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Platelets to the Rescue? A Literature Review of the Safety and Efficacy of Platelet-Rich Plasma for Symptomatic Osteoarthritis of the Knee

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Background

Osteoarthritis of the knee is one of the most common joint disorders in the United States with rising prevalence due to obesity and an aging population.

Regarding non-surgical approaches to management, there has been growing interest in the use of intra-articular injections with Platelet Rich Plasma (PRP).

Statement of the Problem

The use of Intra-articular PRP injections for symptomatic osteoarthritis of the knee is in its infancy there have been many problems with evaluating platelet-rich plasma in the literature including: poor and inconsistent study designs, differences in platelet separation techniques, use of variety of measurement scales and indexes, lacking objective quantity and quality of PRP that was utilized.

In reflection ,current clinical guideline recommendations put forth by the American Academy of Orthopedic Surgeons (2013) **does not recommend nor disapprove the use of IAI of PRP** for the treatment of symptomatic OA of the knee .

Literature Review

A comprehensive review of eighteen clinical control trials studies was performed. The primary scope of this review focuses on outcomes related to safety (adverse events) and efficacy based on Western Ontario and McMaster University Osteoarthritis Index (WOMAC) .

Research Question

Primary Research questions

In patients with symptomatic osteoarthritis of the knee,…

- is platelet rich plasma safe?
- does platelet rich plasma improve pain, stiffness, and physical function?
- does one injection versus more than one injection improve outcomes?
- are there trends in the type of PRP that is most effective?

Adverse Effects by Study

Table A3

Study	Reported Adverse Effects
(Baltzer, Moser, Jansen, & Krauspe, 2009)	Localized pressure, pain, swelling, tenderness, and heat that lasted up to 2 days
(Beselga García-Escudero & Miguel Hernández Trillos, 2015)	No severe adverse effects
(Cerza et al., 2012)	No observed adverse reactions
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	†
(Duymus et al., 2017)	†
(Filardo et al., 2012a)	No severe adverse events observed. Transient pain and swelling in both groups with more incidence in double spin group
(Filardo et al., 2012b)	Minor events. Mild pain and effusion
(Filardo et al., 2015)	Transient post injection pain and swelling.
(Gobbi, Lad, & Karnatzikos, 2015)	†
(Gormell et al., 2017)	‡
(Jang, Kim, & Cha, 2013)	†
(Kon et al., 2011)	No observed adverse reactions
(Liu, 2018)	No side-effects observed
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	Syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia. Higher incidence in those that received 2 injections
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	Transient local pain and swelling with no significant complications There was modest pain persisting 1-week after injection with no long-term complications.
(Smith, 2016)	No observed adverse reactions
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	Mild pain which resolved after 2 days with no severe adverse events

† = Not discussed. ‡ = Not discussed but has outcome measurement for adverse events

