, M.D., Zhixu He, Ph.D., Liping Shu, Ph.D., Xuanze Li, M.D., Minxian Ma, M.D., and Chuan Ye, Ph.D.

Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 37, No 3 (March), 2021: pp 903-915

- Prospective cohort study
- Level of Evidence: II
- 122 knees (78 patients with knee osteoarthritis) were randomly divided into HA, PRP, and PRP+HA groups



painweek

33

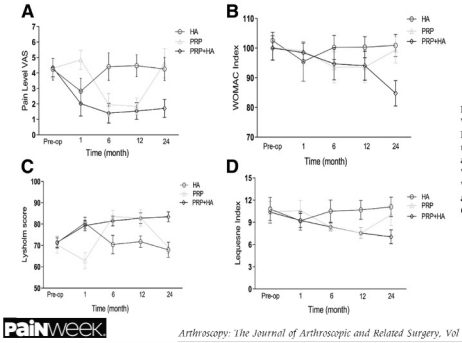


Fig 3. (A, B, C, D) The VAS, WOMAC, Lequesne, and Lysholm scores at each follow-up time point. (HA, hyaluronic acid; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

PainWeek

Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 37, No 3 (March), 2021: pp 903-915

34

Table 3. Comparison of Treatment Complications Among the Three Groups

Complications	HA	PRP	PRP+HA	*P* Value
Infection	0	0	0	
Fever	0	0	0	
Joint swelling	1	4	0	
Pain after injection	0	5	2	
Hematoma	0	0	0	
Rash	0	0	0	
Muscle atrophy	0	0	0	
Venous thrombosis	0	0	0	
Incidence	1/34	9/40	2/48	$P = .008$

NOTE. Comparison of treatment complications among the 3 groups (Fisher exact test = 9.12, $P = .008$). The incidence of complications in the PRP group was greater than that in the HA and PRP+HA groups ($P = .02$; $P = .02$, respectively), and there was no significant difference between the HA group and PRP+HA group ($P = 1.00$).

HA, hyaluronic acid; PRP, platelet-rich plasma.

PainWeek

Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 37, No 3 (March), 2021: pp 903-915

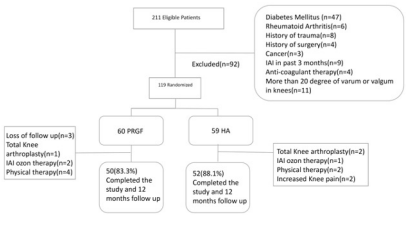
35

Platelet-Rich Plasma-Derived Growth Factor vs Hyaluronic Acid Injection in the Individuals with Knee Osteoarthritis: A One Year Randomized Clinical Trial

Seyed Ahmad Raeissadat[1]
Azadeh Gharooee Ahangar[2]
Seyed Mansoor Rayegani[1]
Mohammadreza Minator Sajadi[3]
Adel Ebrahimpour[3]
Pegah Yavari[1]

Journal of Pain Research 2020:13 1699–1711

- Single-masked RCT
- 102 participants with symptomatic knee osteoarthritis
- Received 2 intra-articular injections of PRP-derived growth factor (PGRF) 3 weeks apart, or received 3 weekly injections of HA
- 12-month follow-up



PainWeek

36

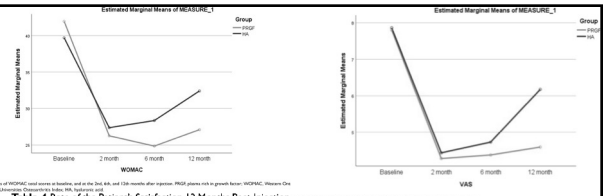


Table 4 Rate of the Patient's Satisfaction 12 Months Post-Injection

	PRGF	HA	P-value	Statistical Test
Very Poor	11 (21.6%)	5(9.8%)	0001>	Mann–Whitney
Poor	7 (13.7%)	22 (43.1%)		
Regular	11 (21.6%)	10 (19.6%)		
Good	17 (33.3%)	6 (11.8%)		
Very Good	11 (21.6%)	2 (3.9%)		

37

Corticosteroids or platelet-rich plasma injections for rotator cuff tendinopathy: a randomized clinical trial study

Haleh Dadgostar[1], Farinaz Fahimipour[1*], Alireza Pahlevan Sabagh[2], Peyman Arasteh[3] and Mohammad Razi[2]

Dadgostar *et al. Journal of Orthopaedic Surgery and Research* (2021) 16:333

- Double-blind RCT; 3-month follow-up
- 58 patients with diagnosis of rotator cuff tendinitis randomized:
  - –PRP group (n=30): 3cc of PRP was injected within the subacromial joint and another 3cc was injected at the site of the tendon tear, under the guide of sonography
  - –Corticosteroid group (n=28): 1cc of Depo-medrol 40mg and 1cc of lidocaine (2%) was injected within the subacromial joint

38

Table 2 Comparison of PRP and corticosteroid groups during a 3-month follow-up.

Variables	Groups										
	PRP					Corticosteroid				*p* value	Fisher value	Effect size
	Baseline	1st week	1st Month	3rd Month		Baseline	1st week	1st Month	3rd Month			
VAS**	6.66 ± 2.26	5.36 ± 1.89	3.75 ± 2.15	3.08 ± 2.14		5.53 ± 1.80	4.86 ± 1.99	3.84 ± 2.07	3.88 ± 1.99	0.023	3.868	0.670
Flexion—degrees**	116.90 ± 37.58	118.40 ± 40.03	132.73 ± 39.06	139.50 ± 34.6		135.42 ± 35.70	139.42 ± 36.80	140.09 ± 36.98	148.65 ± 34.5	0.112	2.326	0.041
Extension—degrees**	35.16 ± 10.78	37.50 ± 10.40	46.16 ± 11.19	50.33 ± 9.18		41.42 ± 10.87	42.69 ± 13.05	50.76 ± 9.02	52.50 ± 8.15	0.302	1.220	0.022
Abduction—degrees**	102.83 ± 36.07	107.43 ± 37.19	115.66 ± 36.75	141.83 ± 36.04		118.46 ± 41.43	119.61 ± 41.10	127.50 ± 43.68	138.26 ± 40.24	0.081	2.572	0.045
Adduction—degrees**	20.50 ± 8.23	21.16 ± 8.37	26.50 ± 4.57	28 ± 3.61		23.21 ± 7.09	26.53 ± 6.28	27.69 ± 4.73	28.46 ± 4.18	0.011	5.087	0.086
Internal rotation—degrees**	64.26 ± 17.06	68.50 ± 17.12	78.50 ± 13.3	82.16 ± 10.39		60.17 ± 19.41	63.84 ± 22.64	77.50 ± 15.18	79.61 ± 13.55	0.741	0.333	0.006
External rotation—degrees**	59.66 ± 23.81	65.83 ± 23.12	74.83 ± 20.36	76.66 ± 18.30		57.14 ± 24.69	60.19 ± 26.81	64.03 ± 26.42	65.57 ± 26.39	0.036	3.475	0.060
WORC score**	32.85 ± 19.43		40.66 ±18.76	49.93 ± 22.36		35.56 ± 17.97		44.87 ± 21.59	48.46 ± 20.60	0.315	1.166	0.021
DASH score**	54.02 ± 18.24		48.83 ± 13.53	40.83 ± 18.19		52.50 ± 20.32		44.77 ± 17.89	41.05 ± 15.69	0.520	0.658	0.012
Supra-spinatus thickness—mm*	6.97 ± 1.46			6.36 ± 1.06		7.47 ± 1.38			7.40 ± 1.07	0.119	2.509	0.044

