

PLATELET RICH PLASMA AND STEM CELLS IN MANAGEMENT OF CHRONIC PAIN

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Disclosures and Conflicts of Interest

- None

Learning Objectives

- Define Platelet Rich Plasma
- Review biological mechanisms of action of PRP
- Discuss evidence for PRP in OA
- Discuss evidence for PRP in tendinopathy
- Explore safety of PRP
- Briefly review Stem Cell Therapy

What is Platelet Rich Plasma?

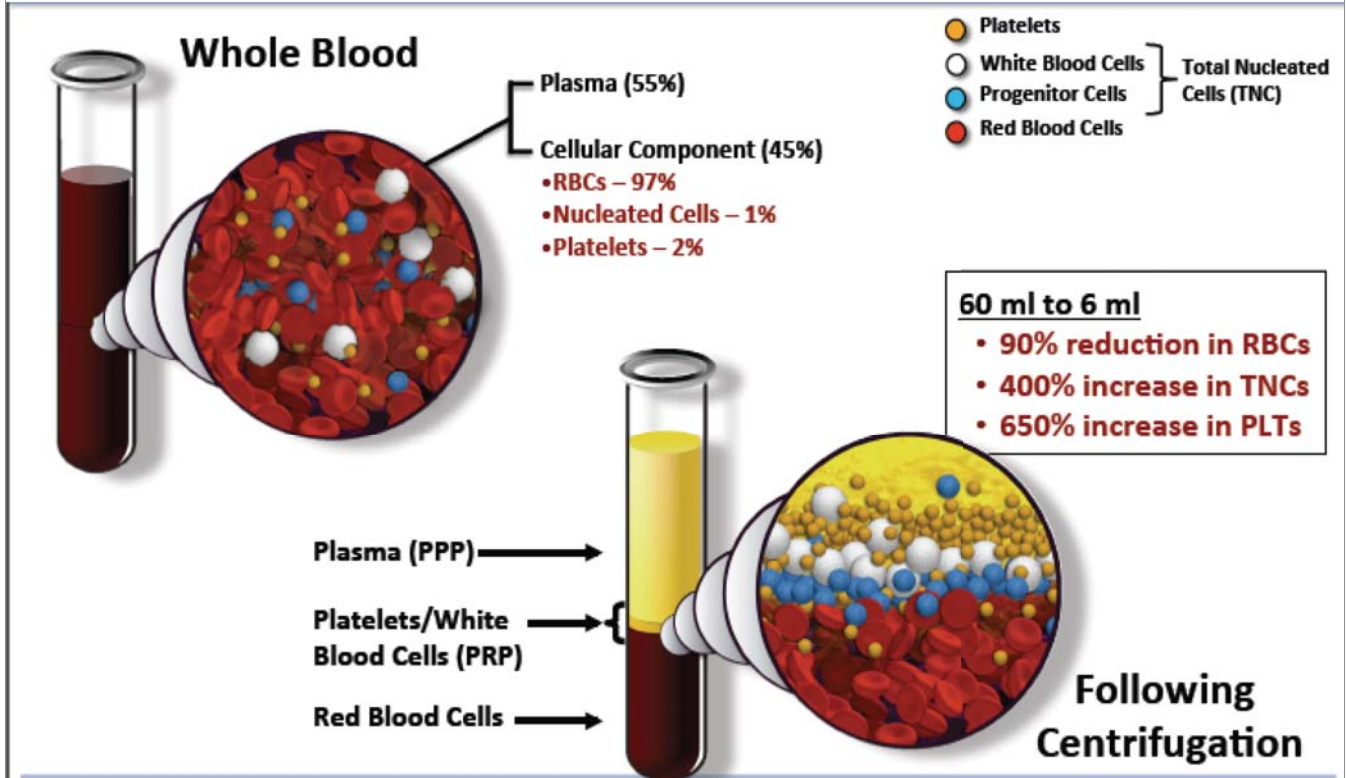
Regenerative Medicine

- Replace/regenerate cells/tissues/organs
- Restore normal function

PRP

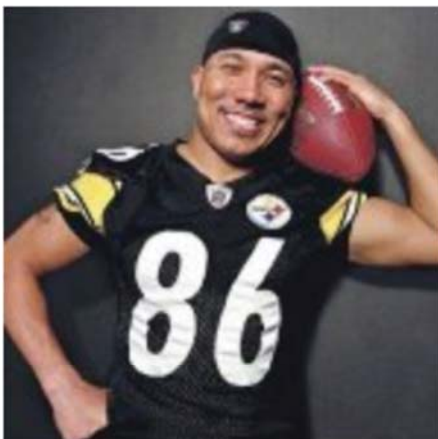
- **Considered form of regenerative medicine**
- **Autologous blood product**
- **PLT count > Plasma level**

How Is PRP Extracted?

