PainWeek®

Regenerative Therapy for Chronic Pain: Fact or Fiction?

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Disclosure

- No Financial Disclosures
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- Member of ASIPP – Research and Education Committee; ASA – Vice Chair Chronic and Cancer Pain Research Committee, AAPM – Scientific Abstracts Committee
- Section Editor – Pain Physician
- Assistant Editor – Anesthesia & Analgesia; Associate Editor – BMC Anesthesiology; Editorial Board – Pain Medicine Case Reports

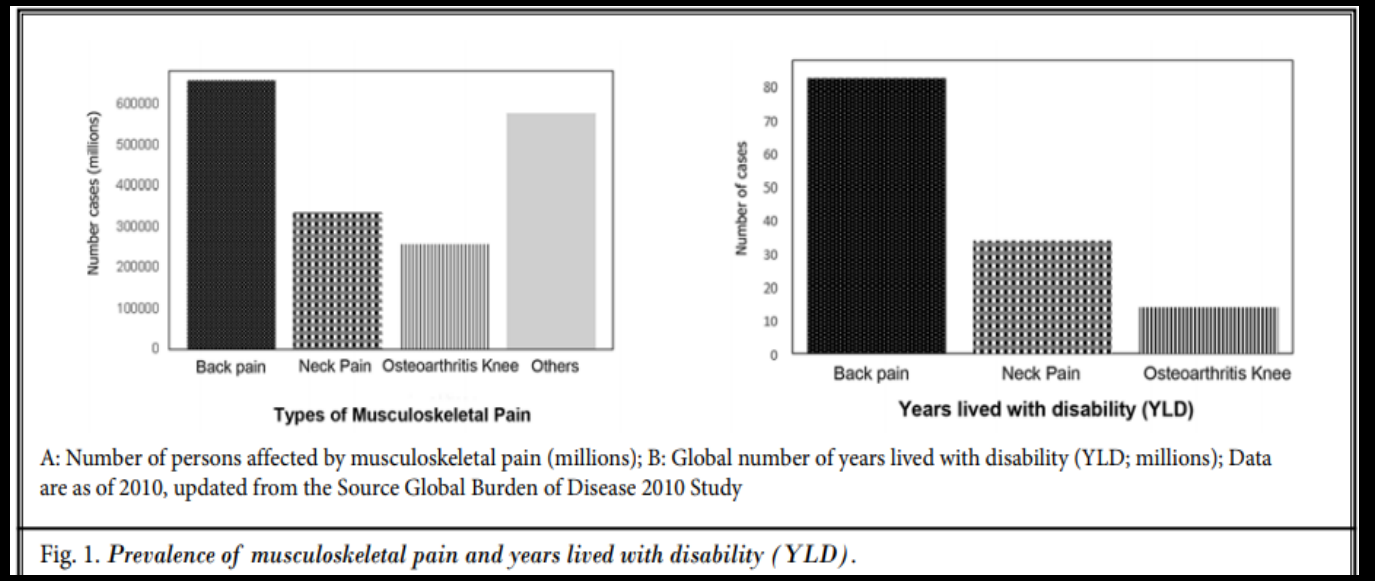
Learning Objectives

- 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)

Impact of Chronic LBP

- LBP has a significant economic burden (>$100 billion per year in the US)
- LBP ranks as the #1 disease process contributing to YLD
- Despite these costs, treatments have remained marginally effective

Years lived with Disability (YLD)



A: Number of persons affected by musculoskeletal pain (millions); B: Global number of years lived with disability (YLD; millions); Data are as of 2010, updated from the Source Global Burden of Disease 2010 Study

Fig. 1. *Prevalence of musculoskeletal pain and years lived with disability (YLD).*

Pain Physician 2019; 22:S1-S74

- Ex: 40% of patients postoperatively develop post-surgery ("failed back") syndrome requiring further treatment

Pathophysiology Underlying LBP

- Discogenic pain
- ↓ water content of the nucleus--→fissuring annulus--→bulging disc
- Altered disc mechanics, neurovascular compression, chemical irritation via annular fissures near nerve roots

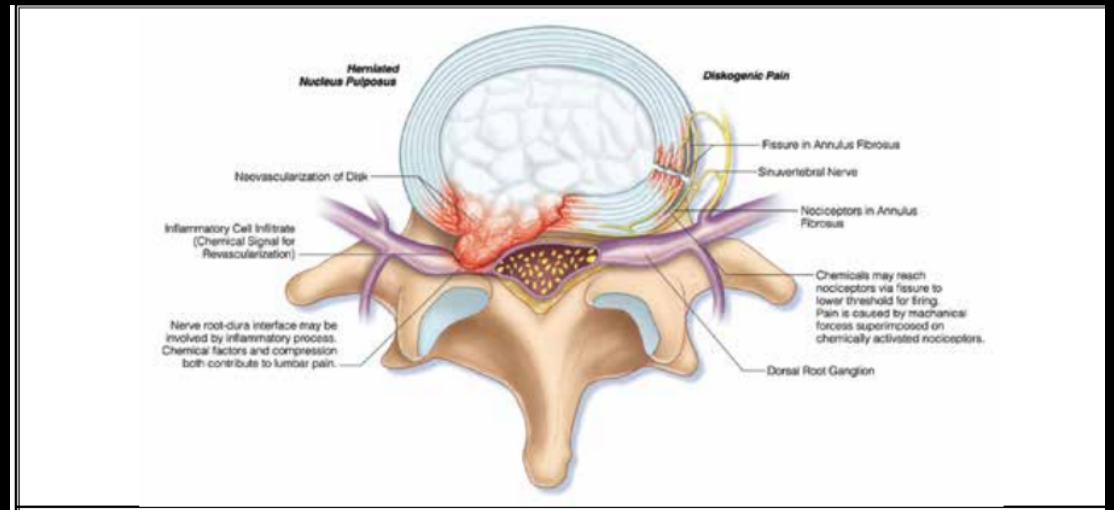


Fig. 14. *Pathophysiology of disk-related pain.* **Pain Physician 2019; 22:S1-S74**

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

Pathophysiology Underlying LBP

- Many etiologies:
  - Degenerative facet disease, spondylolisthesis, discogenic pain
  - Seronegative spondyloarthropathies
  - Spinal stenosis, foraminal narrowing
  - Post lumbar surgery syndrome

- Regardless of etiology, the end-result is similar:
- Altered mechanics, neurovascular compression, local chemical irritation
- Maladaptive response, chronic pain

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

Goals of Regenerative Therapy

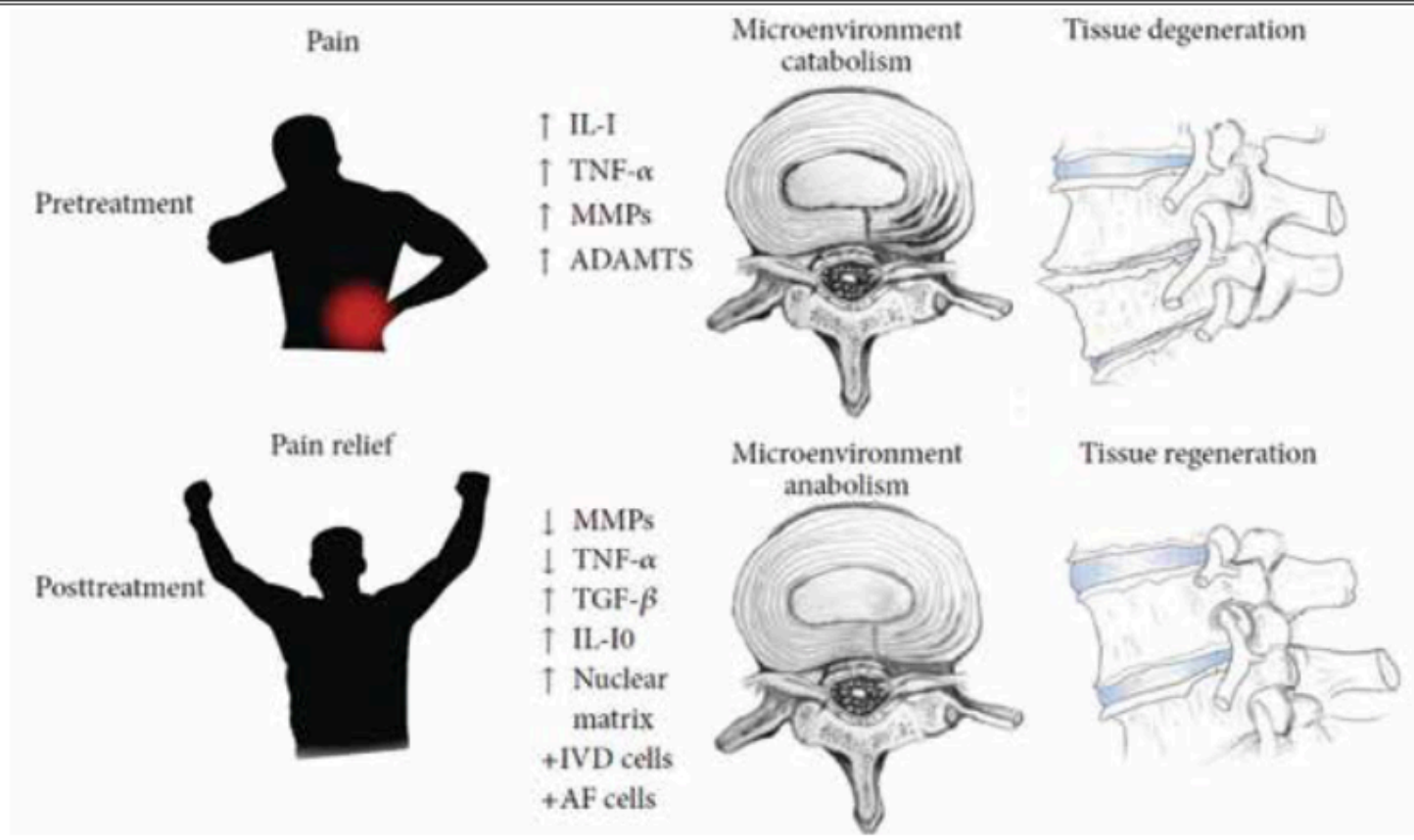


Fig. 24. *Goals of interventional treatment (pain relief, improved disc microenvironment, and tissue regeneration).*

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Currently Available Biologics (PRP)

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

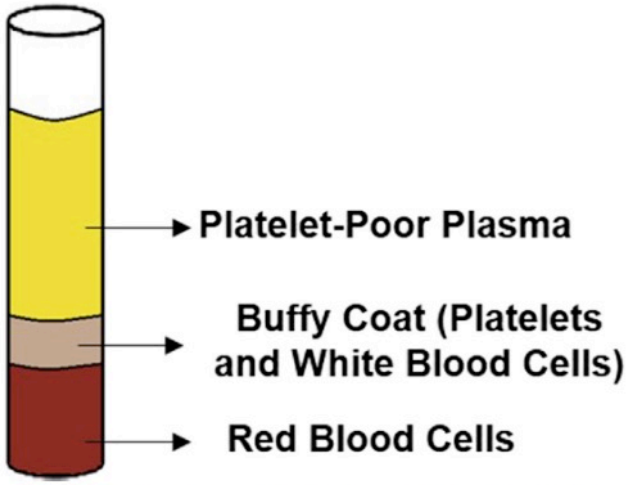

Fig. 1. Example of platelet-rich plasma (PRP) preparation. The buffy coat is the PRP, PRP-related growth factors.

Med Clin N Am 100 (2016) 199–217

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.

Med Clin N Am 100 (2016) 199–217

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

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

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

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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

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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)

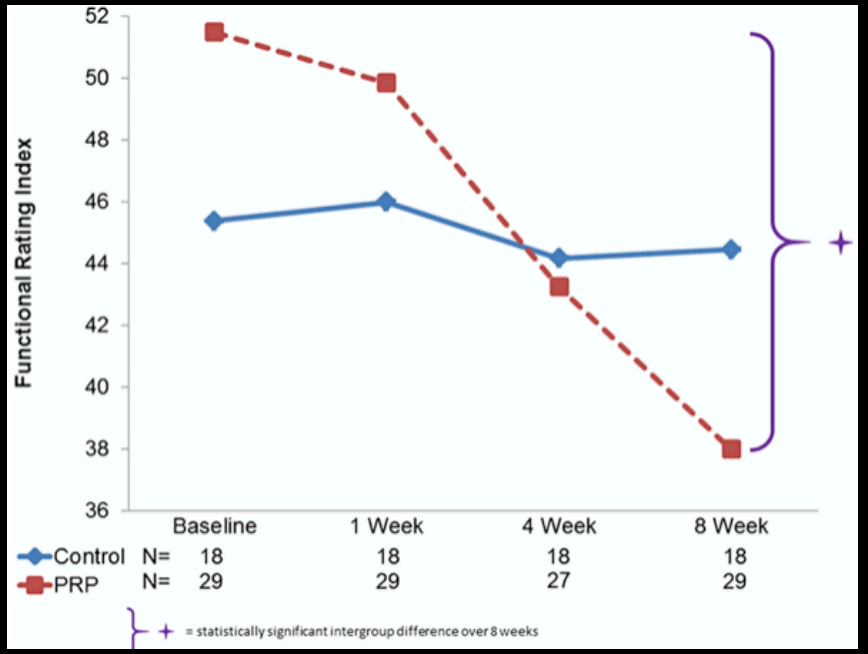

Figure 2. Change in Functional Rating Index over time from baseline to 8 weeks for control and platelet-rich plasma (PRP) groups. N indicates the number observations analyzed at the given time point.