PRP platelet-rich plasma, *VAS* Visual Analogue Scale, *WORC* Western Ontario Rotator Cuff, *DASH* Disability of Arm-Hand-Shoulder, *Effect size* Eta squared
*$p = 0.051$, **$p < 0.001$, these two represent difference and changes during follow-up in the PRP and corticosteroid groups separately

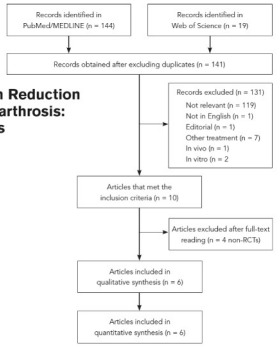
39

Fulong Li, MS
Chuanbin Wu, MS
Haijiang Sun, MS
Qing Zhou, DDS, PhD

Effect of Platelet-Rich Plasma Injections on Pain Reduction in Patients with Temporomandibular Joint Osteoarthrosis: A Meta-Analysis of Randomized Controlled Trials

J Oral Facial Pain Headache. 2020 Spring;34(2):149-156.

- Meta-analysis including 6 RCTs to determine the effect of PRP injections on pain reduction in patients with temporomandibular joint osteoarthritis



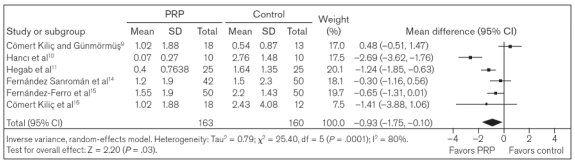


Fig 2 Forest plot of comparison of pain outcomes between PRP and control groups in all six included RCTs.

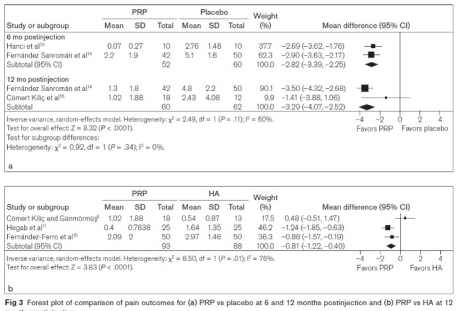


Fig 3 Forest plot of comparison of pain outcomes for **(a)** PRP vs placebo at 6 and 12 months postinjection and **(b)** PRP vs HA at 12 months postinjection.

Currently Available Biologics (MSC)

- Mesenchymal stem cells or medicinal signaling cells (MSC; progenitor cells) – cell therapy
- Lack of MHC-II – conforms to variety of cellular environments without risk for rejection during allogenic transfer
- Derived from various tissues: bone-marrow, adipose, exosomes, A2M, etc
- Stimulates differentiation of host tissues into necessary components
- To be classified as a medical signaling cell MSCs must:
  1) Be capable of division and self-renewal for long periods of time
  2) Unspecialized
  3) Can give rise to specialized cell types

PainWeek

43

Currently Available Biologics (MSC)

- Local paracrine influence (e.g. catabolic cytokines) alters differentiation and thus efficacy of MSC
- MSC require lower local levels of inflammation to have their desired anabolic regenerative effects
- Most effective in degenerative diseases – environments with little active inflammation (contrasted with PRP)
- Several well designed animal studies have demonstrated ↑ disk height following treatment w/ MSCs

PainWeek

44

MSC Variables

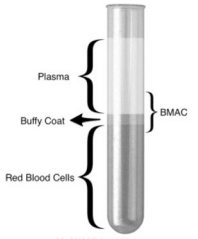
- MSC sources (BM, adipose, organ, cloned, etc) – source-dependent activities
- Importance of origin (tissue type & location)
- Differences in immunophenotype, cytokine profile, proteome analysis
- Equivalency of MSC populations derived from distinct anatomic origins is debated
- BM-derived MSC – most commonly utilized type of adult stem cells; home to site of injury well, integrating into host marrow, bone, and cartilage; osteogenic potential
- Adipose MSCs – pro-angiogenic properties (potential for benefit in less vascular regions, e.g., avascular zone of knee meniscus)
- Cloned human MSCs isolated from fat – default to adipogenic potential
- Variation & Mixture of MSCs (tissue source & location) – may provide best outcome

PainWeek

45

Production of Bone Marrow Concentrate (BMC)

- Bone marrow aspirate is first centrifuged
- This process results in 3 layers with the plasma in the supernatant, the buffy coat in the middle, and the red blood cell layer in the infranatant
- To create BMC, the buffy coat is isolated which contains MSCs
- MSCs are largely credited w/ the therapeutic potential of BMC to treat musculoskeletal pathology due to their differentiation ability



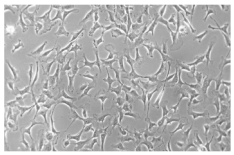
Heliyon 4 (2018) e00871.