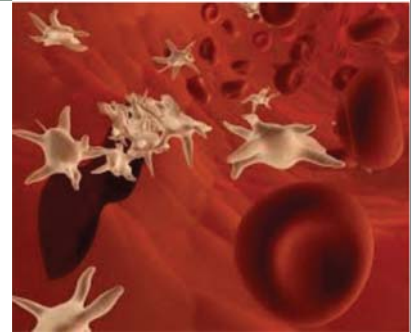


History of PRP

- First described 1972
- Accelerated use in sports medicine over last 15 years in context of high profile cases

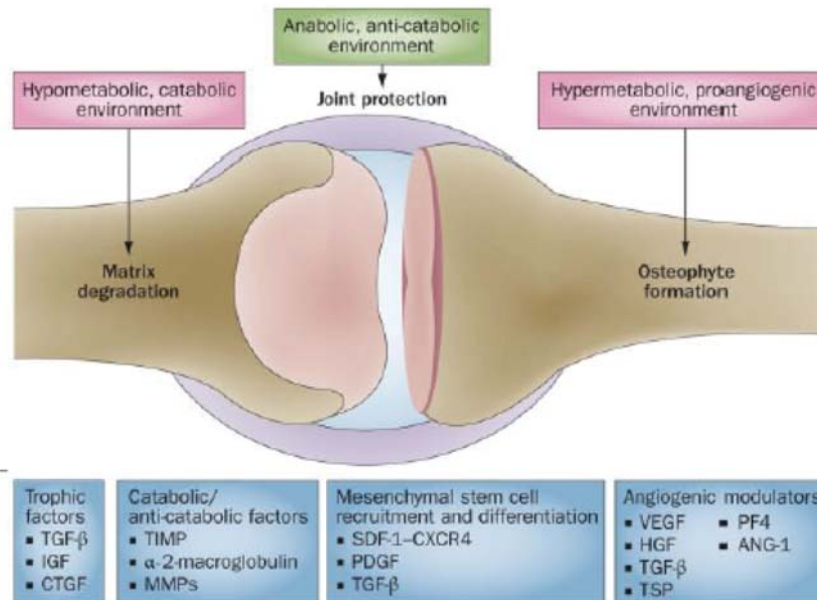


Biologic Rational for PRP



- **Platelets are a source of growth factors**
 - Platelet derived growth factors (PDGF)
 - Transforming growth factors B1 (TGF-B1)
 - Insulin-like growth factor (IGF-1)
 - Fibroblast growth factors (FGF-2)
 - Vascular endothelial growth factor A (VEGF-A)
- **Growth factors are polypeptide signal proteins instrumental in modulating cellular functions**
 - Tissue regeneration
 - Cell proliferation, differentiation and migration
 - Angiogenesis
 - Modulation of inflammation

Figure 3 Synthetic and degradative processes can be modified with autologous blood products



Andia, I. & Maffulli, N. (2013) Platelet-rich plasma for managing pain and inflammation in osteoarthritis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.141

Effects of PRP

- **Positive effects**

- Proliferation and recruitment of stem cells
- Release of trophic factors
- Modulate inflammation

- **Potential detrimental effects**

- Trophic factors may promote osteophyte formation
- Potential catabolic effects

- **Balance of effect dependent on various factors**

Variables in PRP Treatment

- Equipment and delivery methods
- Timing, Frequency and Dosage
- **PRP Content**
 - Leukocyte rich vs. poor
 - Plt concentration
- Patient Factors
- Adjuvant Meds
 - Anticoagulant
 - pre-activation