Conclusions:

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

PM&R
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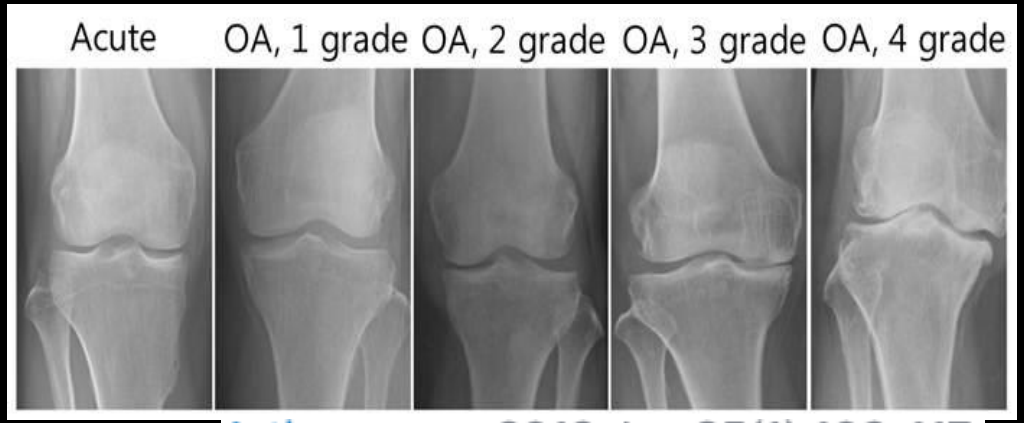
Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial

Kuan-Yu Lin [1], Chia-Chi Yang [2], Chien-Jen Hsu [3], Ming-Long Yeh [4], Jenn-Huei Renn [5]

- Aim: compare long-term clinical outcomes from intra-articular injections of hyaluronic acid (HA), PRP, & normal saline (NS) in pts with knee OA
- 87 knees (53pts) – randomly assigned to receiving 3 weekly injections of either HA (29 knees); or leukocyte-poor PRP (31 knees); or NS sham (27 knees)
- Outcome measures: WOMAC (Western Ontario & McMaster Universities Osteoarthritis Index) & IKDC (International Knee Documentation Committee subjective) scores collected at baseline & subsequent follow-ups through 12mo to assess function

- All 3 groups had significant improvement (1 month); only the PRP-grp sustained significant improvement in function (WOMAC (↑ by 21%); IKDC (↑40%)PRP-gr.)



Arthroscopy. 2019 Jan;35(1):106-117.

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Results:

Intergroup comparisons (beyond 1st month):

- PRP vs. NS gr: **significant difference** in all functional measures
- HA vs NS gr: no significant difference in either functional outcome
- Only the PRP gr. achieved minimal clinically important difference in the WOMAC at every eval (through 12mo), & in the IKDC score (through 6mo)

Conclusions:

In patients with mild-mod knee OA, intra-articular injections of leukocyte-poor PRP provides clinically significant functional improvements lasting for at least 1yr

Arthroscopy. 2019 Jan;35(1):106-117.

Intraarticular injection of platelet-rich plasma in knee osteoarthritis: single versus triple application approach. Pilot study

Mario Simental-Mendía [1], Carlos Alberto Acosta-Olivo [1], Alejandra Nohemí Hernández-Rodríguez [1], Oscar Rubén Santos-Santos [1], Santiago de la Garza-Castro [1], Víctor Manuel Peña-Martínez [1], Félix Vilchez-Cavazos [1]

- Aim: compare clinical efficacy of single vs. triple intra-articular PRP injections on pain relief & functional improvement for pts with mild knee OA
- 35 total pts. – clinical & radiologic knee OA grade 1-2
  - Randomized into single application (n=18) & triple application (n=17) of PRP
  - Follow-up assessments @ wks: 6, 12, 24, 36, & 48 post-Tx
- Outcome measures: **VAS** & **WOMAC**, to assess pain & functionality, respectively
- 2mL LA w/ 2% lidocaine
- Prior to application, PRP was activated using 0.75mL of 10% Ca-gluconate

TABLE I. COMPARISON OF THE BASELINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN BOTH STUDY GROUPS

	Comparative demographics		
	Single injection	Triple injection	p value
Patients, (n)	18	17	
Age, mean (SD)	54.6±11.6	60.1±10.6	0.2982
Gender, female, n (%)	17 (94.4)	12 (70.6)	0.0877
BMI, mean (SD), kg/m^2	29.6±5.9	31.5±4.8	0.8786
Kellgren-Lawrence			
Grade I, (n)	1	1	1.0000
Grade II, (n)	17	16	
VAS, mean (SD), 0-10 cm	7.3±2.1	6.6±2.4	0.4081
WOMAC Total, mean (SD)	44.2±19.7	41.4±15.5	0.6427
Pain, mean (SD)	9.7±3.1	9.1±3.0	0.5608
Stiffness, mean (SD)	3.7±1.7	3.2±1.9	0.3790
Functionality, mean (SD)	30.7±15.7	29.06±12.65	0.7332
SF-12 MCS, mean (SD)	51.1±8.6	51.7±12.9	0.8735
SF-12 PCS, mean (SD)	33.8±8.4	37.0±6.8	0.2353

BMI, body mass index; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; SF-12, Health Survey 12v2; MSC, Mental Component Summary; PCS, Physical Component Summary

Acta Reumatol Port. Apr-Jun 2019;44(2):138-144.

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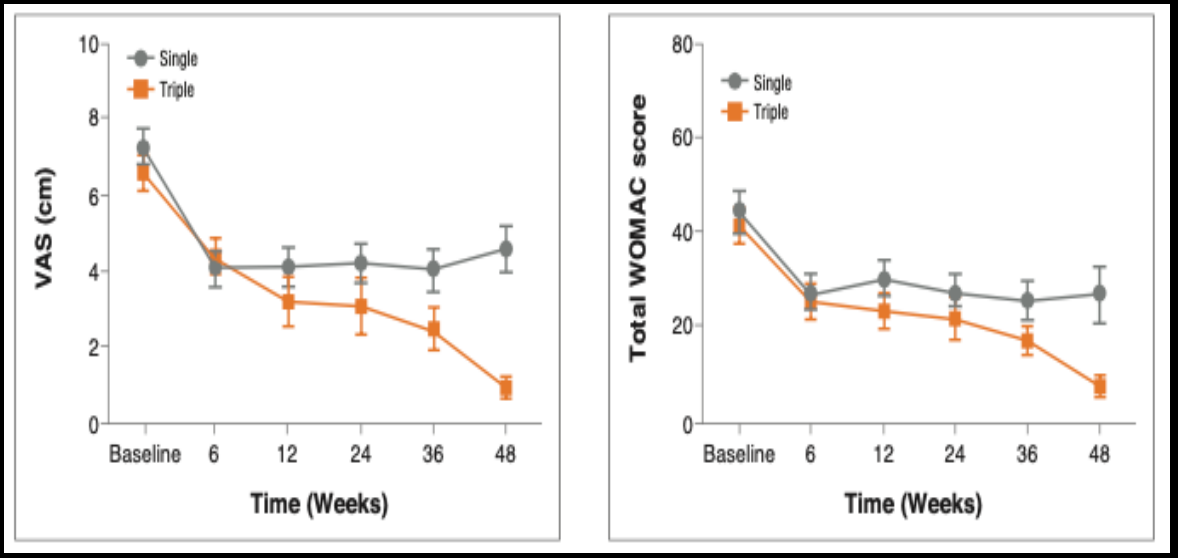

TABLE III. CLINICAL EVALUATIONS PERFORMED AT BASELINE AND AT 48 WEEKS POST-TREATMENT

	Single injection			Triple injection		
Scale analyzed	Baseline	48 weeks	p value	Baseline	48 weeks	p value
VAS, mean (SD), 0-10 cm	7.3±2.1	4.6±2.7[a]	0.0049	6.6±2.4	0.9±1.4[a]	<0.0001
WOMAC Total, mean (SD)	44.2±19.7	26.7±24.9[b]	0.0269	41.4±15.5	7.2±7.3[b]	<0.0001
Pain, mean (SD)	9.7±3.1	5.1±4.9	0.0431	9.1±3.0	1.9±2.0	<0.0001
Stiffness, mean (SD)	3.7±1.7	3.8±6.0	ns	3.2±1.9	0.7±0.8	0.0071
Functionality, mean (SD)	30.7±15.7	17.8±17.7[c]	0.0199	29.1±12.7	4.5±5.2[c]	<0.0001
SF-12 MCS, mean (SD)	51.1±8.6	53.6±8.8	ns	51.7±12.9	48.3±9.9	ns
SF-12 PCS, mean (SD)	33.8±8.4	42.8±9.0[d]	0.0360	37.0±6.8	52.9±8.7[d]	0.0030

- @ 48-wk follow-up – triple application showed significantly better improvement in level of pain & knee functionality (VAS & WOMAC) vs. single-application grp
- Both treatments significantly ↓ VAS & total WOMAC scores
- **Conclusions:** in pts with mild OA, triple infiltration of autologous PRP is clinically more effective than single application @ 48wks

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Acta Reumatol Port. Apr-Jun 2019;44(2):138-144.

Platelet-rich plasma prevents blood loss and pain and enhances early functional outcome after total knee arthroplasty: a prospective randomised controlled study

Aditya K Aggarwal [1], V S Shashikanth, Neelam Marwaha

- Aim: determine if PRP helps with blood loss, post-op pain, & wound-healing following TKA
- 40 pts. – knee arthritis, undergoing TKA
- randomly assigned to either control-gr. or PRP-gr.
- control-gr. – no intervention
- PRP-gr. – application of autologous platelet gel over wound, capsule, medial & lateral recesses during TKA
- Outcome measures: Post-op blood loss (Hb, units transfused), pain (VAS & opioid intake), joint functionality (ROM, KSS-knee society score & WOMAC), wound score

Preoperative demographic data in bilateral and unilateral total knee arthroplasty (TKA) with statistical analysis

Description	Bilateral TKA		*P* value	Unilateral TKA		*P* value
	APG (*n* = 10)	Control (*n* = 9)		APG (*n* = 7)	Control (*n* = 14)	
Age	57.10 ± 10.04	62.89.10 ± 7.88	0.184	56.43 ± 7.59	53.79 ± 9.75	0.539
BMI	27.02 ± 2.11	27.23 ± 2.40	0.840	27.47 ± 2.15	26.52 ± 2.99	0.465
Hb	11.88 ± 1.23	11.86 ± 0.53	0.976	12.06 ± 1.46	12.84 ± 1.47	0.265
Mean VAS	6.55 ± 1.36	7.39 ± 1.09	0.044	6.43 ± 1.13	7.36 ± 1.28	0.120
ROM	76.3 ± 8.7	76.9 ± 7.3	0.793	85.7 ± 13.0	76.8 ± 9.7	0.092
KSS	80.05 ± 8.83	82.11 ± 9.42	0.491	89.71 ± 12.23	80.14 ± 12.93	0.120
WOMAC	71.30 ± 4.75	71.50 ± 6.21	0.911	69.00 ± 6.27	68.50 ± 7.90	0.886
Platelet count (PRP in millions)	334.00 ± 129.58	–		257.71 ± 104.11	–	

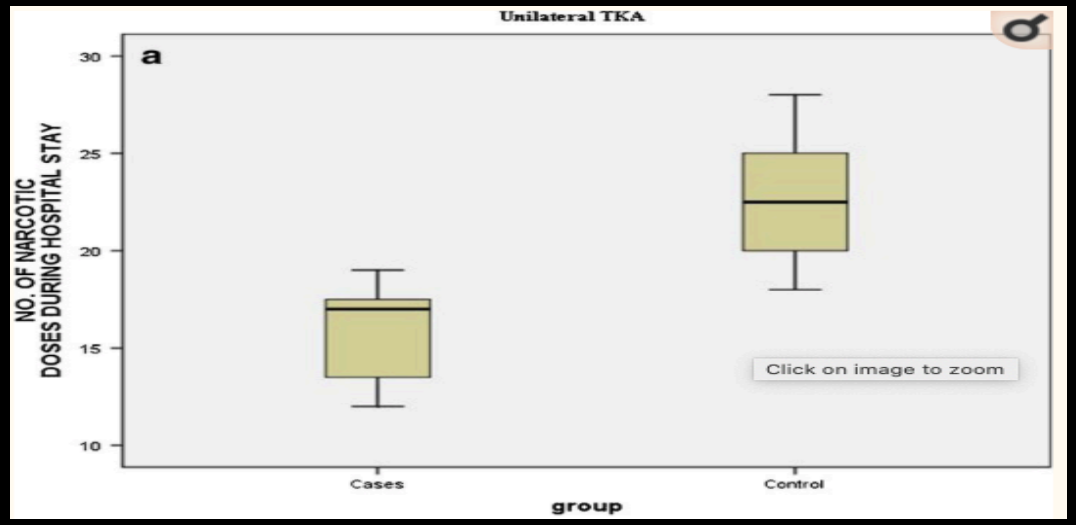
Int Orthop. 2014 Feb;38(2):387-95.