PainWeek

46

BM-MSC Background Information

- MSCs have been shown to induce endogenous stem cell activity
- They secrete bioactive factors that promote tissue healing
- BM-MSC facilitate the regeneration of damaged tissue and have lead to the development of many new therapies



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.promocell.com%2Fproduct%2Fhuman-mesenchymal-stem-cells-hmsc%2F&psig=AOvVaw19j1UEv4EtJLNBE7TMvE1_&ust=1596038331735000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCJjzlKSo8OoCFQAAAAAdAAAAABAD

PainWeek

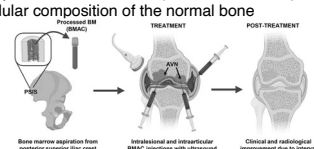
47

MSC Role in Repair of Injured Bone

Intralesional Injection of Bone Marrow Aspirate Concentrate for the Treatment of Osteonecrosis of the Knee Secondary to Systemic Lupus Erythematosus: A Case Report

Dimitrios Kouroupis[1], Amir F. Ahari[1], Diego Correa[1,2] and Ilsam Shammas[1,2]*

- Bone marrow is a multifunctional mixture of RBCs, platelets, and nucleated cells that include multipotent stem cells and progenitor cells
- Nucleated cells within this mixture have hematopoietic, angiogenic, and osteogenic potential
- Intraosseous injection of BMC can help heal a fracture by replenishing the native and healthy cellular composition of the normal bone



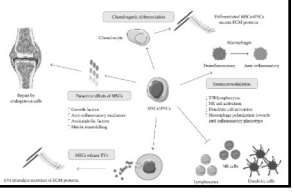
Front Bioeng Biotechnol. 2020; 8: 202.

PainWeek

48

BM-MSC Role in Repair of Cartilage

- Injury to cartilage can naturally expose the subchondral bone marrow
- In the marrow are a variety of cellular components such as MSCs and a variety of growth factors (GF) that assist in healing and repair
- Cartilage repair also involves GFs which all play different roles and lead to the process chondrocyte differentiation of MSCs



Review Article

Stem Cells for Cartilage Repair: Preclinical Studies and Insights in Translational Animal Models and Outcome Measures

Melissa Lo Monaco,[1,2] Greet Merckx,[1] Jessica Ratajczak,[1] Pascal Gervois,[1] Petra Hilkens,[1] Peter Clegg,[2] Annelies Bronckaers,[1] Jean-Michel Vandeweerd,[2] and Ivo Lambrichts[1]

Stem Cells International
Volume 2018, Article ID 9079538

PAINWEEK

49

Techniques Using MSC to Repair Cartilage

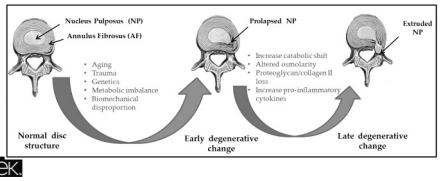
- Surgical micro drilling techniques used to treat cartilage lesions which initiates a healing response by releasing healing cells from the subchondral plate
- However, this type 1 cartilage is fibrous and is not the original type 2 hyaline cartilage
- BMC therapy has been shown to produce type II cartilage hyaline cartilage which has the original tissue strength

PAINWEEK

50

Pathophysiology of Degenerative Disc Disease

- Degeneration of the intervertebral discs is one of the leading causes of chronic LBP
- During the degenerative process discs undergo morphologic changes leading to tears and dehydration



International Journal of Molecular Sciences
MDPI

Review

Intervertebral Disc Nucleus Repair: Hype or Hope?

Gauri Tendulkar, Tao Chen, Sabrina Ehnert, Hans-Peter Kaps and Andreas K Nüssler *

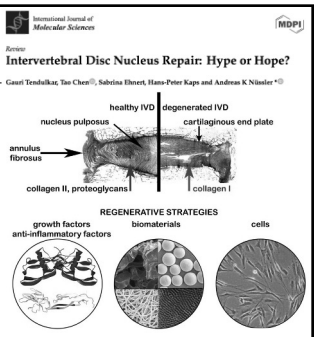
Int. J. Mol. Sci. **2019**, *20*, 3622

PAINWEEK

51

BMC to Treat Degenerative Disc Disease

- BMC Tx's in DDD repopulate the IV-disc and restore functional tissue
- BM-MSCs have also been shown to differentiate into nucleus pulposus-like cells and stimulate production of a new cell matrix



PainWeek

52

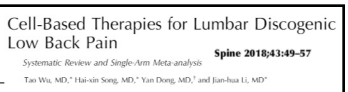
BMC to Treat Spinal Fusion

- BM-MSCs that have been modified genetically to express specific genes & differentiate into terminal cells are also currently being investigated for spine fusion.
- BMC MSCs with the ability to differentiate into adipocytes, osteoblasts, & chondroblasts provide an important source of bone formation to enhance spinal fusion

PainWeek

53

Outcomes of MSC Used in Disc Injections



- Wu et al. reported the results of 6 studies with a 44.2-point decrease in pooled mean pain scores
- In addition there was a 32.2 point pooled mean difference in the ODI w/ no adverse effects
- Based on multiple systematic reviews, as well as randomized and nonrandomized studies, there is level III evidence for intradiscal injections of BMC.

PainWeek

54

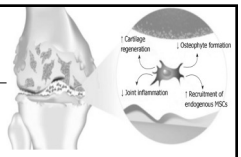
BMC-MSC for the Treatment of Hip Disorders

- Evidence supports the use of BM-MSCs for the treatment of osteonecrosis of the femoral head
- Patients reported improved pain and MRI showed evidence of regeneration after BM-MSC treatment
- Chahla et al. showed in a review article the successful use of BMC for hip osteoarthritis with good clinical results and no adverse effects reported

PAINWEEK

55

MSC for Knee Osteoarthritis



- It was concluded that intraarticular MSCs provided improvement in pain and function in knee osteoarthritis
- BM-MSCs also showed efficacy for cartilage repair in osteoarthritis
- 2 recent RCTs have showed BMC injections to treat knee osteoarthritis
- Centeno et al. published a randomized, cross-over trial of high-dose BMC injected vs. physical therapy, which showed excellent results compared with control
- Overall, the evidence is highest for knee osteoarthritis with level II evidence-based on multiple trials and systemic reviews

PAINWEEK

56

Intervertebral Disc Repair by Allogeneic Mesenchymal Bone Marrow Cells: A Randomized Controlled Trial

David C Noriega [1], Francisco Ardura, Rubén Hernández-Ramajo, Miguel Ángel Martín-Ferrero, Israel Sánchez-Lite, Borja Toribio, Mercedes Alberca, Verónica García, José M Moraleda, Ana Sánchez, Javier García-Sancho

- Aim: To determine the efficacy of allogenic BM-MSCs in the treatment of degenerative disc disease
- 24 pts diagnosed w/ lumbar disk degeneration were randomized into into 2 groups
- The test group received allogeneic BM-MSCs by intradiscal injection of 25×10 cells per segment under local anesthesia
- The control group received a sham infiltration of paravertebral musculature w/ the anesthetic
- Clinical outcomes were followed up for 1 year & included evaluation of pain, disability & quality of life; disc quality was followed up by MRI