PRP Contents

- PLT concentration either ($>5x$ or $< 5x$ baseline)
- Leukocyte Rich (LR) or Leukocyte Poor (LP)
- Generally LR PRP has PLT concentration $> 5x$
 - Higher GF concentrations
 - More catabolic and proinflammatory cytokines
 - Possible higher rate of acute inflammatory response 5 days post
 - No significant difference inflammatory response 14 days

Mishra Classification of PRP components

TABLE 1
Platelet-Rich Plasma Classification System

Type	White Blood Cells	Activated?
1	Increased over baseline	No
2	Increased over baseline	Yes
3	Minimal or no white blood cells	No
4	Minimal or no white blood cells	Yes

A: Platelets $>5\times$ baseline
B: Platelets $<5\times$ baseline

What is the evidence for PRP in Chronic Pain Management?

Osteoarthritis

- **Knee OA**
- Hip OA

Other

- Muscle strain
- **Plantar fasciitis**

Tendinopathy management

- **Lateral epicondylar tendinopathy**
- Rotator cuff tendinopathy
- Achilles tendinopathy
- Patellar tendinopathy
- Gluteal tendinopathy

Arthroscopy. 2016 Dec 22. pii: S0749-8063(16)30780-0. doi: 10.1016/j.arthro.2016.09.024. [Epub ahead of print]

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

Dai WL¹, Zhou AG¹, Zhang H¹, Zhang J².

- **Meta-analysis, 10 RCTs, 1069 patients**
- **PRP better than Hyaluronic Acid at 12 Mo**
 - WOMAC pain score, mean difference -2.83
 - 95% CI -4.26 to -1.39, P < .05
 - WOMAC function score, mean difference -12.53
 - 95% CI -14.58 to -10.47, P < .05
 - 12 months WOMAC pain and function scores exceeded the MCID
 - (-0.79 for WOMAC pain and -2.85 for WOMAC function)
- **PRP better than saline at 6 and 12 Mo**