Platelet-rich plasma prevents blood loss and pain and enhances early functional outcome after total knee arthroplasty: a prospective randomised controlled study

Aditya K Aggarwal [1], V S Shashikanth, Neelam Marwaha

Units of blood transfused:

- significantly fewer units of blood needed in PRP-gr. vs. controls



Post-op narcotic doses:

- significantly fewer doses of narcotics needed for PRP-gr. vs. controls in unilat & bilat TKA

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Results:

Significant benefits for PRP-gr. vs. controls:

- Post-op Hb reduction & need for blood
- Post-op pain scores & need for narcotics
- ROM, KSS, & WOMAC scores at 3mo (not maintained @ 6mo FU)
- no significant diff. in wound scores

Conclusions:

- PRP has significant benefit w/ TKA in immediate post-op period (blood loss & pain/narcotics)
- PRP has short-term clinical benefits w/TKA maintained through 3mo follow-up (ROM, KSS, WOMAC)

Description	Bilateral TKA		*P* value	Unilateral TKA		*P* value
	APG (*n* = 10)	Control (*n* = 9)		APG (*n* = 7)	Control (*n* = 14)	
POD0 Hb	9.60 ± 1.57	8.68 ± 1.04	0.153	11.03 ± 1.43	11.51 ± 1.50	0.493
POD3 Hb	9.62 ± 0.97	7.60 ± 0.42	0.00	10.49 ± 1.42	9.72 ± 1.35	0.024
Blood units transfused	1.00 ± 0.67	2.22 ± 0.44	0.00	0.00 ± 0.00	0.93 ± 0.26	0.00
VAS 6 weeks	2.70 ± 0.57	4.06 ± 0.94	0.00	2.57 ± 0.54	3.57 ± 1.09	0.01
VAS 12 weeks	1.60 ± 0.59	2.33 ± 0.49	0.00	1.57 ± 0.54	2.29 ± 0.91	0.03
Narcotics	14.90 ± 2.03	22.44 ± 3.39	0.00	15.71 ± 2.69	22.79 ± 3.07	0.00
ROM POD5	79.3 ± 3.4	72.2 ± 3.5	0.00	80.0 ± 4.1	76.8 ± 5.0	0.00
ROM 6 weeks	95.5 ± 3.9	85.0 ± 4.5	0.00	97.9 ± 2.7	89.6 ± 4.9	0.00
ROM 12 weeks	97.3 ± 2.5	92.8 ± 4.3	0.01	98.6 ± 2.4	95.4 ± 4.1	0.01
Wound score	30.0 ± 12.1	36.3 ± 12.5	0.121	33.7 ± 12.7	33.1 ± 12.9	0.915
KSS 6 weeks	158.90 ± 3.09	149.17 ± 7.52	0.00	159.14 ± 3.24	148.79 ± 9.23	0.00
KSS 3 months	167.00 ± 2.84	161.33 ± 5.18	0.00	167.00 ± 1.73	161.85 ± 5.87	0.01
KSS 6 months	178.25 ± 2.45	177.28 ± 3.70	0.340	178.57 ± 1.81	177.36 ± 5.26	0.447
WOMAC 6 weeks	17.20 ± 2.31	22.61 ± 3.47	0.00	17.57 ± 2.23	23.21 ± 4.49	0.00
WOMAC 3 months	11.05 ± 1.43	14.61 ± 2.73	0.00	10.14 ± 1.22	14.21 ± 3.02	0.00
WOMAC 6 months	7.70 ± 0.98	8.17 ± 1.65	0.291	7.14 ± 0.69	7.86 ± 1.23	0.173

Int Orthop. 2014 Feb;38(2):387-95.

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

Jiuping Wu, MSc*; Jingjing Zhou, MSc†; Chibing Liu, MSc*; Jun Zhang, MSc*; Wei Xiong, MSc*; Yang Lv, MSc*; Rui Liu, MSc*; Ruiqiang 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**)

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

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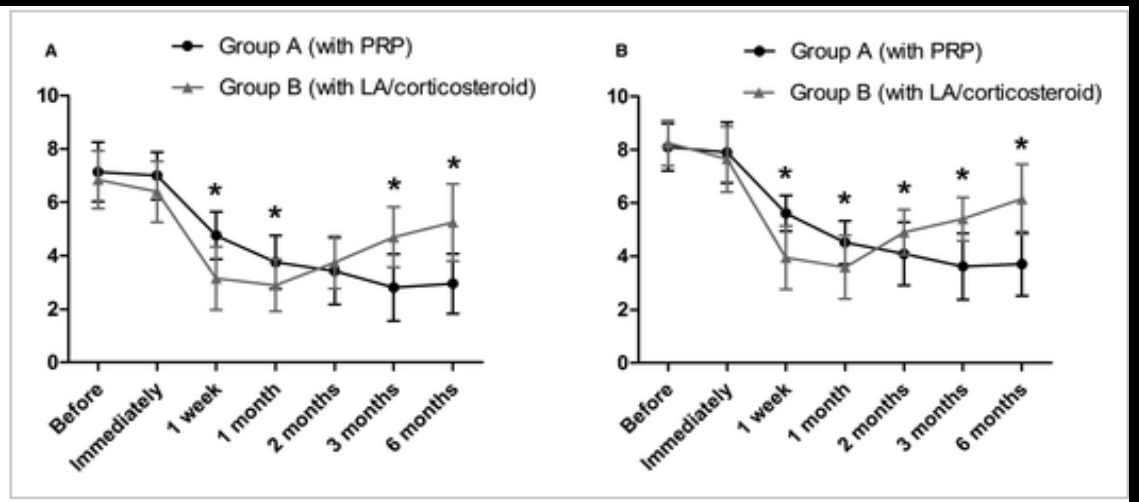


The visual analog scale scores of low back pain at rest (A) and during flexion (B). *Significant difference between groups ($P < 0.01$). PRP , platelet-rich plasma; LA , local anesthetic.

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 ± 7.25	0.95
BMI	22.56 ± 1.39	22.38 ± 1.45	0.66
VAS at rest	7.09 ± 1.08	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	16.70 ± 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%)	0.767
Right	7 (30.43%)	6 (26.08%)	
Bilateral	11 (47.83%)	10 (43.49%)	
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

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

Jiuping Wu, MSc*; Jingjing Zhou, MSc†; Chibing Liu, MSc*; Jun Zhang, MSc*; Wei Xiong, MSc*; Yang Lv, MSc*; Rui Liu, MSc*; Ruiqiang Wang, MSc*; Zhenwu Du, MD, PhD*; Guizhen Zhang, MD, PhD*; Qinyi Liu, MD, PhD*

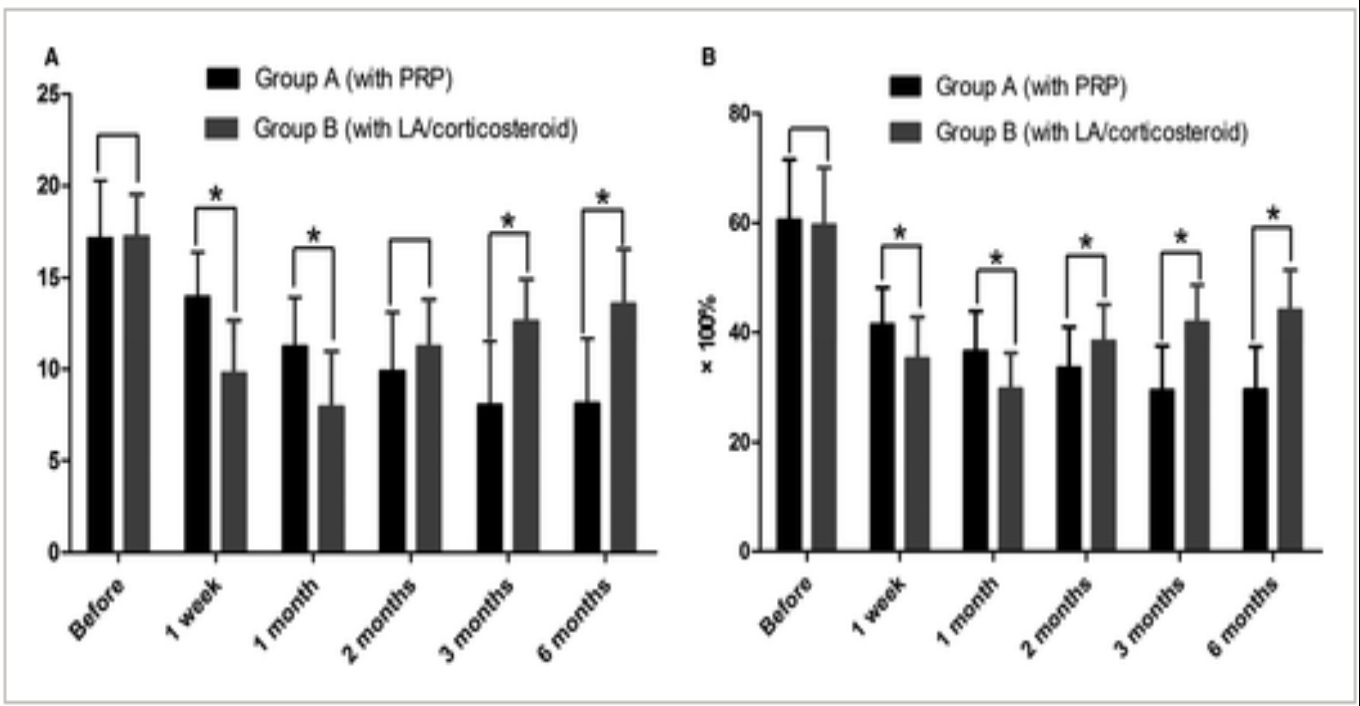
*Department of Orthopaedics, The Second Hospital, Jilin University, Changchun, Jilin; †Department of Imaging and Nuclear Medicine, The Second Hospital, Jilin University, Changchun, Jilin, China

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.

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

PainWeek

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.