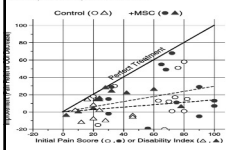
PAINWEEK

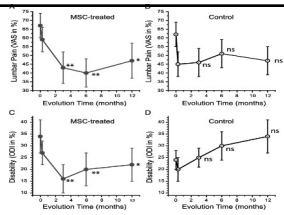
(*Transplantation* 2017;101: 1945–1951)

57

Intervertebral Disc Repair by Allogeneic Mesenchymal Bone Marrow Cells: A Randomized Controlled Trial

David C Noriega [1], Francisco Ardura, Rubén Hernández-Ramajo, Miguel Angel Martín-Ferrero, Israel Sánchez-Lite, Borja Toribio, Mercedes Alberca, Verónica García, José M Moraleda, Ana Sánchez, Javier García-Sancho





Primary Outcome: There was a clear analgesic effect of the allogeneic MSC on average, 28% improvement in pain and disability 1 year after the intervention vs. only 15% recovery in the sham-treated controls

The improvement was statistically significant in the cell-treated group but not in the control group.

Both lumbar pain and disability were significantly reduced @ 3 months after MSC transplantation, and maintained @ 6 and 12 months

Conclusions: Allogeneic MSC therapy was shown to provided pain relief, and improve disc quality in pts with DDD

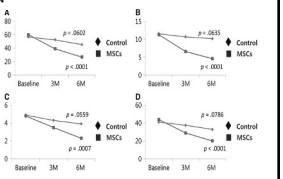
(*Transplantation* 2017;101: 1945–1951)

58

Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial

Woo-Suk Lee, [a] Hwan Jin Kim, [b,c] Kang-Il Kim, [b,c] Gi Beom Kim, [b,c] Wook Jin [d]

- Aim: to determine the efficacy and safety of adipose-derived (AD)-MSCs for patients w/ knee OA
- Methods: MSCs were administered to 12 patients (MSC group), and the group was compared with 12 knees with injection of normal saline (control group) the patients were followed up for 6 months.
- Primary outcome: Single injection of AD-MSCs led to a significant improvement of the WOMAC score @ 6 months.
- There was no significant change in WOMAC score in the control group



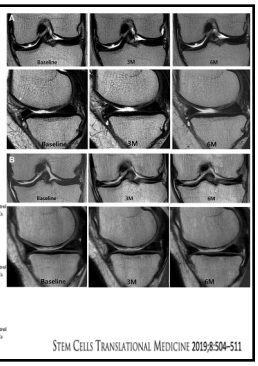
Stem Cells Translational Medicine 2019;8:504–511

59

Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial

Woo-Suk Lee, [a] Hwan Jin Kim, [b,c] Kang-Il Kim, [b,c] Gi Beom Kim, [b,c] Wook Jin [d]

- Pain scores were significantly reduced
- No adverse effects were reported in either group
- In MRI, there was no significant change of cartilage defect @ 6 months in MSC group, whereas the defect in the control group was ↑

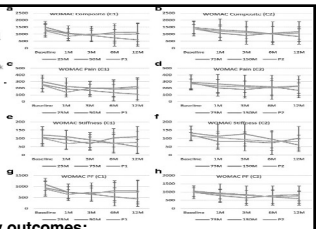


Stem Cells Translational Medicine 2019;8:504–511

60

Efficacy and safety of adult human bone marrow–derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel®): preclinical and clinical trial in osteoarthritis of the knee joint

Pawan Kumar Gupta [1], Anoop Chullikana [2], Mathiyazhagan Rengasamy [2], Naresh Shetty [3], Vivek Pandey [4], Vikas Agarwal [5], Shrikant Yeshwant Waghi [6], Prasanth Kulapurathu Vellotare [2], Devi Damodaran [2], Pachaiyappan Viswanathan [2], Charan Thej [2, 7], Sudha Balasubramanian [2], Anish Sen Majumdar [8]



- Aim: to determine the safety and effectiveness of allogenic mesenchymal stromal cells for knee OA
- 60 OA pts were randomized to receive different doses of BM-MSC (25, 50, 75, or 150 million cells) or placebo
- MSCs were administered by injection into the knee joint, followed by 2 ml hyaluronic acid

Primary outcomes:

- Improvement was seen in the 25-million-cell dose group in all subjective parameters (VAS, ICOAP, and WOMAC-OA scores)
- The only adverse effects reported were injection site pain and knee swelling

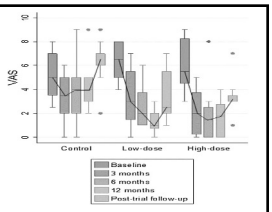
painweek

Arthritis Research & Therapy (2016) 18:301

61

Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II)

José M. Lamo-Espinosa[1*], Gonzalo Mora[1*], Juan F. Blanco[2,3], Froilán Granero-Moltó[2,3,4,5], Jorge M. Nuñez-Córdoba[2,6], Carmen Sánchez-Echenique[1], José M. Bondía[6], Jesús Dámaso Aquerreta[6], Enrique J. Andreu[1,6], Enrique Ornilla[6], Eva M. Villarón[1,6,7,8], Andrés Valenti-Azcárate[7], Fermín Sánchez-Guijo[1,9,10,11], María Consuelo del Cañizo[1,9,10,11], Juan Ramón Valenti-Nin[1] and Felipe Prósper[1,9,11,12]



- **Aim:** To determine the effectiveness of different doses of BM-MSCs long term in patients with knee OA
- 30 pts w/ knee OA were randomly assigned to control group, intraarticularly administered hyaluronic acid (HA) alone, or to 2 treatment groups, HA together w/ 10×10^6 or 100×10^6 cultured BM-MSCs
- After an initial 12 month FU up they were seen again 4 years and AE and clinical evolution were recorded

Primary outcomes:

- BM-MSCs-administered patients improved according to VAS, median value
- (IQR) for Control, Low-dose and High-dose groups changed from 5 (3, 7), 7 (5, 8) and 6 (4, 8) to 7 (6, 7), 2 (2, 5) and 3 (3, 4), respectively

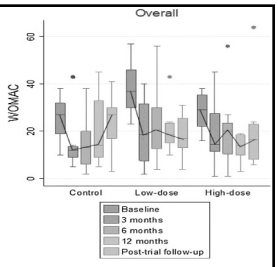
painweek

J Transl Med (2016) 14:246

62

Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II)