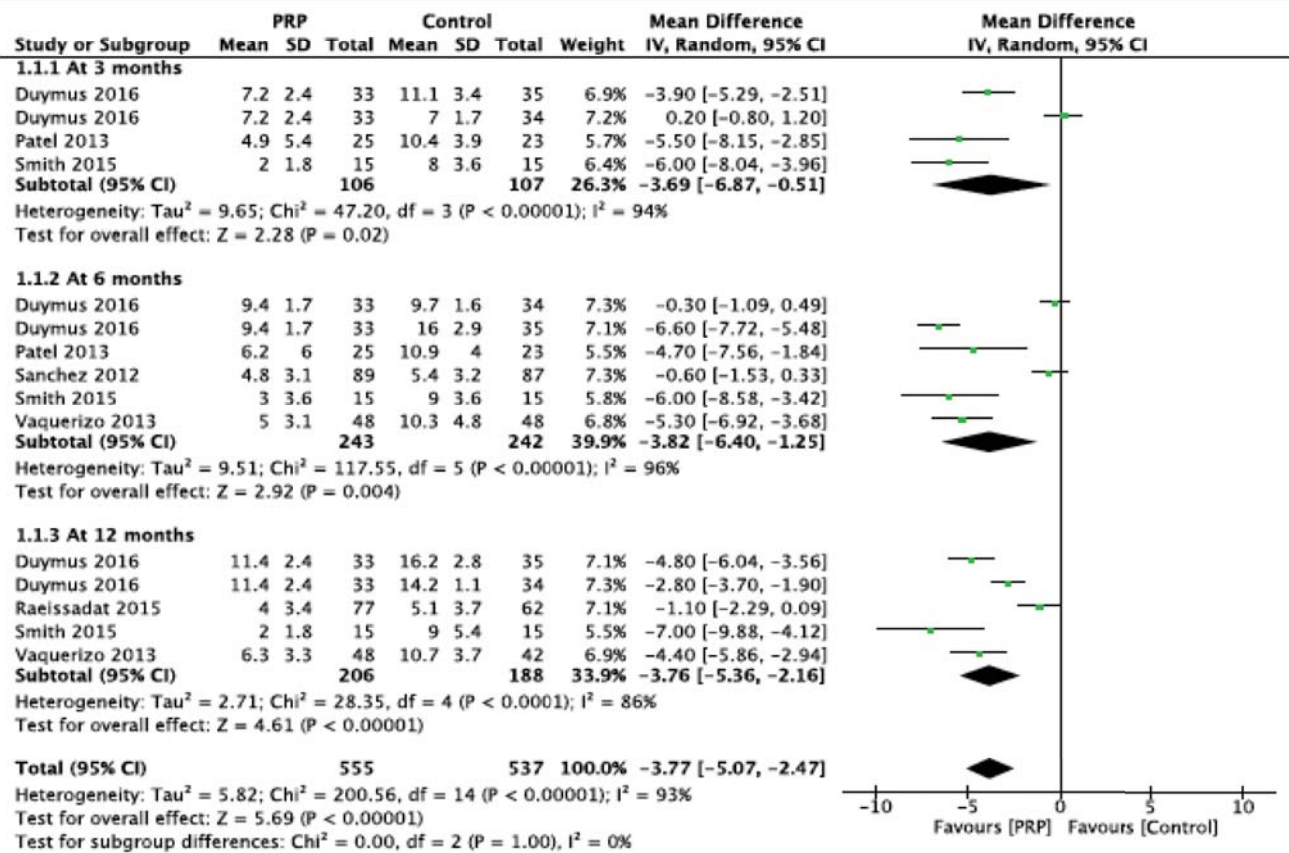


Fig. 3 Forest plots investigating the effect of PRP on WOMAC pain subscores at 3, 6 and 12 months compared with control. (IV, inverse variance; M-H, Mantel-Haenszel; CI, confidence interval)

Shen et al Journal of Ortho Sx and Res 2017

Orthop J Sports Med. 2017 Feb 13;5(2):2325967116689386. doi: 10.1177/2325967116689386. eCollection 2017 Feb.

Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis: A Prospective, Randomized, Double-Blinded Clinical Trial.

Joshi Jubert N¹, Rodríguez L², Reverté-Vinaixa MM¹, Navarro A³.

Intervention: PRP single injection vs. Bupi/betamethasone

Population: KL grade 3 and 4

Outcomes: Primary endpoint VAS at 1, 3 and 6 months

Result:

- No difference between IACS and PRP
- SF 36 and quality of life indicators at 6 months improved more in PRP group vs. IACS

Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial.

Görmeli G¹, Görmeli CA², Ataoğlu B³, Çolak C⁴, Aslantürk O⁵, Ertem K⁵.

Intervention: PRP-1, PRP-3, HA-3, NS-3 (control)

Population: Early OA or Advanced OA

Outcome: 6 months EQ-VAS and IKDC

Results:

- All groups improved (Early and Advanced) compared to control
- Early OA: PRP-3 group significantly improved compared to others
- Advanced OA: no additional improvement with multiple PRP injections

Epub 2020 Apr 17.

Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

John W Belk¹, Matthew J Kraeutler², Darby A Houck¹, Jesse A Goodrich¹, Jason L Dragoo¹, Eric C McCarty¹

Meta-analysis, 18 RCTs, 1608 patients

**PRP better than Hyaluronic Acid mean duration 11.1 mo
WOMAC score, mean imp. 44.7% vs 12.6% (P 0.01)**

Leukocyte-poor better than Leukocyte-rich

Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis.

Riboh JC¹, Saltzman BM², Yanke AB², Fortier L³, Cole BJ².

- **Meta-analysis, 6 RCTs, 2 PCS, 1055 patients**
- **LP-PRP better than HA and placebo**
 - HA WOMAC scores mean difference, -21.14; 95% CI, -39.63 to -2.65
 - Placebo WOMAC mean difference, -17.84; 95% CI, -34.95 to -0.73
- **LR-PRP no different than HA**
- **AE no difference LR-PRP and LP-PRP**
 - OR 0.78; 95% CI, 0.05-11.93
- **AE PRP greater than HA**
 - odds ratio, 5.63; 95% CI, 1.38-22.90
 - nearly all local swelling and pain

PRP Knee OA Adverse Events

- **No difference PRP vs. HA or Saline**
- AE PRP 73/352 = 20.7%
- **AE minor, all self resolved**
 - pain, swelling, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia
- **No major AE**