Results:

Follow-up (1 month)

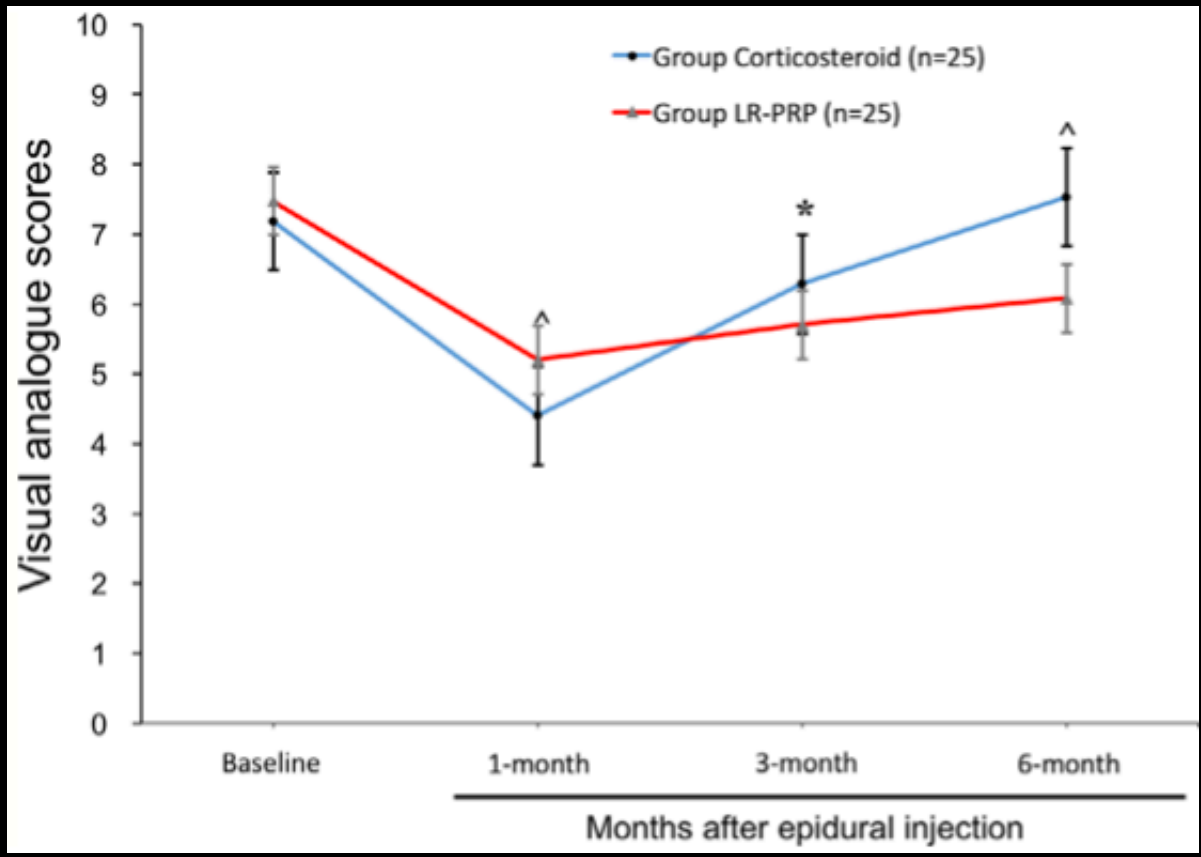
- both groups improved significantly from baseline pain
- CS-gr. had significantly lower pain scores

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*



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

	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

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

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

Currently Available Biologics (MSC)

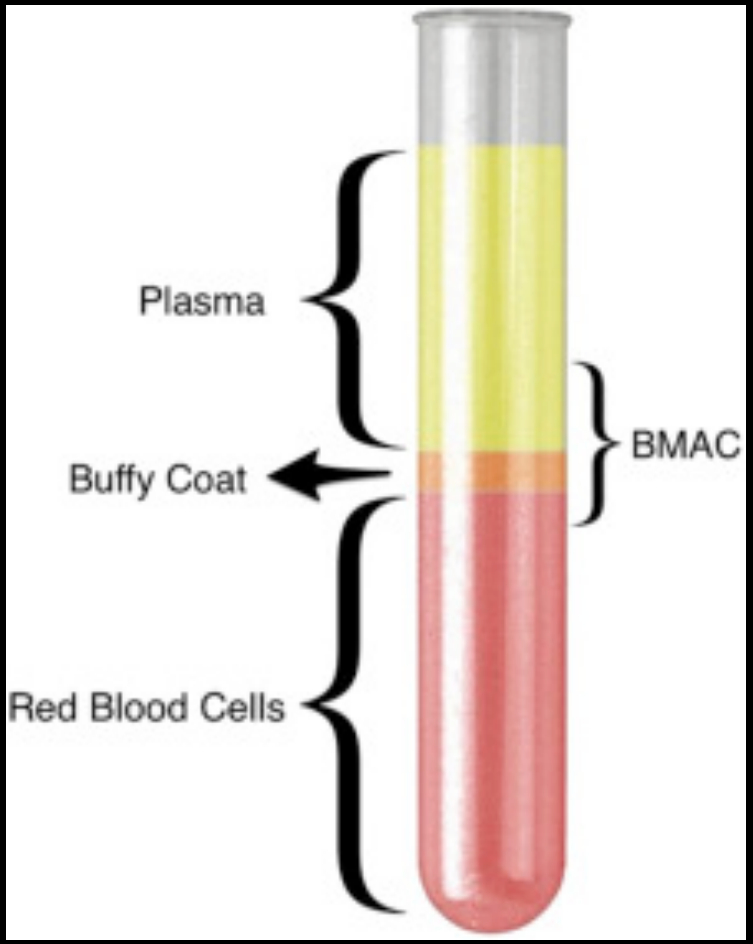
- Local paracrine influence (e.g. catabolic cytokines) alters differentiation and thus efficacy of MSC
- MSC require lower local levels of inflammation to have their desired anabolic regenerative effects
- Most effective in degenerative diseases – environments with little active inflammation (contrasted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

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

Production of Bone Marrow Concentrate (BMC)

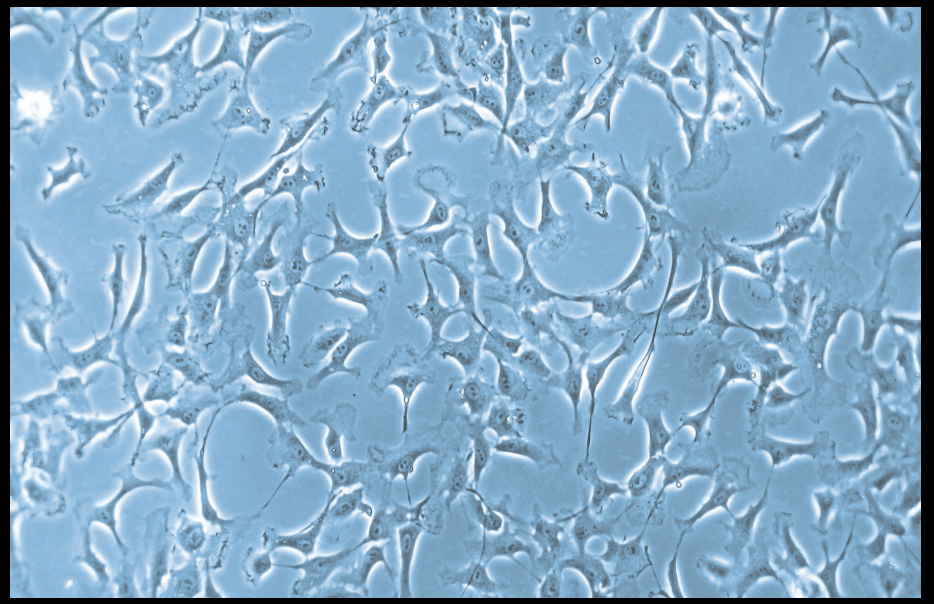
- Bone marrow aspirate is first centrifuged
- This process results in 3 layers with the plasma in the supernatant, the buffy coat in the middle, and the red blood cell layer in the infranatant
- To create BMC, the buffy coat is isolated which contains MSCs
- MSCs are largely credited w/ the therapeutic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



Heliyon 4 (2018) e00871.

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



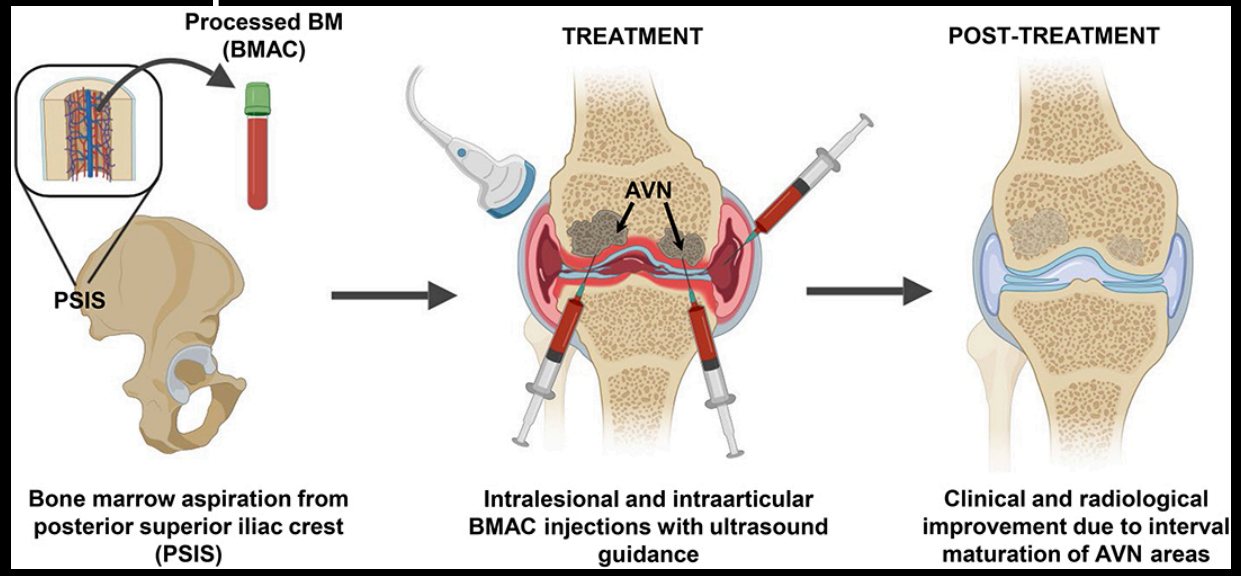
https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.promocell.com%2Fproduct%2Fhuman-mesenchymal-stem-cells-hmsc%2F&psig=AOvVaw19j1UEv4EfJLNBE7TMvE1_&ust=1596038331735000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCJjzlKSo8OoCFQAAAAAdAAAAABAD

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[2], Diego Correa[1,3†] and Riam Shammaa[2,4†]*

- 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.

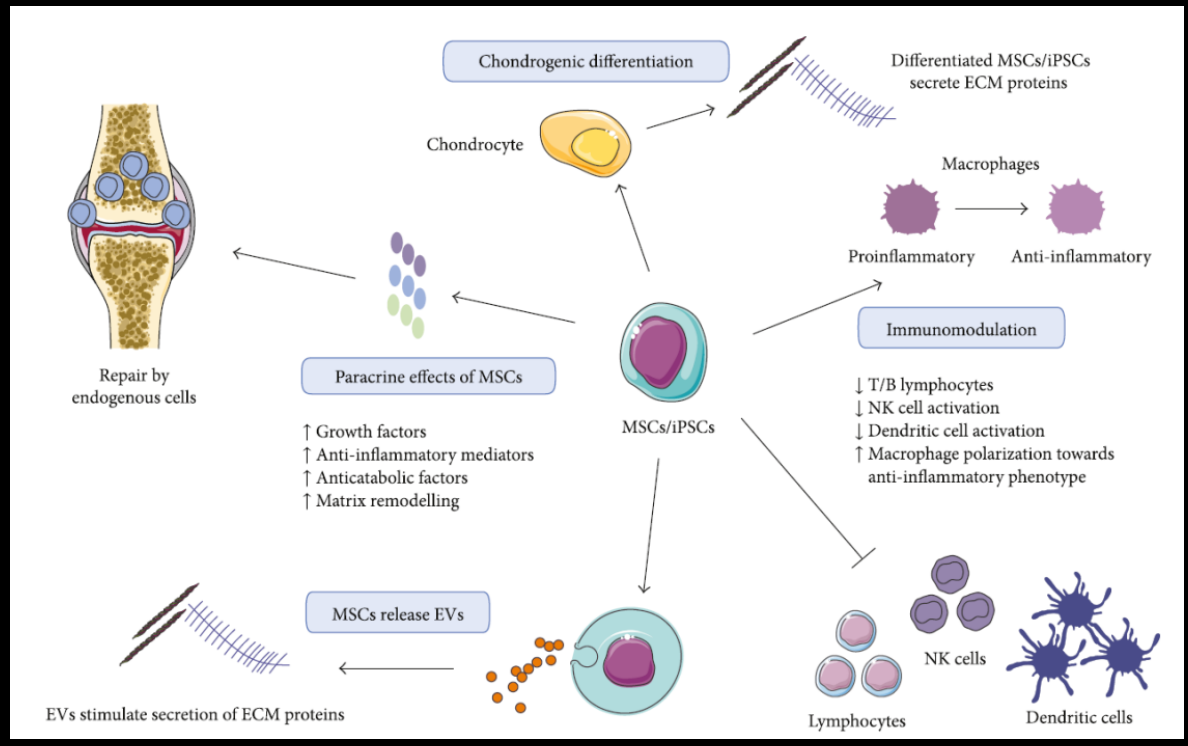
BM-MSC Role in Repair of Cartilage

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,[3] Annelies Bronckaers,[1] Jean-Michel Vandeweerd,[2] and Ivo Lambrichts[1]