José María Lamo-Espinosa[1*], Gonzalo Mora[1*], Juan F. Blanco[2,3], Froilán Granero-Moltó[2,3], Jorge María Núñez-Córdoba[4,5,6], Silvia López Elío[1], Enrique Andreu[1], Fermín Sánchez-Guijo[6], José Dámaso Aquerreta[7], José María Bondía[8], Andrés Valenti-Azcárate[7], María del Consuelo del Cañizo[6], Eva María Villarón[6], Juan Ramón Valenti-Nin[1] and Felipe Prósper[1,9*]



- At the end of follow up (Low-dose vs. Control group, p=0.01; High-dose vs. Control group, p=0.004). Patients receiving BM-MSCs also improved clinically according to WOMAC
- **Conclusions:** intraarticular injection of autologous BM-MSCs is a safe procedure that results in long-term clinical and functional improvement of patients with OA of the knee

painweek

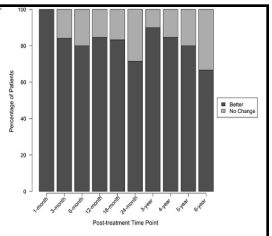
J Transl Med (2018) 16:213

63

Treatment of lumbar degenerative disc disease-associated radicular pain with culture-expanded autologous mesenchymal stem cells: a pilot study on safety and efficacy

Christopher Centeno[1,2], Jason Markle[1], Ehren Dodson[2*@], Ian Stemper[2], Christopher J. Williams[1], Matthew Hyzy[1], Thomas Ichim[3] and Michael Freeman[4]

- Aim: To determine the effectiveness of autologous MSCs for the treatment of DDD
- 33 pts. w/ LBP and disc degeneration were treated with autologous bone marrow-derived MSCs
- Measured outcomes included NPS, a modified single assessment numeric evaluation (SANE) rating, functional rating index (FRI), measurement of the intervertebral disc posterior dimension



- NPS change scores relative to baseline were significant @ 3, 36, 48, 60, and 72 months post-treatment
- The average modified SANE ratings showed a mean improvement of 60% at 3 years post-treatment *J Transl Med (2017) 15:197*

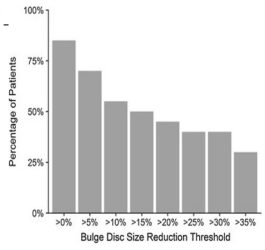
painweek

64

Treatment of lumbar degenerative disc disease-associated radicular pain with culture-expanded autologous mesenchymal stem cells: a pilot study on safety and efficacy

Christopher Centeno[1,2], Jason Markle[1], Ehren Dodson[2*@], Ian Stemper[2], Christopher J. Williams[1], Matthew Hyzy[1], Thomas Ichim[3] and Michael Freeman[4]

- FRI post-Tx change score avg. exceeded the min clinically important difference @ all time points except 12 months
- On post-Tx MRI 85% had a reduction in disc bulge size, with an **avg reduction size of 23%**
- **Conclusion** – the use of BM-MSCs lead to significant improvements in pain, function, and overall subjective improvement through 6 years of follow-up



J Transl Med (2017) 15:197

painweek

65

Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up

Kenneth A Pettine [1], Richard K Suzuki [2], Theodore T Sand [2], Matthew B Murphy [3] [4]

- **Aim:** To assess safety and feasibility of intradiscal (BMC) injections to treat low back discogenic pain as an alternative to surgery
- 26 pts suffering from DDD were injected with 2 ml autologous BMC into the nucleus pulposus of treated lumbar discs
- A sample aliquot of BMC was characterized by flow cytometry and CFU-F assay to determine cell accurate cell content
- Improvement in pain and disability scores and 12 month post-injection MRI were compared

painweek

Int Orthop. 2017 Oct;41(10):2097-2103.

66

Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up

Kenneth A Pettine [1], Richard K Suzuki [2], Theodore T Sand [2], Matthew B Murphy [3] [4]

- **Primary outcomes:** After 36 months, only 6 pts. progressed to surgery
- 1 year MRI indicated 40% of patients improved one modified Pfirrmann grade and no patient worsened radiographically.
- Average CD34+ of 1.82 million per ml in the BMC. Patients with greater concentrations of CFU-F (>2000 per ml) and CD34+ cells (>2 million per ml) in BMC tended to have significantly better clinical improvement.
- **Conclusions:** this study provides evidence of safety and feasibility of intradiscal BMC therapy as a surgical alternative, the study showed that greater concentrations of cells in BMC also lead to improved clinical results

PainWeek

Int Orthop. 2017 Oct;41(10):2097-2103.

67

Safety and tolerability of intradiscal implantation of combined autologous adipose-derived mesenchymal stem cells and hyaluronic acid in patients with chronic discogenic low back pain: 1-year follow-up of a phase I study

Hemant Kumar [1], Doo-Hoe Ha [2], Eun-Jong Lee [3], Jun Hee Park [4], Jeong Hyun Shim [4], Tae-Keun Ahn [5], Kyoung-Tae Kim [6], Alexander E Ropper [7], Seil Sohn [1], Chung-Hun Kim [8], Devang Kashyap Thakor [9], Soo-Hong Lee [10], In-Bo Han [11]

- **Aim:** determine safety & tolerability of adipose tissue-derived MSCs (AT-MSCs) for Tx in pts w/ chronic discogenic LBP
- 10 total patients – chronic LBP (≥3mo), pain (VAS) ≥4/10, disability (ODI) ≥30%
- All pts received: 1 intra-discal injection of HA + autologous AT-MSCs

  Lower-dose grp: HA + 2×10^7 cells/disc

  Higher-dose grp: HA + 4×10^7 cells/disc
- **Outcome measures:** Pain (VAS), functionality (ODI), & any tolerability issues or adverse events related to Tx w/12mo FU

PainWeek

Stem Cell Res Ther. 2017 Nov 15;8(1):262.