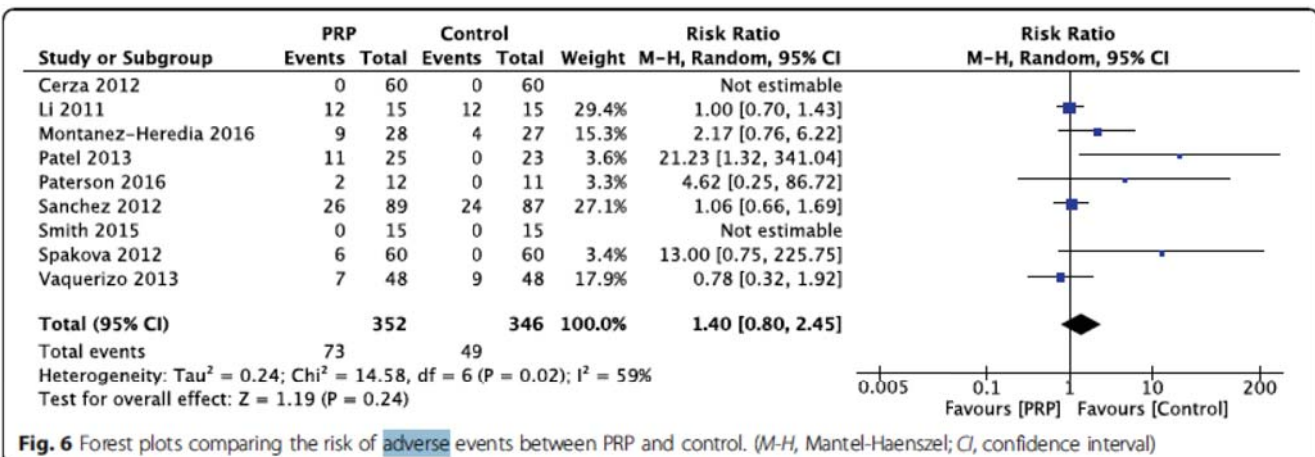


Fig. 6 Forest plots comparing the risk of adverse events between PRP and control. (M-H, Mantel-Haenszel; CI, confidence interval)

PRP Knee OA Literature Review

- PRP improves pain and function up to 12 mo.
- Safety similar to other injections (HA, Saline)
- Better results with early OA
- Suggests multiple PRP injections may be more beneficial than single injection for mild-mod OA
- Hip OA - Limited evidence for benefit

Lateral Epicondylar Tendinopathy – Systematic Reviews

- Ahmad et al (Nov 2013)
 - Suggests PRP may be a benefit over standard treatment as a second line intervention
- De Vos et al (Feb 2014)
 - Strong evidence that PRP injections are not efficacious in management of chronic lateral elbow tendinopathy
- Simental-Mendia (2020)
 - PRP injection was not superior to placebo for relieving pain and joint functionality in chronic lateral epicondylitis

Randomized Controlled Trials

	Study	Participants	Intervention	Control	Outcome	Time frame	Results
HQ	Peerbooms et al 2010 and Gosens et al 2011	100	1x injection 3mL PRP Unactivated	corticosteroid	25% reduction in VAS score or DASH score	24 months	Significant benefit
HQ	Thanasas et al 2011	28	1x injection 3mL PRP Unactivated	Autologous whole blood	VAS score Liverpool elbow score	6 months	Non-significant benefit
HQ	Creaney et al 2011	150	2x injections Monthly 1.5mL PRP Unactivated	Autologous whole blood	25 point improvement in PRTEE score	6 months	Non-significant benefit
LQ	Omar et al 2012	30	1x injection PRP Unknown amount of activation	corticosteroid	VAS score DASH score	1, 5 months	Non-significant benefit
HQ	Krogh et al 2013	60	1x injection 3-3.5mL PRP Unknown activation	Glucocorticoid Or Saline	Improvement in PRTEE score	12 months	No benefit
LQ	Mishra et al 2014	230	1x injection 2-3mL PRP Unactivated	Bupivacaine	25% reduction in VAS	3, 6 months	Significant benefit