- 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



Stem Cells International
Volume 2018, Article ID 9079538,

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

Pathophysiology of Degenerative Disc Disease

International Journal of *Molecular Sciences*

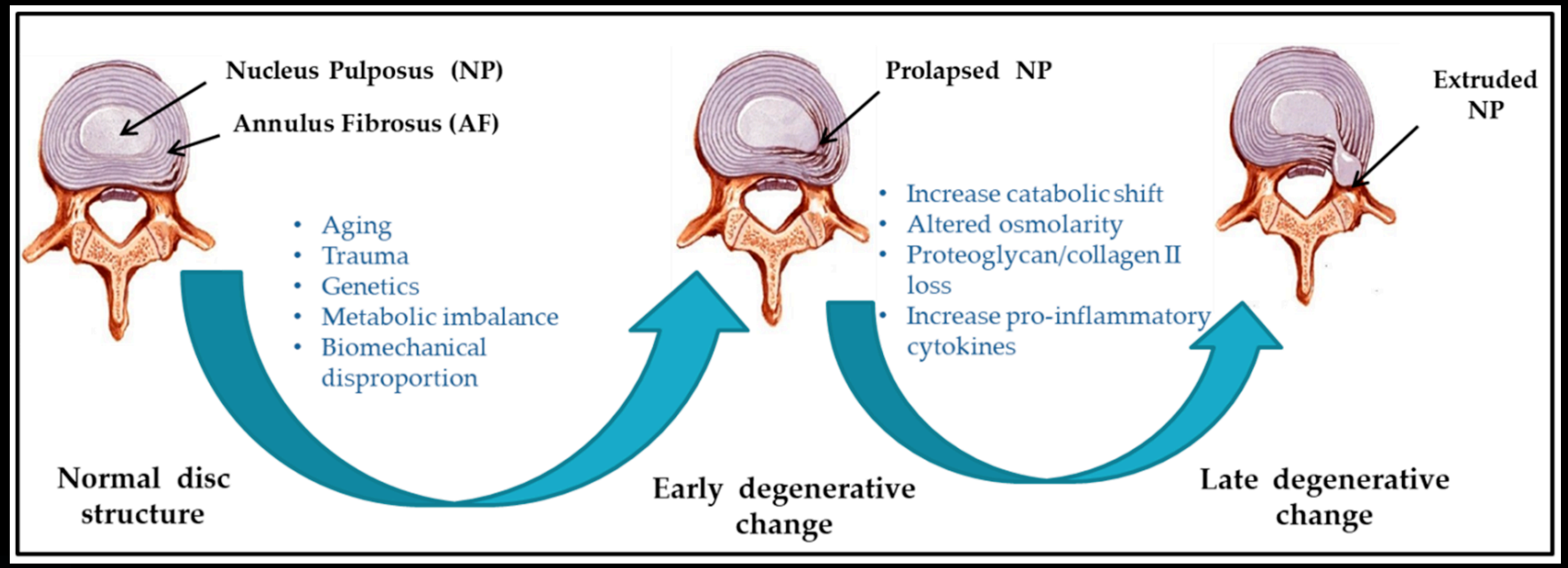
MDPI

Review

Intervertebral Disc Nucleus Repair: Hype or Hope?

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

- 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



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

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

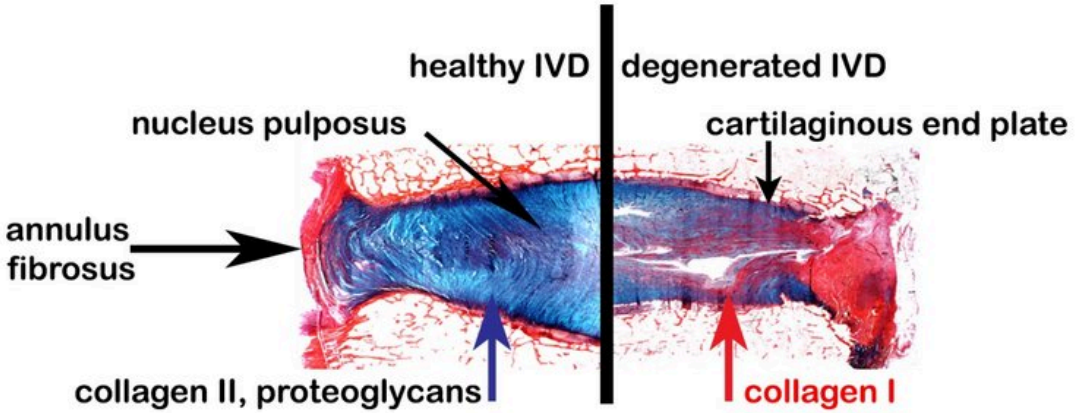
International Journal of *Molecular Sciences*

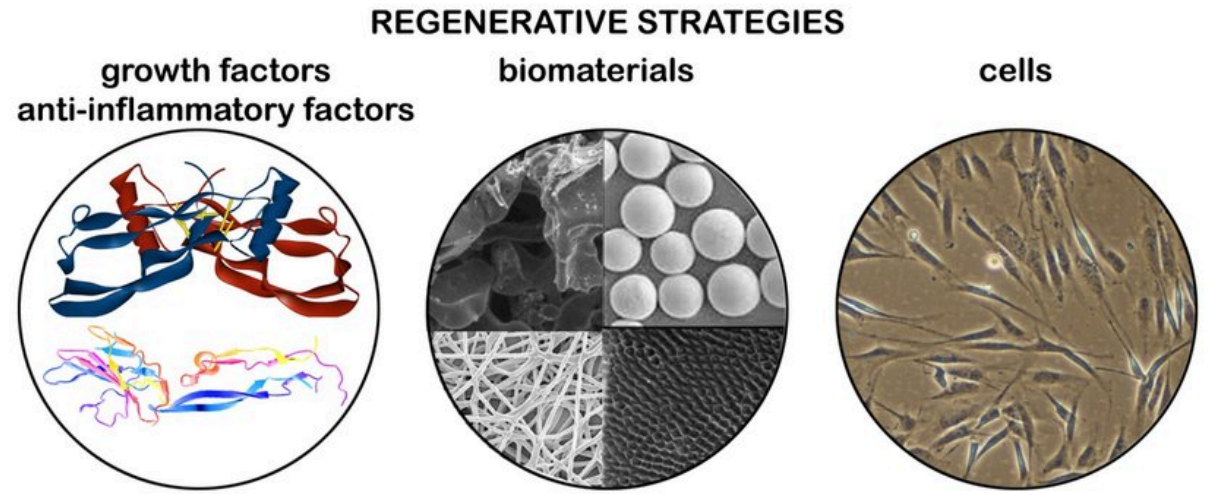
MDPI

Review

Intervertebral Disc Nucleus Repair: Hype or Hope?

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





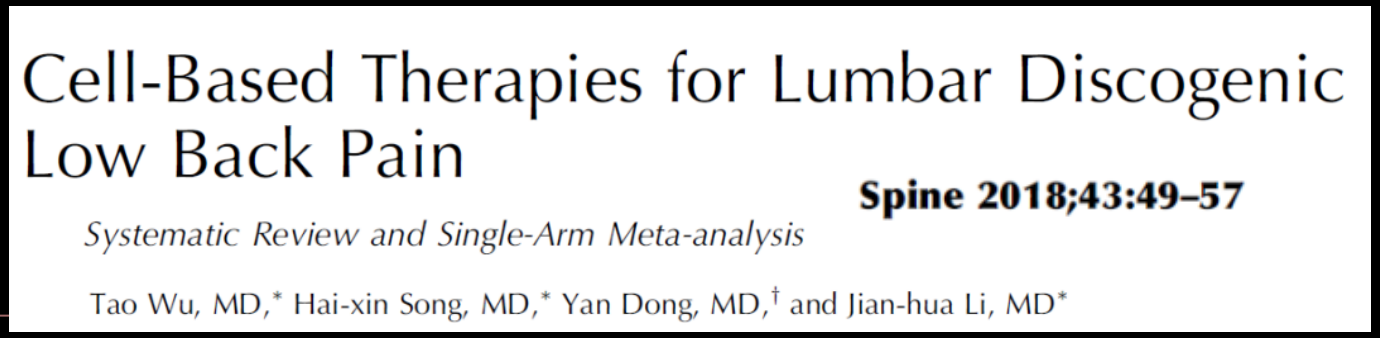
Int. J. Mol. Sci. **2019**, *20*, 3622;

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

Outcomes of MSC Used in Disc Injections



Cell-Based Therapies for Lumbar Discogenic Low Back Pain

Systematic Review and Single-Arm Meta-analysis

Spine 2018;43:49–57

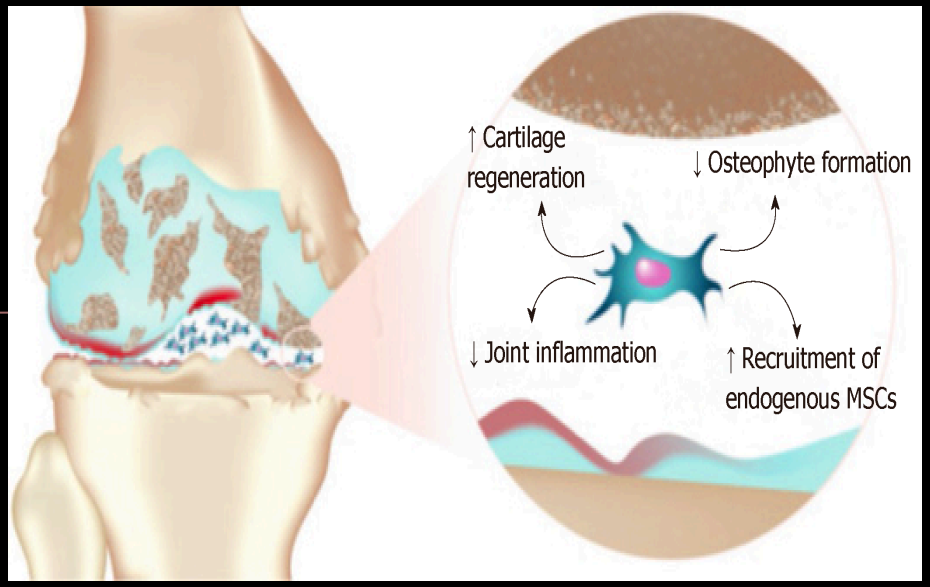
Tao Wu, MD,* Hai-xin Song, MD,* Yan Dong, MD,† and Jian-hua Li, MD*

- 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.

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

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

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

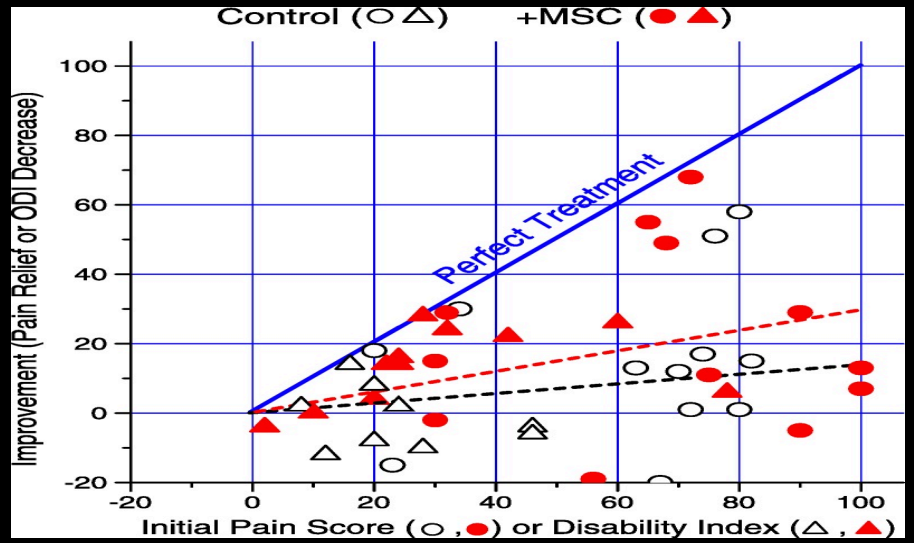
David C Noriega [1], Francisco Ardura, Rubén Hernández-Ramajo, Miguel Ángel Martín-Ferrero, Israel Sánchez-Lite, Borja Toribio, Mercedes Alberca, Verónica García, José M Moraleda, Ana Sánchez, Javier García-Sancho