68

Patient number

	1	2	3	4	5	6	7	8	9	10
Sex (M/F)	F	F	F	M	M	M	F	M	M	M
Age (years)	37	42	49	42	44	41	33	32	64	54
BMI (kg/m^2)	27.9	22.6	26.5	22.2	28.3	38	20.2	26.7	23.1	23.5
Hypertension (yes/no)	N	N	Y	N	N	Y	N	N	N	N
Diabetes mellitus (yes/no)	N	N	N	N	N	N	N	N	N	N
Smoking history (yes/no)	N	N	N	N	N	Y	N	N	Y	N
Duration of LBP (months)	96	12	14	29	7	37	96	72	36	84
Implanted disc level	L4/5	L4/5	L4/5	L4/5	L4/5	L4/5, L5/S1	L4/5	L4/5	L4/5	L4/5
Preoperative VAS	8	7	6	7	4	7	6	6	6	7
Preoperative ODI	46	34	30	50	32	72	54	32	32	60

- Single injection at L4/L5 for all pts, additional L5/S1 for pt #6

Comparison of patients' outcomes according to time points

	VAS			ODI		
	Mean	*P* value_WSR	*P* value_paired *t*	Mean	*P* value_WSR	*P* value_paired *t*
Baseline–1 week	0.5	0.4766	0.5212	-10.6	0.0977	0.00489
Baseline–1 month	1.9	0.0098	0.0044	11.6	0.002	0.0014
Baseline–3 months	2.15	0.0156	0.014	11.09	0.0117	0.006
Baseline–6 months	3.3	0.0039	0.0008	21.52	0.002	0.0016
Baseline–9 months	3.4	0.0039	0.0012	22.72	0.002	0.0002
Baseline–12 months	3.6	0.002	0.0003	26.02	0.002	0.0004
Baseline–mean of each visit	2.475	0.0039	0.001	13.725	0.002	0.0018

Follow up (12 months):

- No adverse effects or tolerability issues reported
- In 6/10 pts pain and functionality improved significantly
- No significant differences observed btw the 2 groups of differing AT-MSC dose

Conclusions:

- Combined Tx with HA & autologous AT-MSCs is safe & tolerable. Further studies needed to better assess efficacy

PainWeek

Stem Cell Res Ther. 2017 Nov 15;8(1):262.

69

Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)

Laxmaiah Manchikanti, MD, Christopher J. Centeno, MD, Sairam Atluri, MD, Sherri L. Albers, DO, Shane Shapiro, MD, Gerard A. Malanga, MD, Alaa Abd-Elsayed, MD, Mairin Jerome, MD, Joshua A. Hirsch, MD, Alan D. Kaye, MD, PhD, Steve M. Aydin, DO, Douglas Beall, MD, Don Buford, MD, Joanne Borg Stein, MD, Ricardo Buenaventura, MD, Joseph A. Cabaret, MD, Aaron K. Calodney, MD, Kenneth D. Candido, MD, Cameron Carter, MD, Richard Latchaw, MD, Sudhir Diwan, MD, Ehren Dodson, PhD, Zachary Fauser, MD, Michael Frederickson, MD, Christopher G. Gharibo, MD, Mayank Gupta, MD, Adam M. Kaye, PharmD, FASCP, FCPhA, Nebojsa Nick Knezevic, MD, PhD, Radomir Kosanovic, MD, Matthew Lucas, DO, Maarrawi V. Manchikanti, ES, R. Amadeus Mixon, MD, Kenneth Mautner, MD, Samuel Murata, MD, Annu Navani, MD, Vidyasagar Pampati, MSc, Sarah Pattoniya, DO, Ramarao Pasupuleti, MD, Cyril Phillip, MD, Mahendra Sanapati, MD, Theodore Sand, PhD, Rinoo Shah, MD, Amol Soin, MD, Ian Stemper, MS, Bradley W. Wargo, DO, and Philippe Hernigou, MD

Table 4. *Characteristics of MSCs and minimally manipulated cell preparations of BMC.*

Cell Type	Definition
MSCs	Three minimum characteristics: 1. Capable of division and self-renewal for long periods of time 2. Unspecialized 3. Can give rise to specialized cell types
BMC, minimally manipulated autologous cell preparations	Cleared for homologous use Processing must not alter the relevant biological characteristics of cells or tissues Mixed cell populations, with variable composition Stem or progenitor cells may be present at lower prevalence Biological attributes and function highly variable

Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)

Pain Physician 2020; 23:E85-E131

- **Statement 1** Based on a review of the literature in discussing the preparation of BMC using accepted methodologies, there is strong evidence of minimal manipulation in its preparation, and moderate evidence for homologous utility for various musculoskeletal and spinal conditions qualifies for the same surgical exemption.
- **Statement 2** Assessment of clinical effectiveness based on extensive literature shows emerging evidence for multiple musculoskeletal and spinal conditions.
  - –The evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials and nonrandomized studies. There is level III evidence for knee cartilage conditions.
  - –Based on the relevant systematic reviews, randomized trials, and nonrandomized studies, the evidence for disc injections is level III.
  - –Based on the available literature without appropriate systematic reviews or randomized controlled trials, the evidence for all other conditions is level IV or limited for BMC injections.

Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)

Pain Physician 2020; 23:E85-E131

- **Statement 3** Based on an extensive review of the literature, there is strong evidence for the safety of BMC when performed by trained physicians with the appropriate precautions under image guidance utilizing a sterile technique.
- **Statement 4** Musculoskeletal disorders and spinal disorders with related disability for economic and human toll, despite advancements with a wide array of treatment modalities.
- **Statement 5** The 21st Century Cures Act was enacted in December 2016 with provisions to accelerate the development and translation of promising new therapies into clinical evaluation and use.
- **Statement 6** Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders and spine. With mixed results, these therapies are greatly outpacing the evidence. The reckless publicity with unsubstantiated claims of beneficial outcomes having putative potential, and has led the FDA Federal Trade Commission (FTC) to issue multiple warnings. Thus the US FDA is considering the appropriateness of using various therapies, including BMC, for homologous use.

Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)

Pain Physician 2020; 23:E85-E131

- **Statement 7** Since the 1980's and the description of mesenchymal stem cells by Caplan et al, (now called medicinal signaling cells), the use of BMC in musculoskeletal and spinal disorders has been increasing in the management of pain and promoting tissue healing.
- **Statement 8** The Public Health Service Act (PHSA) of the FDA requires minimal manipulation under same surgical procedure exemption. Homologous use of BMC in musculoskeletal and spinal disorders is provided by preclinical and clinical evidence.
- **Statement 9** If the FDA does not accept BMC as homologous, then it will require an Investigational New Drug (IND) classification with FDA (351) cellular drug approval for use.
- **Statement 10** This literature review and these position statements establish compliance with the FDA's intent and corroborates its present description of BMC as homologous with same surgical exemption, and exempt from IND, for use of BMC for treatment of musculoskeletal tissues, such as cartilage, bones, ligaments, muscles, tendons, and spinal discs.

painweek

73

Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature

Archives of Orthopaedic and Trauma Surgery (2020) 140:853–868

Filippo Migliorini[1] · Björn Rath[1] · Giorgia Colarossi[2] · Arne Driessen[1] · Markus Tingart[1] · Marc Niewiera[1] · Jörg Eschweiler[1]