Lateral Epicondylitis - Evidence

- 6 RCTs
- Compare 1 – 2 injections of unactivated PRP against different controls (LA, steroid, whole blood, saline)
- Almost all studies showed significant improvement in both intervention and control groups
- Largest RCT n=230 (Mishra et al)
 - Shows significant benefit PRP > bupi (VAS and tenderness 24 wks)
 - Study criticism (ITT, loss of data at 24 Mo endpoint)
- Other RCTs
 - 1 shows significant benefit against steroids
 - 3 show non-significant benefit against steroid, whole blood
 - 1 shows no benefit against saline, steroid

PRP Tendinopathy

- Rotator cuff tendinopathy (3 RCTs)
- **Patellar tendinopathy (2 RCTs)**
- Achilles tendinopathy (4 RCTs)

Am J Sports Med. 2017 Jan;45(1):226-233. doi: 10.1177/0363546516643716. Epub 2016 Jul 21.

The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials.

Fitzpatrick J¹, Bulsara M², Zheng MH¹.

Study Design: meta-analysis of the outcomes of the PRP groups by preparation method and injection technique in tendinopathy

Methods:

- 18 studies (1088 participants)
- Lateral epicondylitis
- Achilles tendinopathy
- Patellar tendinopathy
- Rotator cuff tendon

Results: LR-PRP significant improvement vs. LP-PRP

(SMD 36.38; 95% CI, 34.00-38.77) vs. (SMD 26.77; 95% CI, 18.31-35.22)

PRP for Other Conditions

- **Plantar fasciitis (9 RCTs)**
- Muscle strain (No RCTs)

Review > J Foot Ankle Surg. May-Jun 2020;59(3):546-552. doi: 10.1053/j.jfas.2019.10.003.

Platelet-Rich Plasma Versus Corticosteroids in the Treatment of Chronic Plantar Fasciitis: A Systematic Review and Meta-analysis of Prospective Comparative Studies

Nedal Alkhatib¹, Motasem Salameh¹, Abdulaziz F Ahmed¹, Eslam Alkaramany¹, Ghalib Ahmed², Mohamed M Mekhaimar³, Jasim Alsaedi⁴

Meta-analysis, 13 prospective studies, 679 patients

PRP better than Steroids at 6 months

- **AOFAS** Mean difference 13.33(95% CI 8.72 to 17.94; $I^2 = 89\%$; $p < .001$)
- **VAS** -1.22 (95% CI -2.03 to -0.41; $I^2 = 85\%$; $p < .001$)

Stem Cell Therapy in Chronic Pain

- MSC
 - Easy availability (fat, bone marrow)
 - Long term renewal
 - Ability to differentiate along several cell lineages
- OA, MSK conditions, neuropathic pain, discogenic pain
- Regulation in Canada
- Future directions

Health Canada Policy Paper on Autologous Cell Therapy Products

Date modified: 2020-01-17

Health Canada Policy Position Paper – Autologous Cell Therapy Products

Statement 4: There exists confusion regarding the regulatory status of autologous cell therapy products that are processed using equipment that has an authorized medical device licence. Clarity is needed and Health Canada plans to develop separate criteria to address this issue. Regardless, a medical device licence for a piece of manufacturing equipment does not by default constitute authorization for cell therapy products that are processed using an authorized medical device. Unless a device has received Health Canada authorization for specific therapeutic indications for the cell therapy output, the pertinent *Food and Drug Regulations* requirements apply to the cell therapy manufacturer.

NOTE THIS DOES NOT PERTAIN TO PRP

Summary

- PRP autologous blood product with PLT > baseline plasma
- PRP is a type of regenerative and immunomodulatory therapy with evidence in specific conditions
 - Osteoarthritis knee
 - Tendinopathy (distinct types)
 - Plantar Fasciitis
- Further studies required
 - Guide therapy
 - PRP content
 - Number and timing of injections
- Stem cells an evolving therapy
 - Further studies required, increased regulatory environment

Works Cited

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- Robh et al. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med*. 2016 Mar; 44 (3):792-800
- Mishra et al. Efficacy of Platelet-Rich Plasma for Chronic Tennis Elbow. *Am J Sports Med* 2014;42(2):463-71
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- de Vos et al. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. *Br J Sports Med* 2014;48:952-956
- [Chakravarthy et a. Stem Cell Therapy for Chronic Pain Management: Review of Uses, Advances, and Adverse Effects.](#) *Pain Physician*. 2017 May;20(4):293-305.
- <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/cell-therapy-policy.html>