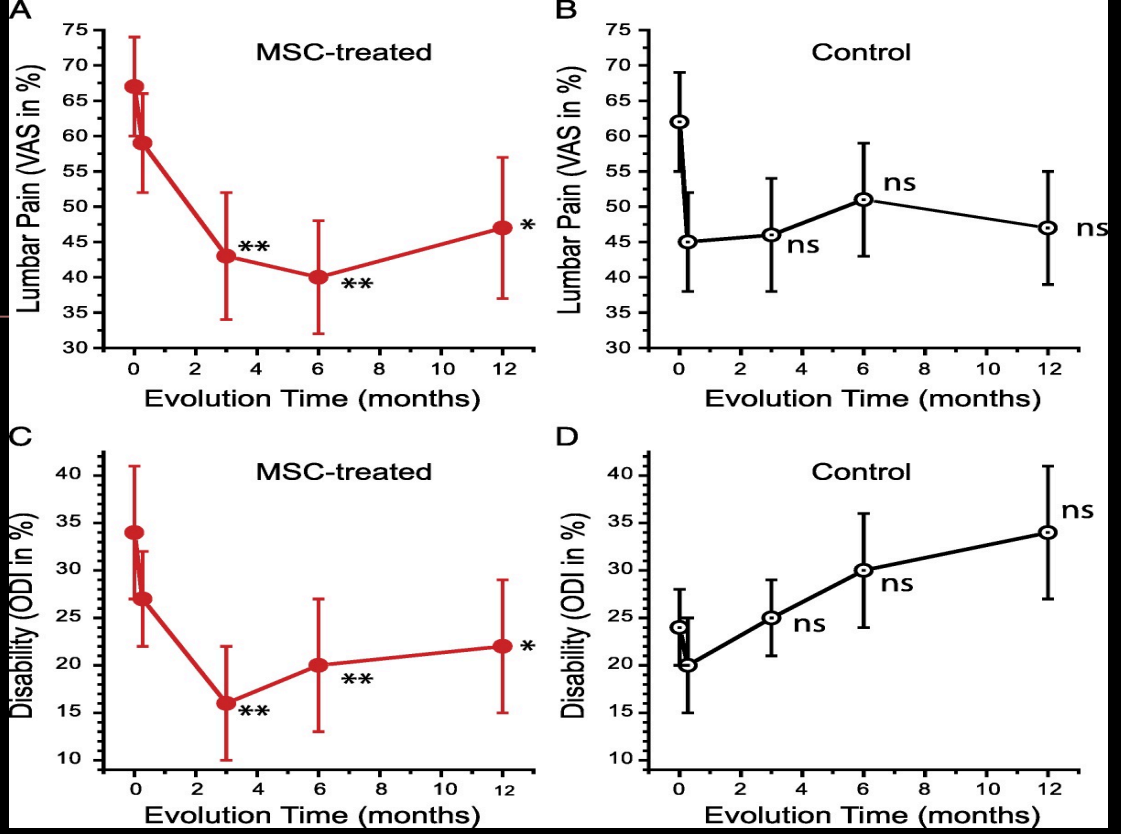
- Aim: To determine the efficacy of allogenic BM-MSCs in the treatment of degenerative disc disease
- 24 pts diagnosed w/ lumbar disk degeneration were randomized into into 2 groups
- The test group received allogeneic BM-MSCs by intradiscal injection of 25×10 cells per segment under local anesthesia
- 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

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

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





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

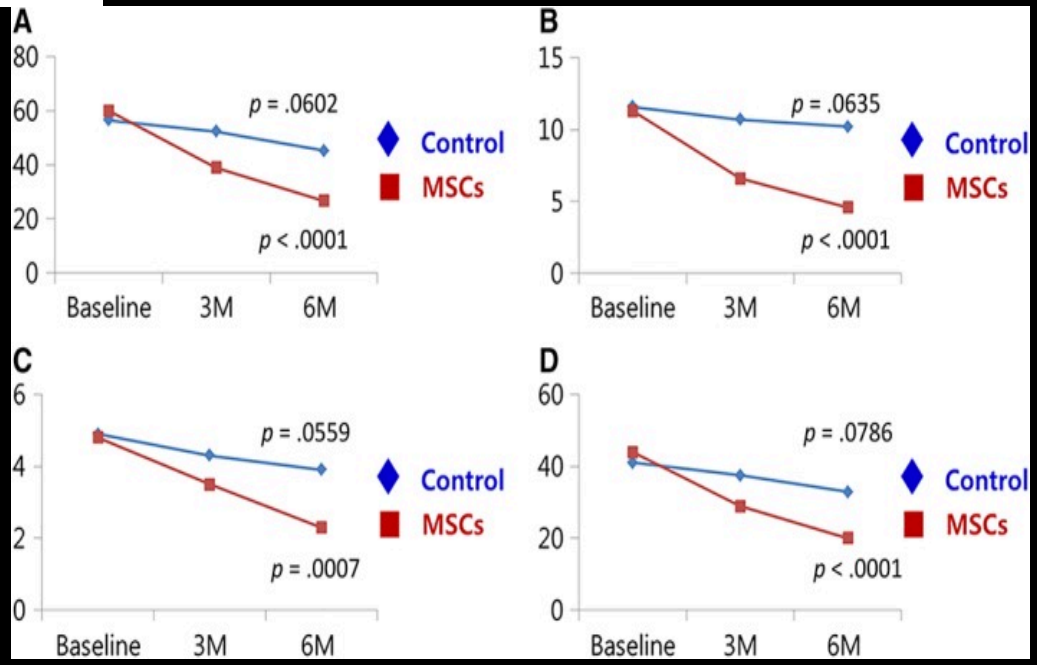
PainWeek

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

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



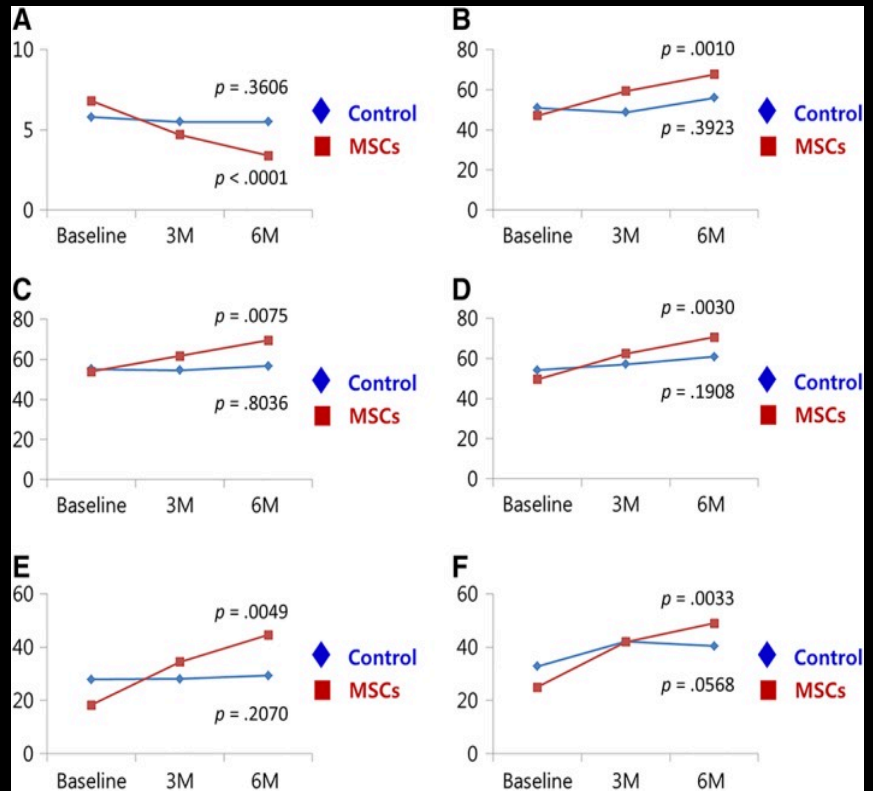
PainWeek

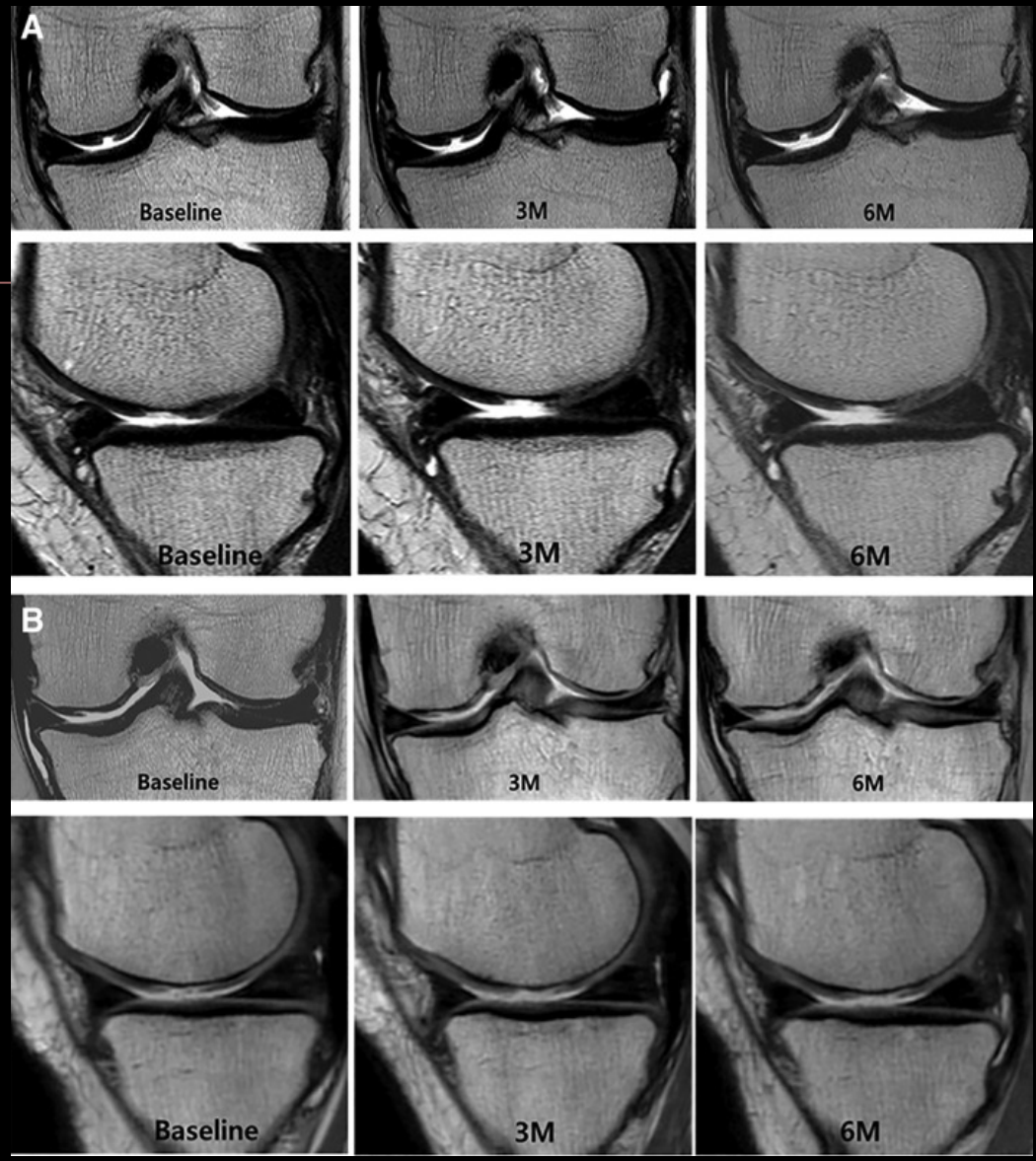
Stem Cells Translational Medicine 2019;8:504–511