- Hypothesis: stem cell therapy is a viable option for idiopathic knee OA, delaying or avoiding joint replacement
- Systematic Review with 18 studies included, n = 1069 treated knees

Table 2 Overall results of the comparisons

Outcome	Baseline		6 Months		12 Months		Estimated effect, IV, Random [95% confidence interval]			
	Mean	SD	Mean	SD	Mean	SD	0–6 Months	*p*	0–12 Months	*p*
VAS	55.28	18.37	25.66	15.10	20.08	91.54	30.98 [24.07 to 37.89]	< 0.0001	36.91 [30.39 to 43.43]	< 0.0001
WOMAC	25.66	15.10	34.65	24.79	24.98	14.39	25.23 [14.93 to 35.53]	< 0.0001	15.60 [10.10 to 21.10]	< 0.0001
Walking Distance	71.90	28.41	310.24	160.69	578.33	270.31	152.22 [−309.03 to 4.58]	0.06	316.72 [−696.54 to 63.10]	0.10
Lequesne Scale	33.76	19.72			20.70	19.07			12.90 [−1.35 to 27.15]	0.08
KOOS										
Overall	41.07	12.17	36.93	38.56	65.13	13.56	8.47 [15.78 to −32.72]	0.49	18.94 [27.00 to 10.88]	< 0.0001
Symptoms	51.27	15.21	81.71	13.46	69.57	14.99	10.40 [19.88 to 0.92]	0.03	14.14 [21.35 to 6.93]	0.001
Pain	49.55	14.51	85.28	5.34	69.57	14.99	21.30 [29.69 to 12.91]	< 0.0001	22.03 [29.39 to 14.67]	< 0.0001
Function	50.36	18.90	87.76	4.33	76.87	16.02	17.80 [26.31 to 9.29]	< 0.0001	21.54 [28.84 to 14.24]	< 0.0001
Recreation	27.84	17.46	74.00	8.96	57.97	21.17	23.60 [34.27 to 12.93]	< 0.0001	23.07 [32.10 to 14.04]	< 0.0001
Quality of life	32.69	23.40	63.00	17.39	54.87	17.01	14.30 [4.41 to 24.19]	0.005	14.07 [38.98 to −10.84]	0.27

painweek

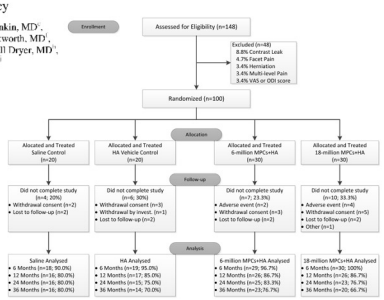
74

Allogeneic mesenchymal precursor cells treatment for chronic low back pain associated with degenerative disc disease: a prospective randomized, placebo-controlled 36-month study of safety and efficacy

Kasra Amirdelfan, MD[a,*], Hyun Bae, MD[b], Tory McJunkin, MD[c], Michael DePalma, MD[d], Kee Kim, MD[e], William J. Beckworth, MD[f], Gary Ghiselli, MD[g], James Scott Rainbridge, MD[g,1], Randall Dryer, MD[h], Timothy R. Deer, MD[i], Roger D. Brown, BA[j]

The Spine Journal 21 (2021) 212–230

- Multicenter RCT to evaluate a single intradiscal injection of STRO-3+ adult allogeneic mesenchymal precursor cells (MPCs) combined with hyaluronic acid (HA) in subjects with chronic low back pain associated with degenerative disc disease, through 36-month follow-up
- Treatment groups: 6 million MPCs with HA, 18 million MPCs with HA, HA vehicle control, or saline control



painweek

75

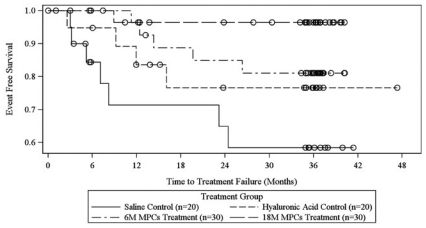


Fig. 2. Time to post-treatment intervention/failure. Kaplan-Meier analysis of the time to first PTI/failure shows a significant difference between the four treatment groups. The 18 million MPC group was superior to the saline and HA control groups through 36 months while the 6 million MPC group had fewer PTIs than both controls.

76

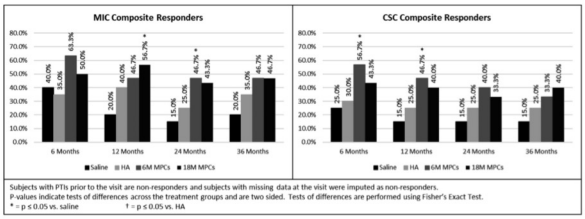


Fig. 10. MIC and CSC composite responders. Composite responder analyses evaluated the reduction in both VAS and ODI scores with no PTI using the respective MIC and CSC thresholds. For the MIC thresholds, 18 million MPC was superior (*) to saline at 12 months while 6 million MPC was superior to saline at 24 months. For the CSC thresholds, 6 million MPC was superior to saline at 6 and 12 months.

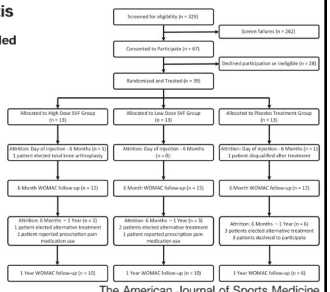
77

Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis

A Double-Blinded Prospective Randomized Controlled Clinical Trial

Jaime R. Garza,* MD, Richard E. Campbell,† BS, Fotios P. Tjoumakaris,‡ MD, Kevin B. Freedman,‡ MD, Lawrence S. Miller,‡ MD, Daniel Santa Maria,§ MD, and Bradford S. Tucker,‡‖ MD

- Multisite prospective double-blinded randomized placebo-controlled, Level of evidence: 1
- 39 adult patients with symptomatic knee OA randomized to high-dose stromal vascular fraction (SVF), low-dose SVF, or placebo (1:1:1)



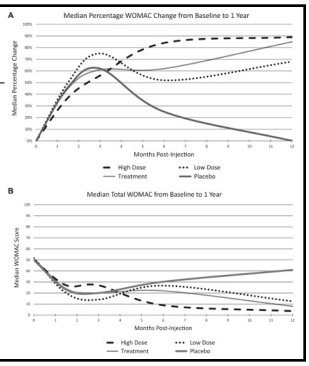
The American Journal of Sports Medicine
2020;48(3):588–598

78

Previously Published WOMAC Percentage Change for MCID Calculation[a]

Treatment	Percentage Change From Baseline at 6 mo	Participants, n
Total knee arthroplasty[7,10,13,14]	54	1451
Corticosteroids[5,18,20,25]	26	362
Hyaluronic acid[1,3,18,53]	33	433
Normal saline[1,20,25]	22	250

[a]MCID, minimal clinically important difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.