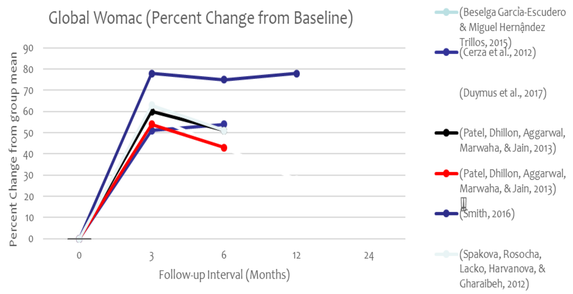
Injections by Study: Number and Cycles

TABLE B11

Study	Total IAI	# IAI (at each interval)	IAI Interval (weeks)	# Cycles	Cycle Interval (weeks)
(Baltzer, Moser, Jansen, & Krauspe, 2009)	6	2	1	3	1
(Beselga García-Escudero & Miguel Hernández Trillos, 2015)	4	1	1	Na	Na
(Cerza et al., 2012)	4	1	1	Na	Na
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	3	1	1	Na	Na
(Duymus et al., 2017)	2	1	4	Na	Na
(Filardo et al., 2012a)	4	1	3	Na	Na
(Filardo et al., 2012b)	3	1	1	Na	Na
(Filardo et al., 2015)	3	1	1	Na	Na
(Gobbi, Lad, & Karnatzikos, 2015)	3	1	4	Na	Na
(Gobbi, Lad, & Karnatzikos, 2015) ‼	3	1	4	2	4
(Gormell et al., 2017)	1	1	Na	Na	Na
(Gormell et al., 2017) ‡	3	1	1	Na	Na
(Jang, Kim, & Cha, 2013)	1	1	Na	Na	Na
(Kon et al., 2011)	3	1	2	Na	Na
(Liu, 2018)	3	1	4	Na	Na
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	1	1	Na	Na	Na
(Beyergani et al., 2014)	2	1	3	Na	Na
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	3	1	4	Na	Na
(Smith, 2016)	3	1	1	Na	Na
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	3	1	1	Na	Na

‡ = Insufficient data, Na= Not applicable, ‼= 2nd group in study

Symptom Relief



PRP by Study: Preparation, Activation, and Anticoagulation

Table A4

Study	# Spins	Spin 1 (speed, min)	Spin 2 (speed, min)	Spin 3 (Speed, min)	Comments
(Baltzer, Moser, Jansen, & Krauspe, 2009)	1	†	Na	Na	IL-1Ra was added to final product Platelets were frozen for subsequent injections
(Beselga García-Escudero & Miguel Hernández Trillos, 2015)	1	3000 G, 10	Na	Na	Platelets incubated 37 degreuse Celcius for 6 hours, filtered, then frozen for subsequent injections
(Cerza et al., 2012)	†	†	†	†	preparation not discussed
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	1	1500 rpm, 5	Na	Na	Platelets may have been frozen (not specified) for subsequent injections
(Duymus et al., 2017)	1	3700 rpm, 7	Na	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2012a)	1	580 rpm, 8	Na	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2012b)‼	2	1800 rpm, 15	2500 rpm, 10	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2012b)	2	1480 rpm, 6	3400 rpm, 15	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2015)	2	1480 rpm, 6	3400 rpm, 15	Na	Prolonged cycles of PRP were injected (1 IAI per month/ 3-month intervals)
(Gobbi, Lad, & Karnatzikos, 2015)	1	3500 rpm, 5	Na	Na	Platelets were frozen for subsequent injections
(Gormell et al., 2017)	2	1500 rpm, 6	3500 rpm, 12	Na	Platelets were autologous platelet separator
(Jang, Kim, & Cha, 2013)	†	†	†	†	
(Kon et al., 2011)	2	1480 rpm, 6	3400 rpm, 14	Na	Platelets were frozen for subsequent injections
(Liu, 2018)	1	900 rpm, 7 min	Na	Na	Leukocyte removal was not discussed
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	1	1500 rpm, 15	Na	Na	Leukocytes removed with filter
(Beyergani et al., 2014)	2	1600 rpm, 15	2800 rpm, 7	Na	
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	1	1700 G, 15	Na	Na	Platelets may have been frozen (not specified) for subsequent injections
(Smith, 2016)	1	1500 rpm, 5	Na	Na	Leukocytes removed with filter
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	3	3200 rpm, 15	1500, 10	3200, 10	

‡ = insufficient data, Na= Not applicable, † = Not discussed, ‼= 2nd group in study

Table A5

Study	Classification	Anticoagulant	Activation
(Baltzer, Moser, Jansen, & Krauspe, 2009)	LP-PRP or LR-PRP* with IL-1Ra	Yes†	‡
(Beselga García-Escudero & Miguel Hernández Trillos, 2015)	LP-PRP* or LR-PRP*	Yes†	No
(Cerza et al., 2012)	LP-PRP	Sodium citrate	‡
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	LP-PRP	No	No
(Duymus et al., 2017)	LP-PRP	Yes†	‡
(Filardo et al., 2012a) ‼	PRGF (LP-PRP*) and LR-PRP	Yes†	CaCl2
(Filardo et al., 2012b)	LR-PRP	Yes†	‡
(Filardo et al., 2015)	LP-PRP or LR-PRP*	Yes†	CaCl2
(Gobbi, Lad, & Karnatzikos, 2015)	LP-PRP	‡	Collagen or Von Willebrand Factor
(Gormell et al., 2017)	LP-PRP or LR-PRP*	Sodium citrate	CaCl2
(Jang, Kim, & Cha, 2013)	LP-PRP or LR-PRP*	ACD-A	No
(Kon et al., 2011)	LR-PRP*	Yes†	CaCl2
(Liu, 2018)	LP-PRP*	ACD-A	Calcium gluconate
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	LP-PRP*	CPD-A1	CaCl2
(Beyergani et al., 2014)	LR-PRP	ACD-A	No
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	LP-PRP*	ACD-A	Bovine thrombin + CaCl2
(Smith, 2016)	LP-PRFM	No	No
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	LR-PRP*	Sodium citrate	No