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 ↑





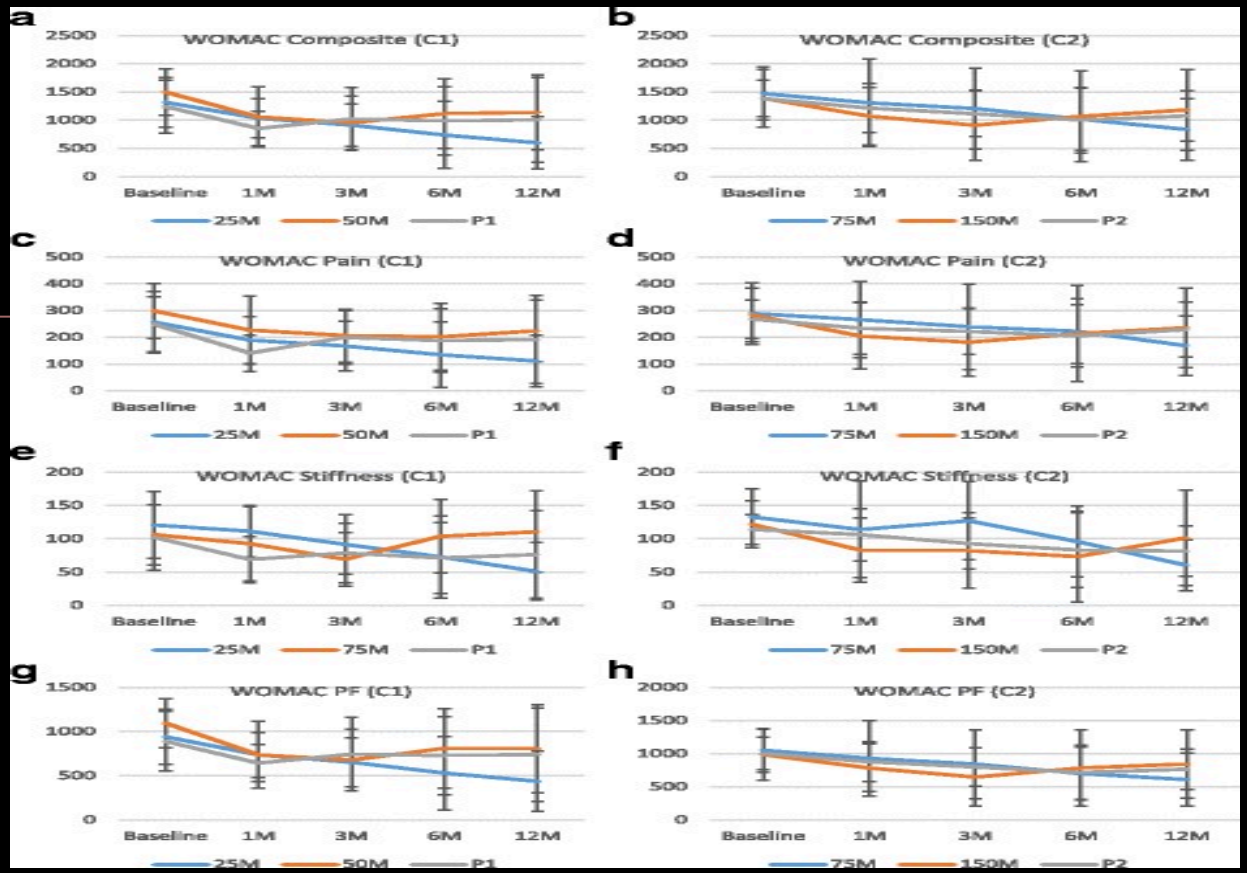
PainWeek

Stem Cells Translational Medicine 2019;8:504–511

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 Wagh [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

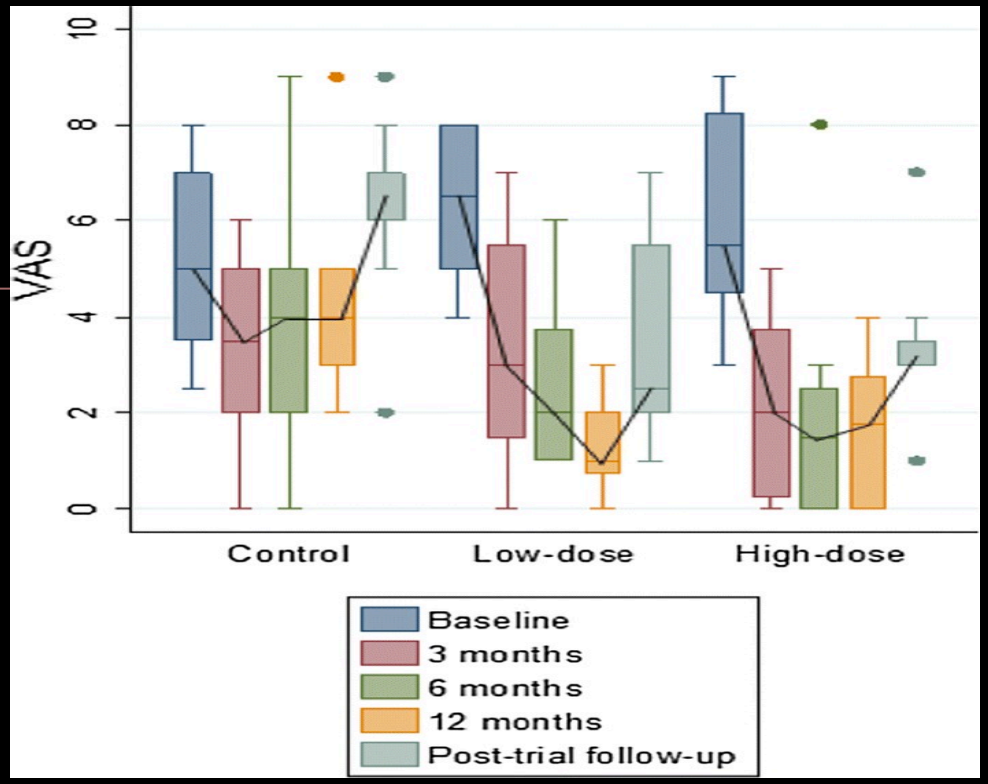
PainWeek

Arthritis Research & Therapy (2016) 18:301

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

- **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

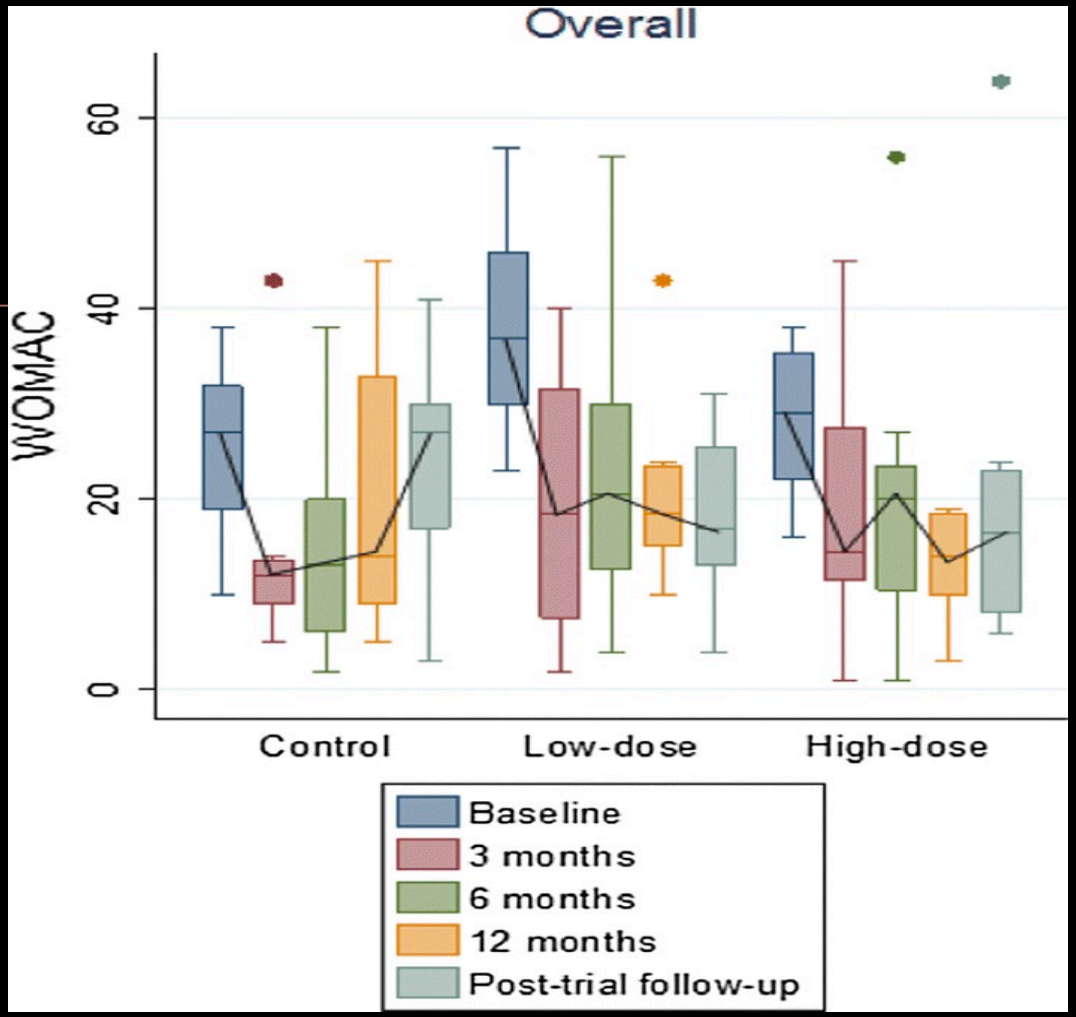
J Transl Med (2016) 14:246

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

- 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

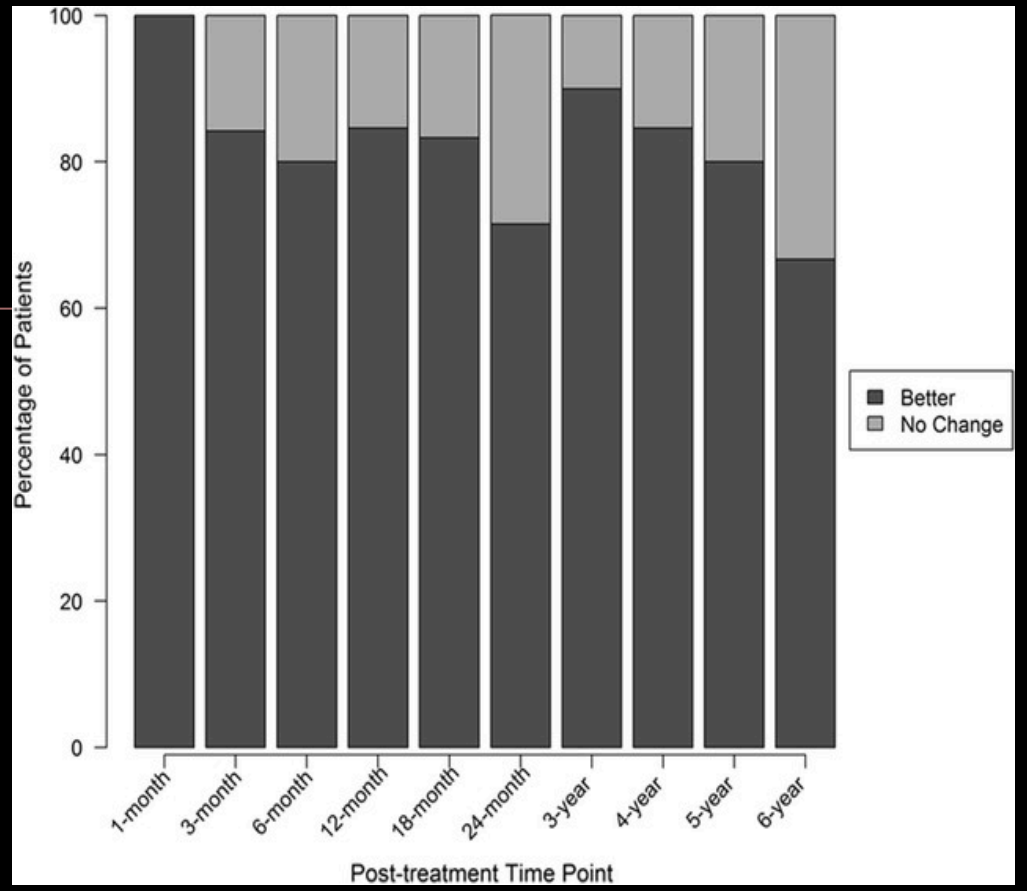
- **Conclusions:** intraarticular injection of autologous BM-MSCs is a safe procedure that results in long-term clinical and functional improvement of patients with OA of the knee