The American Journal of Sports Medicine
2020;48(3):588–598

PainWeek

79

Do Regenerative Medicine Therapies Provide Long-Term Relief in Chronic Low Back Pain: A Systematic Review and Metaanalysis

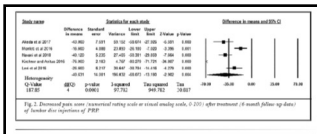
Jaya Sanapati, MD[1], Laxmaiah Manchikanti, MD[2], Sairam Atluri, MD[3], Sheldon Jordan, MD[4] Sheri L. Albers, DO[5], Miguel A. Pappolla, MD, PhD[6], Alan D. Kaye, MD, PhD[7], Kenneth D. Candido, MD[8], Vidyasagar Pampati, MSc[2], and Joshua A. Hirsch, MD[9]

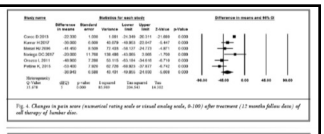
- The systematic review focused on all types of evaluations of PRP and stem cell injections
- The primary outcome measured was relief of pain and the secondary outcome measured was functional status improvement
- The study focused on reviews of pts suffering from CLBP, pts suffering from pain due to fractures, malignancies and inflammatory conditions were excluded
- In total 21 injection studies met inclusion criteria
- This included 12 lumbar disc injections, 5 epidural, 3 lumbar facet joint, and 3 sacroiliac joint studies

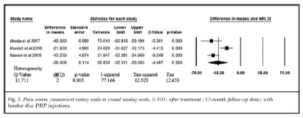
PainWeek

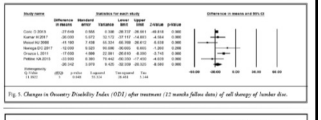
Pain Physician 2018; 21:515-540

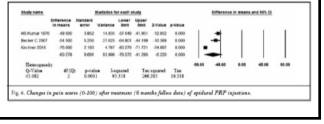
80











PainWeek

81

Do Regenerative Medicine Therapies Provide Long-Term Relief in Chronic Low Back Pain: A Systematic Review and Metaanalysis

Jaya Sanapati, MD[1], Laxmaiah Manchikanti, MD[2], Sairam Atluri, MD[3], Sheldon Jordan, MD[4], Sheri L. Albers, DO[5], Miguel A. Pappolla, MD, PhD[6], Alan D. Kaye, MD, PhD[7], Kenneth D. Candido, MD[8], Vidyasagar Pampati, MSc[1], and Joshua A. Hirsch, MD[9]

Primary Outcomes:

- MSCs and PRP were shown to be effective in treating back pain with disc injections showing the strongest evidence
- RCT and observational studies for disc injections of PRP and MSCs showed Level 3 evidence
- Epidural injections demonstrated Level 4 evidence
- Lumbar facet joint injections and sacroiliac joint injections demonstrated Level 4 evidence

Conclusions:

- The findings of this systematic review show that MSCs and PRP are effective in treating back pain due to degenerative disc disease, radicular pain, facet joint pain, and sacroiliac joint pain, with variable levels of evidence

PainWeek

Pain Physician 2018; 21:515-540

82

Suggested Contraindications

- Hematologic blood dyscrasias
- Platelet dysfunction
- Septicemia or fever
- Cutaneous infections in the area to be injected
- Anemia (Hgb < 10 g/dl)
- Malignancy, particularly w/ hematologic or bony involvement
- Allergy to bovine products if bovine thrombus is to be used
- Severe psychiatric impairment or unrealistic expectation
- Genetic abnormalities in host cells when using autologous therapy

PainWeek

83

Potential Adverse Consequences of Biologics

- Infection
- Tissue rejection and changes to cell characteristics that alter how they respond
- Initial worsening of pain after the procedure. PRP derives its benefit from localized inflammation
- Transient worsening of pain and sensations of pressure in joint is common
- Idea that MSC therapies may cause induction of neoplasms – unfounded
- Multicenter analysis of over 2,300 patients using MSCs for MSK conditions; after 9 years, only 7 pts developed a neoplasm – lower than rate of neoplasia in general public

PainWeek

84

Current Strategies

- Patient candidacy requirements must be met, relative contraindications must be addressed
- Imaging modalities must demonstrate & localize the pathology to be treated
- Procedure should be performed under direct visualization
- Patient should avoid corticosteroids for 2-3 weeks, and NSAIDs for 1 week, prior to the procedure.
- Any specific anticoagulation precautions must be addressed as per relevant guidelines
- Anti-anxiety medications should be used judiciously to ensure patient is alert and arousable at all times

PainWeek

85

Current Strategies

- PRP injectate – should be at least 2.5x > than that found in the peripheral plasma at baseline
- If frozen medium used – cells should be used within 24hrs of thawing
- When extracting MSCs, consider location and tissue type related to the pathologic site in question
- 19G needle found to result in less apoptosis, but MSC viability and differentiation capacity is not affected by gage of needle for extraction
- 2mL syringe recommended – best to avoid over-inflation; this size is consistent with that used in currently successful studies

PainWeek

86

Post-Procedure Recommendations

- Instruct pts. to rest and partially immobilize injected site for at minimum 2 days, up to 2 weeks
- Patients should avoid NSAIDs/Anti-inflammatory medications for at least a few weeks. Effectiveness of therapy is dependent on the inflammatory state of the site
- Follow-up every 2-4weeks is appropriate; however frequent repeat imaging is not recommended
- Main outcomes of interest are pain and functional improvements, not structural changes
- Repeat injections may be considered based on patient response and extent of the pathology

PainWeek

87

When to Consider Regenerative Therapy

- Current literature suggests biologics to be more beneficial compared to standard non-interventional care such as NSAIDs and rest
- Biologics are considered by many to be a more effective and cost-effective approach
- Based on current literature – Guidelines suggest Biologics be considered upon initial failure of conservative therapy, especially for Tx of lumbar discs, facet, & SIJ pathologies
- For tendinopathy, research suggests to consider biologic regenerative therapy after failure of conservative therapy & US-guided corticosteroid injection
- Regenerative therapy shows a great amount of promise in improving musculoskeletal conditions and providing patients an effective treatment option for their pain

painweek

88

89