PRP= Platelet-Rich Plasma, PRFM = Platelet-Rich Fibrin Matrix, PRGF= Plasma Rich in Growth Factors, LP= Leukocyte-Poor, LR= Leukocyte-Rich
CPD-A1 = Citrate Phosphate Dextrose and Adenine, ACD-Citrate dextrose-A, IL-1Ra= interleukin-1 Receptor Agonist
*= Defined through analysis of reported preparation method with assistance from Dr. Launchbury
† = assumed from preparation method. ‡= Unknown/ not enough information. ‼= Study has 2 types of ACS

Discussion

Safety

- No severe long-term complications observed in any study
- Common Transient injection reactions: localized pressure, pain, swelling, tenderness
- $CaCl_2$ may contribute to adverse effects
- Higher concentrations of platelets and/or leukocytes may attribute to adverse effects

Efficacy

- There is evidence to suggest PRP improves pain stiffness and physical function for short-term (< 6 months) management
- Multiple studies suggested that higher concentrations of PRP did not correlate with clinical outcomes.
- Multiple doses and/or cyclical injections as well as PRP preparations with concentrated growth factors may be advantageous for more substantial and longer term benefits.

Trends in Efficacy

- The influence of patient age on PRP effectiveness is controversial with conflicting studies
- More favorable outcomes have been observed in those with mild-moderate osteoarthritis.
- Multiple doses and/or cyclical injections may not provide additional benefit for those with moderate to severe OA.
- Cole, Karas, Hussey, Pilz, & Fortier (2017) suggested that PRP may be more effective in those who are of healthy weight (BMI 18.5-24).
- Beselga Garcìa-Escudero & Miguel Hernâ̂ndez Trillos (2015) suggested that cyclical doses of PRP in addition to therapeutic exercise may provide sustained improvement of pain and physical function for up to 2 years.

Applicability to Clinical Practice

Utility & Application

- Outpatient setting/ < 1hr
- Safety comparable to other intra-articular injections
- In those that fail traditional therapeutic management, the addition of PRP to other non-invasive modalities may be a great option for those wanting to delay or avoid joint replacement surgery
- Patients that are treated with antiplatelet medications should not receive PRP injections because these medications may inhibit or interfere with the platelet function and decrease efficacy

Cost

- The cost of PRP can range from $400-1500 with discounted rates for multiple or bilateral injections.
- There is currently no insurance coverage for PRP injections, except for special circumstances involving workman's compensation or motor vehicle insurances

The Future of PRP

- In the mist of overwhelming bias and inconsistencies in study designs and wide variability in PRP preparation, current literature may not provide strong evidence to influence changes to future national guideline recommendations
- As the application of PRP is still in its infancy, clinicians implementing PRP injections for OA of the knee should be expected to make changes in the method of preparation and administration in years to come as more clinical trials aim to improve safety and efficacy of PRP and define optimal preparation methods and clinical practice guidelines.

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- *Please see project for complete list of references…*

Acknowledgements

I would like to thank my project advisor, Daryl Sieg, for his guidance throughout this project. I also appreciate Jaden Schoch for his thoughtful statistical insights and Dr. Launchbury for his knowledge and enthusiasm toward this topic. I would also like to thank Marcus Simonich, for helping understand the techniques and technical skills of scholarly writing. Finally, to my family who have provided love and support while I pursue my dreams, I could not have done it without you.