J Transl Med (2018) 16:213

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

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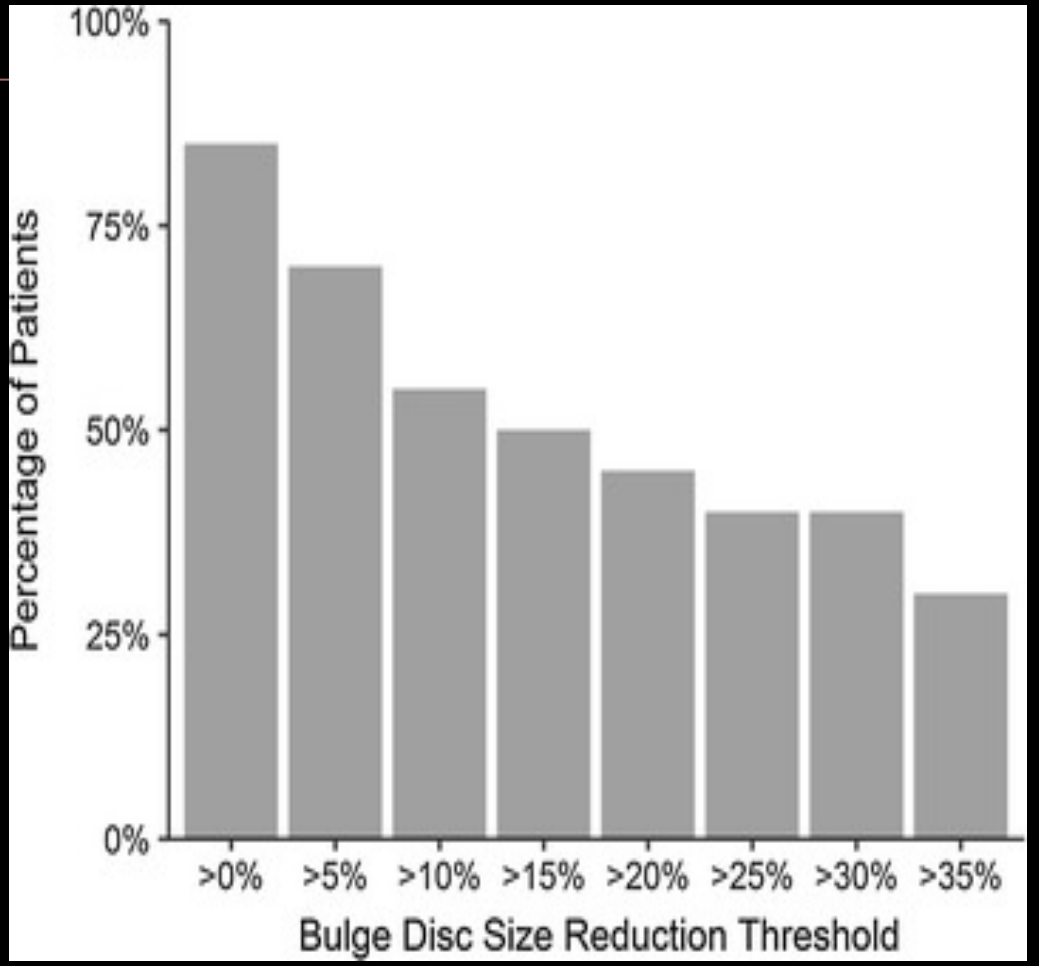
- FRI post-Tx change score avg. exceeded the min clinically important difference @ all time points except 12 months
- On post-Tx MRI 85% had a reduction in disc bulge size, with an **avg reduction size of 23%**
- **Conclusion** – the use of BM-MSCs lead to significant improvements in pain, function,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



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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

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

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- **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

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

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

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

	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	30	32	64	54
BMI (kg/m^2)	27.9	22.6	26.5	22.2	20.3	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	40	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

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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

Pain Physician 2018; 21:515-540

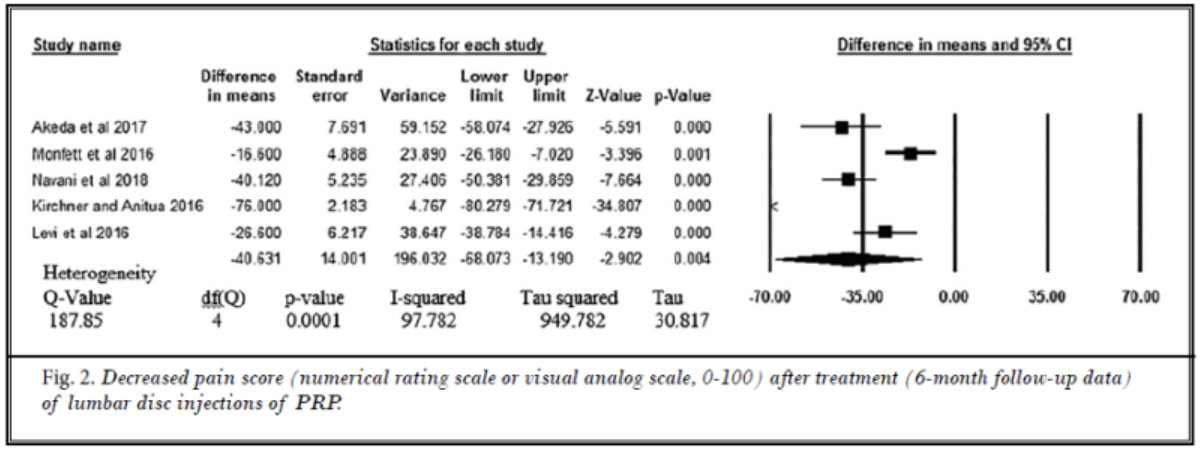

Fig. 2. *Decreased pain score (numerical rating scale or visual analog scale, 0-100) after treatment (6-month follow-up data) of lumbar disc injections of PRP.*

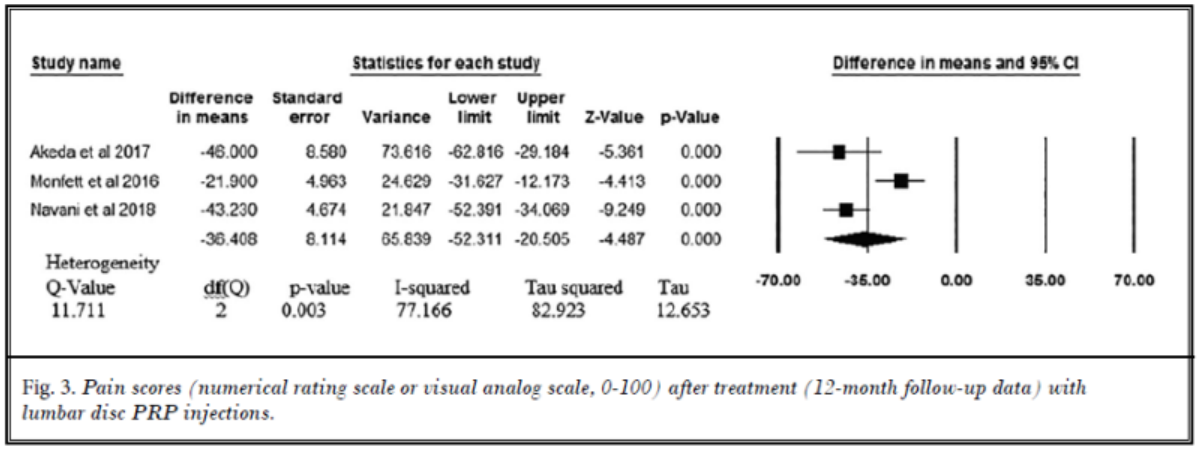

Fig. 3. *Pain scores (numerical rating scale or visual analog scale, 0-100) after treatment (12-month follow-up data) with lumbar disc PRP injections.*

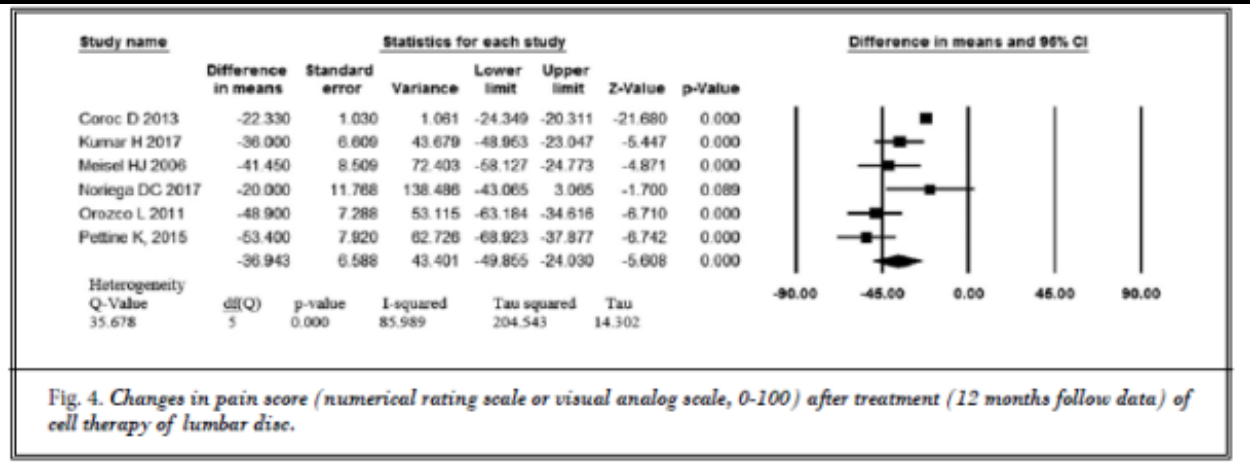

Fig. 4. *Changes in pain score (numerical rating scale or visual analog scale, 0-100) after treatment (12 months follow data) of cell therapy of lumbar disc.*

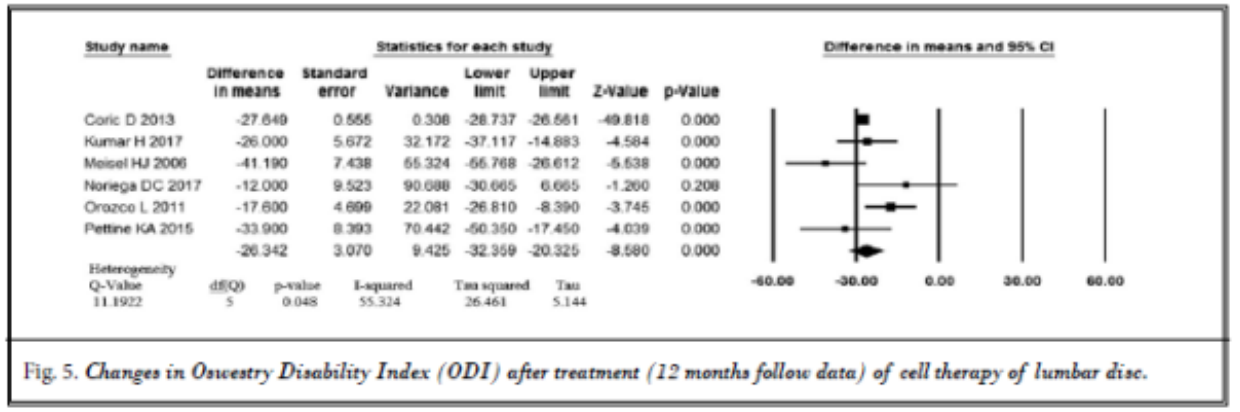

Fig. 5. *Changes in Oswestry Disability Index (ODI) after treatment (12 months follow data) of cell therapy of lumbar disc.*

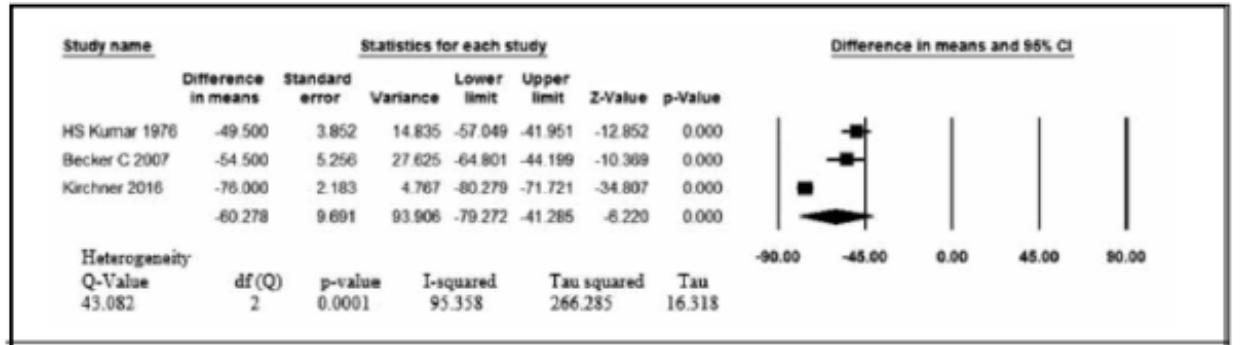

Fig. 6. *Changes in pain scores (0-100) after treatment (6 months follow data) of epidural PRP injections.*

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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

Pain Physician 2018; 21:515-540

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

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

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

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

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

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


Thank you!!!
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